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# Long-term prognostic value of growth differentiation factor-15 in acute coronary syndromes

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A B S T R A C T

*Background:* Growth Differentiation Factor-15 (GDF-15) predicts death and cardiovascular events in acute coronary syndromes (ACS). We aimed to assess the long-term prognostic value of GDF-15 in ACS.
*Methods:* We included 358 patients with ACS who underwent coronary angiography. Plasma GDF-15 was measured and clinical data and long-term events were registered. Incremental value of GDF-15 for prognosing all-cause death above a clinical model including GRACE score, left ventricular ejection fraction < 40%, prior myocardial infarction and age was assessed.
*Results:* GDF-15 concentrations > 1800 ng/L were associated with an increased prevalence of cardiovascular risk factors. During 6.5 years of follow-up 56 patients died, 7 had values of GDF-15 < 1200 ng/L, 7 between 1200 and 1800 ng/L and 42 > 1800 ng/L. After adjustment for potential confounders, GDF-15 > 1800 ng/L were independently associated with all-cause death (HR 4.09; 95% CI 1.57–10.71; $p = .004$) and the composite of major adverse cardiovascular events (MACE) (HR 2.48; 95% CI 1.41–4.34; $p = .001$). For long-term all-cause death a significant increase of ROC curve was seen after addition of GDF-15 to a clinical model 0.876 (95% CI 0.823–0.928; $p = .014$). Same improvements were found for net reclassification improvement (0.776; 95% CI 0.494–1.037; $p < .001$) and integrated discrimination improvement (0.112; 95% CI 0.055–0.169; $p < .001$). Multivariate competing risk model showed a significant association between GDF-15 > 1800 ng/L and the incidence of heart failure but not of myocardial infarction.
*Conclusions:* In the setting of ACS, GDF-15 is associated with long-term all-cause death, MACE and heart failure and provides incremental prognostic value beyond traditional risks factor.

## 1. Introduction

After an acute coronary syndrome (ACS) patients are at high risk of cardiovascular morbidity and mortality. Although in recent decades there have been important advances in the treatment of ACS such as widespread use of dual antiplatelet therapy or angioplasty the management of these patients still is a challenge, especially on the long-term [1]. In this scenario, biomarkers could play an essential role with prognostication and therapeutic decision-making.

Growth Differentiation Factor-15 (GDF-15) is a member of the transforming growth factor-β cytokine superfamily [2] that appears to be involved in the regulation of body weight and food intake acting through the receptor glial cell line-derived neurotrophic factor family receptor α-like [3,4]. Under physiological conditions GDF-15 is weakly expressed by a wide range of cells and tissues except in placenta where is highly produced and secreted [5]. In contrast, GDF-15 increases in the myocardium, arteriosclerotic plaque and other tissues as a result of inflammation, oxidative stress and tissue injury [6,7]. In experimental animal models, GDF-15 seems to protect against cardiac injury by an anti-inflammatory, anti-apoptotic and anti-hypertrophic effects [8–10]. However, the exact biological significance of GDF-15 increase in human heart remains unclear due to a lack of knowledge of the signalling

*Abbreviations:* GDF-15, growth differentiation factor-15; ACS, acute coronary syndromes; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; GRACE, Global Registry of Acute Coronary Events; MACE, major adverse cardiovascular events; ROC, receiver operating characteristic; NRI, net reclassification improvement; IDI, integrated discrimination improvement

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pathways that drive its actions [11].

An increased in circulating concentrations of GDF-15 has been associated with higher prevalence of cardiovascular risk factors and higher incidence of cardiovascular morbidity and mortality [12–16]. In the setting of an ACS, higher GDF-15 concentrations have been found to be prognostic of all-cause mortality, myocardial infarction (MI), heart failure and non-coronary artery bypass grafting-related major bleeding mainly in the short-term [17–22] with limited data on the long-term [23,24] follow-up. In fact, this scenario has been reported in a recent meta-analysis [25] in which very few studies provide long-term outcomes. Moreover, only two studies informed congestive heart failure as outcome with a maximum follow-up of two years and high heterogeneity between them. Therefore, the aim of our study was to analyse the long-term prognostic value of GDF-15 in patients admitted with ACS.

## 2. Materials and methods

### 2.1. Study setting

The Joan XXIII University Hospital is a tertiary hospital located in South Europe (Tarragona, Spain). The Biobank of the Pere Virgili Health Research Institute, registered in the National Biobank Network, processes, stores and manages human biological samples from the Joan XXIII University Hospital.

### 2.2. Study population

This is a retrospective observational study that included consecutive patients admitted to our hospital from January 2011 to December 2014 with ACS who underwent coronary angiography. Acute MI was diagnosed according to the 2012 Universal Definition of MI [26]. Following the European Society of Cardiology guidelines, unstable angina was defined as the presence of ACS symptoms at rest or with minimal exertion in the absence of cardiomyocyte necrosis [27]. To classify and treat the study patients as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina we also used the current European Society of Cardiology guidelines criteria. We excluded patients who suffered a different type of MI than type 1 according the universal definition of MI and those foreign residents that were impossible to follow-up. Hospital Joan XXIII is the only hospital in our region capable of doing angiograms and percutaneous coronary intervention. Hence, many patients were only treated at the hospital during the acute phase and were followed-up by their local cardiologist after discharge. Therefore, of 1083 patients with the diagnosis of ACS and coronary angiography performed, 358 had a long-term follow-up available.

During hospital admission, baseline demographics, cardiovascular risks factors, medical history, ambulatory treatment, previous symptoms and clinical characteristics during admission (physical examination, laboratory findings, coronary angiography information, left ventricular ejection fraction [LVEF] and diagnostic at discharge) were registered. The estimated glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula. Impaired kidney disease was defined as an estimated glomerular filtration rate $< 60$ mL/min/1.73 $m^2$. Cardiac troponin I concentrations were measured with an automated immunoassay (Troponin I-Ultra, Advia Centaur, Siemens Healthineers, Erlangen, Germany). As described by the manufacturer, the cardiac troponin I detection limit is of 0.006 μg/L, the 99th reference percentile is of 0.040 μg/L and can be detected up to 50 μg/L (measured with a coefficient of variation of 8%). LVEF was measured within 24–48 h before discharge by using Simpson's methodology. A moderate to severe reduction of LVEF was defined as LVEF < 40%. Significant three vessels stenosis was defined as an obstruction > 70% in the three main coronary arteries. Syntax Score I was calculated by an experienced interventional cardiologist by using the Syntax Score calculator. An intermediate or high Syntax Score was defined as a score of 23 or more [28]. Similarly, the Global Registry of Acute Coronary Events (GRACE) score was calculated. An intermediate or high GRACE score was defined as a score ≥ 100 in patients with STEMI and ≥ 89 in the remaining patients [29].

### 2.3. GDF-15 analysis

Blood samples were collected into EDTA tubes during coronary angiography. After centrifugation, plasma aliquots were stored at −80 °C until analysis. Plasma GDF-15 concentrations were measured by an electrochemiluminescence immunoassay (Elecsys GDF-15, Roche Diagnostics, Basel, Switzerland). Laboratory measures were performed by investigators in a blinded fashion. According to the manufacturer, the detection limit is of 400 ng/L and the maximum detectable concentration of 20,000 ng/L. The intra and inter-assay imprecisions were < 0.9% and < 2.3%, respectively, in a concentration range between 1100 and 18,600 ng/L. As previously reported, GDF-15 concentration of 1200 ng/L has been was proposed as the upper limit of normality in healthy elderly adults [30] and risk categories were defined as low risk (< 1200 ng/L), intermediate (1200–1800 ng/L) and high risk (> 1800 ng/L) [17].

### 2.4. Follow-up and outcomes

Patients were followed for events for a maximum of 6.5 years. Deaths and hospital re-admissions were identified by telephone interview and/or review of electronic medical records. Follow-up adjudication was performed by an investigator without knowing GDF-15 measurements. Deaths, non-fatal MI and admission for heart failure were recorded during follow-up.

The primary outcome of this study was all-cause death. A secondary outcome was the composite of major adverse cardiovascular events (MACE), which were identified as all-cause death, non-fatal MI and admission for heart failure. For patients with recurrent events the time to the first event was recorded. Individual secondary outcomes were non-fatal MI and admission for heart failure.

### 2.5. Statistical analysis

Categorical variables are expressed as numbers and percentages whereas continuous variables are expressed as the median and interquartile range. Comparisons of categorical data were performed with chi-squared tests whereas continuous data were analysed with the Kruskal-Wallis test. The optimal GDF-15 cut-off point for all-cause death was defined by receiver operating characteristic (ROC) curves. To study the relationship between GDF-15 and outcomes, patients were categorised into groups according their GDF-15 concentrations (low < 1200 ng/L, medium 1200–1800 ng/L, high > 1800 ng/L). Survival probabilities were estimated by the Kaplan-Meier method and compared with the Log-rank test. Kaplan-Meier estimates were also calculated with its confidence interval. To determine if GDF-15 groups were associated with primary and secondary endpoints, univariable and multivariable Cox regressions were performed with the backward stepwise procedure. In the multivariable analysis, clinically relevant and significant variables in the univariable analysis were included. Therefore, multivariable Cox regression analyses were adjusted by age, diabetes mellitus, hypercholesterolemia, medical history of MI and renal impairment, intermediate or high GRACE score, significant three vessels stenosis and LVEF < 40% at discharge. The proportional hazards assumption was analysed by Schoenfeld residuals. Multicollinearity was searched by calculating the variance inflation factor. For heart failure and MI related hospitalization during follow-up, all-cause death was included in all the analyses as a competing risk, and the Gray method was used. Cumulative incidence curves by using the competing risk model were performed. Finally, to estimate the

ability of GDF-15 to improve long-term risk prediction of all-cause death beyond to a clinical model that included age, medical history of MI, GRACE score and LVEF < 40% we performed ROC curve analyses and the Hosmer-Lemeshow test. The clinical model was compared before and after adding cardiac troponin I peak and GDF-15 concentrations (both logarithms transformed). We also calculated the continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) as described by Pencina et al. [31] Differences were considered statistically significant at $p < .05$. STATA 14.2 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

### 2.6. Ethics

The study was approved by the local ethical committee and complies with the Declaration of Helsinki. All patients gave their written consent for participation in the study.

## 3. Results

### 3.1. Baseline characteristics

A total of 358 patients were included in the study. The median (interquartile range) age was 64.8 (55.6–74.3) years and 260 (72.6%) were male. Of all patients, 61.5% were admitted with NSTEMI, 24.0% with STEMI and 14.5% with unstable angina. The median (interquartile range) GDF-15 value was 1328 (930–2171) ng/L. GDF-15 values below 1200 ng/L were observed in 157 patients, between 1200 and 1800 ng/L in 85 subjects and above 1800 ng/L in 116 patients. Patients with higher values of GDF-15 were associated with older age, cardiovascular risk factors (hypertension, diabetes mellitus and hypercholesterolemia), chronic kidney disease and medical history of cardiovascular diseases (MI, cerebrovascular disease and peripheral arterial disease; Table 1). During admission they were more likely to have atrial fibrillation/flutter, worse Killip-Kimball class, renal impairment and higher GRACE score. In addition, they had an increase incidence of coronary stenosis, ventricular dysfunction (LVEF < 40%) and complications during hospitalization. An increased use of statins and lower values of LDL cholesterol were seen among patients with higher values of GDF-15. Regarding the cardiac troponin I peak and discharge diagnostic no differences were found. Finally, only 4 deaths were seen during hospitalization and all of them had values of GDF-15 above 1800 ng/L (Table 2).

### 3.2. Primary endpoint

During 6.5 years of follow-up (median follow-up of 4.9 [interquartile range 4.2–5.8] years), 56 patients died. Of those patients, 7 (4.9%; 95% CI 2.3%–10.0%) had values of GDF-15 below 1200 ng/L, 7 (15.4%; 95% CI 6.3%–34.6%) between 1200 and 1800 ng/L and 42 (44.7%; 95% CI 32.9%–58.6%) above 1800 ng/L (Fig. 1). Only GDF-15 values > 1800 ng/L were associated with an increased risk of all-cause death (unadjusted HR 10.63; 95% CI 4.77–23.69; $p < .001$). After adjustment for potential confounders, higher GDF-15 concentrations were still independently associated with all-cause death (adjusted HR 4.09; 95% CI 1.57–10.71; $p = .004$; Table 3).

### 3.3. Secondary endpoints

A composite of major adverse cardiovascular events was analysed during follow-up. In this way, 101 events of MACE were observed. Of those, 24 (17.5%; 95% CI 11.9%–25.4%) events occurred in patients with low GDF-15 values, 20 (35.4%; 95% CI 22.5%–52.8%) events in medium values and 57 (53.3%; 95% CI 43.8%–63.4%) in high GDF-15 values (Fig. 1). An unadjusted analysis of these data showed that higher GDF-15 values (> 1800 ng/L) had an increased risk of MACE (unadjusted HR 4.36; 95% CI 2.70–7.03; $p < .001$) while medium values were not statistically significant (unadjusted HR 1.54; 95% CI 0.85–2.78; $p = .155$). This excess risk of higher GDF-15 values was partially diminished, but still significant, after adjustment for potential confounders (adjusted HR 2.48; 95% CI 1.41–4.34; $p = .001$).

A total of 59 patients suffered a new MI during follow-up (20 [14.7%; 95% CI 9.5%–22.3%] patients with low GDF-15 values, 14 [22.5%; 95% CI 13.7%–37.0%] with medium GDF-15 values and 25 [23.9%; 95% CI 16.8%–33.4%] in the higher values; Fig. 2). Although higher GDF-15 values (> 1800 ng/L) had an increased risk of new MI (unadjusted competing risk HR 1.89; 95% CI 1.04–3.43; $p = .037$) the multivariate competing risk regression did not reach a statistically significant association.

During the follow-up, 18 patients developed heart failure (0 [0.0%; 95% CI 0.0%–0.0%] patients with low GDF-15 values, 1 [2.4%; 95% CI 0.4%–16.1%] with medium GDF-15 values and 17 [21.2%; 95% CI 12.9%–33.8%] in the higher values; Fig. 2). Univariate competing risk analysis showed a non-significant association between medium GDF-15 values and heart failure but, on the contrary, higher GDF-15 values had a significant increase risk of heart failure (unadjusted competing risk HR 39.53; 95% CI 5.32–293.86; $p < .001$). After adjustment for potential confounders, the higher GDF-15 values persist associated with an increased risk of heart failure (adjusted competing risk HR 30.77; 95% CI 4.09–231.54; $p < .001$).

### 3.4. Analysis of ROC curves and GDF-15 risk prediction

ROC curves were performed to determine whether GDF-15 could improve long-term risk prediction. The best GDF-15 cut-off value for the prediction of all-cause death was 1759 ng/L (area under the curve 0.826; sensitivity 78.3%; specificity 76.2%). ROC curve were 0.825 (95% CI 0.766–0.885) for clinical model, 0.826 (95% CI 0.764–0.887) for GDF-15 alone, 0.826 (95% CI 0.766–0.886) for clinical model with cardiac troponin I peak and 0.876 (95% CI 0.823–0.928) for clinical model including GDF-15. ROC curve analysis showed non-significant differences in the clinical model alone compared to the clinical model with cardiac troponin I peak ($p = .905$) or GDF-15 alone ($p = .993$), however there was a significant difference compared to the clinical model with GDF-15 ($p = .014$). Similar pattern was observed for NRI and IDI. Overall NRI showed a significant improvement of risk prediction between the clinical model alone compared to the clinical model with GDF-15 (0.776; 95% CI 0.494–1.037; $p < .001$) as also was the case for IDI (0.112; 95% CI 0.055–0.169; $p < .001$). This benefit of risk prediction was non-significant between the clinical model alone compared to the clinical model with cardiac troponin I peak (NRI -0.128; 95% CI -0.410–0.154; $p = .813$; IDI 0.002; 95% CI -0.002–0.006; $p = .156$). (Fig. 3).

For MACE outcomes ROC curves were 0.749 (95% CI 0.692–0.806) for clinical model alone and 0.789 (95% CI 0.736–0.842) for clinical model including GDF-15. Compared to clinical model alone ROC curves showed a significant improvement after the addition of GDF-15 to the clinical model ($p = .033$). Overall NRI showed a significant improvement of risk prediction between the clinical model alone compared to the clinical model with GDF-15 (0.582; 95% CI 0.352–0.812; $p < .001$) as also was the case for IDI (0.078; 95% CI 0.044–0.113; $p < .001$).

For heart failure ROC curves were 0.714 (95% CI 0.580–0.849) for clinical model alone and 0.868 (95% CI 0.803–0.933) for clinical model including GDF-15. Compared to clinical model alone ROC curves showed a significant improvement after the addition of GDF-15 to the clinical model ($p = .012$). Overall NRI showed a significant improvement of risk prediction between the clinical model alone compared to the clinical model with GDF-15 (0.943; 95% CI 0.469–1.417; $p < .001$) as also was the case for IDI (0.086; 95% CI 0.034–0.138; $p = .041$).

## 4. Discussion

In this study, we analysed the power of a single value of GDF-15 to stratify the risk of adverse events in ACS patients followed during one of the longest periods reported up to date. We found that GDF-15

**Table 1**
Demographics, cardiovascular risk factors, medical history and ambulatory treatment.

| Variable | GDF-15 Cut-off point (ng/L) | | | | *P* Value |
|---|---|---|---|---|---|
| | Overall (*N* = 358) | < 1200 (*N* = 157) | 1200–1800 (*N* = 85) | > 1800 (*N* = 116) | |
| Demographics | | | | | |
| Age, years | 64.8 (55.6–74.3) | 58.2 (49.4–64.8) | 69.8 (60.2–76.0) | 72.4 (64.6–79.4) | < 0.001 |
| Male sex | 260 (72.6) | 122 (77.7) | 63 (74.1) | 75 (64.7) | 0.054 |
| Cardiovascular risk factors | | | | | |
| Current smoker | 115 (32.1) | 67 (42.7) | 28 (32.9) | 20 (17.2) | < 0.001 |
| Hypertension | 243 (67.9) | 92 (58.6) | 56 (65.9) | 95 (81.9) | < 0.001 |
| Diabetes mellitus | 130 (36.3) | 38 (24.2) | 31 (36.5) | 61 (52.6) | < 0.001 |
| Hypercholesterolemia | 217 (60.6) | 83 (52.9) | 49 (57.7) | 85 (73.3) | 0.002 |
| Obesity (BMI ≥30 kg/m$^2$) | 93 (28.5) | 39 (27.7) | 24 (29.6) | 30 (28.9) | 0.949 |
| Medical history | | | | | |
| Myocardial infarction | 80 (22.4) | 21 (13.4) | 22 (25.9) | 37 (31.9) | 0.001 |
| Heart failure | 4 (1.1) | 0 (0.0) | 1 (1.2) | 3 (2.6) | 0.133 |
| Cerebrovascular disease | 21 (5.9) | 2 (1.3) | 4 (4.7) | 15 (12.9) | < 0.001 |
| Peripheral arterial disease | 38 (10.6) | 6 (3.8) | 3 (3.5) | 29 (25.0) | < 0.001 |
| Chronic kidney disease | 28 (7.8) | 1 (0.6) | 3 (3.5) | 24 (20.7) | < 0.001 |
| PCI | 51 (14.3) | 17 (10.8) | 13 (15.3) | 21 (18.1) | 0.224 |
| Cardiac surgery | 8 (2.3) | 3 (1.9) | 2 (2.4) | 3 (2.6) | 0.929 |
| Ambulatory treatment | | | | | |
| Acetylsalicylic acid | 139 (38.8) | 40 (25.5) | 36 (42.4) | 63 (54.3) | < 0.001 |
| Other antiplatelet drugs | 52 (14.5) | 14 (8.9) | 14 (16.5) | 24 (20.7) | 0.020 |
| Oral anticoagulant | 9 (2.5) | 2 (1.3) | 2 (2.4) | 5 (4.3) | 0.283 |
| Beta blockers | 104 (29.1) | 38 (24.2) | 24 (28.2) | 42 (36.2) | 0.095 |
| ACE inhibitors | 107 (29.9) | 46 (29.3) | 28 (32.9) | 33 (28.5) | 0.772 |
| ARBs | 51 (14.3) | 16 (10.2) | 10 (11.8) | 25 (21.6) | 0.022 |
| MRAs | 7 (2.0) | 2 (1.3) | 1 (1.2) | 4 (3.5) | 0.368 |
| Diuretics | 87 (24.3) | 24 (15.3) | 22 (25.9) | 41 (35.3) | 0.001 |
| Oral antidiabetic drugs | 80 (22.4) | 26 (16.6) | 17 (20.0) | 37 (31.9) | 0.009 |
| Insulin | 31 (8.7) | 3 (1.9) | 9 (10.6) | 19 (16.4) | < 0.001 |
| Statins | 176 (49.2) | 56 (35.7) | 43 (50.6) | 77 (66.4) | < 0.001 |

Data represent the number (percentage) or median (interquartile range). BMI indicates body mass index. PCI indicates percutaneous coronary intervention; ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; MRAs: mineralocorticoid receptor antagonists.

concentrations higher than 1800 ng/L were associated with an increased risk of all-cause death, MACE and hospitalization for heart failure, but not with new admission for MI. Even more, we observed that GDF-15 had an incremental prognostic value beyond a clinical model for all-cause death, MACE and heart failure risk. Finally, higher GDF-15 concentrations in the setting of an ACS were consistently related with an increased prevalence of cardiovascular risk factors, medical history of cardiovascular diseases and worse outcomes during admission. Our results provide updated information on the long-term prognostic role of GDF-15 in ACS, previously analysed in scenarios with different standard of care than the currently available.

As mentioned above, previous investigations about GDF-15 have reported its association with cardiovascular risk morbidity and mortality. Nevertheless, it is unclear which is the main tissue that produce GDF-15 in patients with cardiovascular disease. For now, it has been reported that visceral and subcutaneous adipocytes [32] as well as arteriosclerotic plaques [33,34] are a source of GDF-15. In case of patients with end-stage non-ischaemic dilated cardiomyopathy, cardiac GDF-15 expression is very low suggesting that the increased concentration of circulating GDF-15 may be produced by peripheral tissues [35]. After an acute MI GDF-15 is upregulated in the heart [9]. Thus, circulating GDF-15 level increased significantly after an ACS but the increase has been reported as slight and unrelated to infarct size [17,19,20]. Consistently with this observation, we found that GDF-15 concentrations were not associated with cardiac troponin I peak nor with the type of ACS reflecting their independence of the myocardial damage extension. In fact, circulating levels of GDF-15 after an ACS have been reported to remain relatively stable for 6 months, suggesting an underlaying chronic disease burden [21,23].

In the setting of an ACS, GDF-15 has been related with an increased risk of all-cause death, MI, heart failure and non-coronary artery bypass grafting-related major bleeding after short-term follow-up [17–22]. However, in the long-term follow-up there is a lack of updated information because most of previous findings were done in a time when early revascularization or intense secondary prevention with modern dual antiplatelet therapy, high-dose statins or angiotensin-converting enzyme inhibitors were not the standard of care [23,24,36,37]. In that scenario, our study provides a unique and renewed prognostic information that could be extrapolated to the patients who currently suffer an ACS. Similar to previous publications our study showed that higher GDF-15 values were associated with an increased risk of all-cause death after a long-term follow-up. Of note, we found by ROC curve a GDF-15 value for death risk of 1759 ng/L quite similar than the previously reported of 1800 ng/L. Nevertheless, there are discordant data regarding incremental prognostic value of GDF-15 for long-term mortality risk stratification. Kempf et al. could not find a significant improvement after addition of GDF-15 to a clinical model in an ACS cohort [36]. Similarly, in a study with non-ST-elevation ACS patients, GDF-15 only showed a significant improvement on IDI but not on ROC curve and NRI [24]. Our study, however, demonstrated that the addition of GDF-15 over age, previous MI, GRACE score and LVEF < 40% had an incremental prognostic value with a concordant and significant improvement on ROC curve, NRI and IDI. Furthermore, GDF-15 provided better prognostic information than the cardiac troponin I peak. In that line, Eggers calculated GRACE score in 453 chest pain patients and demonstrated that its predictive value could be enhanced by GDF-15 [37]. However, unlike our study where all patients suffered an ACS, < 50% of the patients in the Eggers study had a final diagnosis of an ACS. In addition, also different from Eggers' study, we evaluated the incremental prognostic value with NRI and IDI beyond a clinical model that includes not only GRACE score but age, prior MI and LVEF < 40%. Based on a population with an acute MI, Skau et al. evaluated GDF-15

**Table 2**
Clinical characteristics during admission.

| Variable | GDF-15 Cut-off point (ng/L) | | | | P value |
|---|---|---|---|---|---|
| | Overall (N = 358) | < 1200 (N = 157) | 1200–1800 (N = 85) | > 1800 (N = 116) | |
| Previous symptoms | | | | | |
| Angina previous month | 74 (20.7) | 29 (18.5) | 17 (20.0) | 28 (24,1) | 0.513 |
| Angina in the previous 24 h | 112 (31.3) | 51 (32.5) | 24 (28.2) | 37 (31.9) | 0.782 |
| Physical examination at admission | | | | | |
| Systolic arterial pressure (mmHg) | 139 (121–153) | 140 (127–155) | 138 (117–150) | 134 (120–153) | 0.125 |
| Atrial fibrillation/flutter | 17 (4.8) | 3 (1.9) | 3 (3.5) | 11 (9.5) | 0.012 |
| Killip class > I | 38 (10.6) | 3 (1.9) | 6 (7.1) | 29 (25.0) | < 0.001 |
| Laboratory findings at admission | | | | | |
| Glycemia (mg/dL) | 121 (100–166) | 113 (98–149) | 120 (97–160) | 147 (104–218) | < 0.001 |
| eGFR (mL/min per 1.73 $m^2$) | 84 (63–98) | 95 (81–104) | 84 (69–93) | 60 (42–80) | < 0.001 |
| LDL cholesterol (mg/dL) | 98.2 (77–118) | 106.9 (84.5–125.5) | 98 (79–117) | 86 (67.5–107.5) | < 0.001 |
| HDL cholesterol (mg/dL) | 37 (31–44) | 37 (31.5–44) | 39 (33–44.5) | 37 (29–44.5) | 0.269 |
| Cardiac troponin I peak (ng/mL) | 3.0 (0.2–21.8) | 2.1 (0.2–20.5) | 2.8 (0.1–21.0) | 3.8 (0.2–25.8) | 0.520 |
| GRACE score | | | | | |
| Intermediate or high GRACE | 228 (63.7) | 59 (37.6) | 65 (76.5) | 104 (89.7) | < 0.001 |
| Coronary angiography | | | | | |
| Significant three vessels stenosis | 82 (22.9) | 23 (14.7) | 21 (24.7) | 38 (32.8) | 0.002 |
| Intermediate or high Syntax Score | 66 (18.9) | 20 (12.9) | 16 (19.3) | 30 (26.8) | 0.017 |
| PCI | 248 (69.3) | 111 (70.7) | 60 (70.6) | 77 (66.4) | 0.713 |
| LVEF at discharge | | | | | |
| LVEF < 40% | 31 (8.9) | 7 (4.6) | 2 (2.4) | 22 (19.1) | < 0.001 |
| Complications during hospitalization | | | | | |
| Complications | 50 (14.0) | 15 (9.6) | 6 (7.1) | 29 (25.0) | < 0.001 |
| Death during hospitalization | 4 (1.1) | 0 (0.0) | 0 (0.0) | 4 (3.5) | 0.015 |
| Discharge diagnostic | | | | | |
| STEMI | 86 (24.0) | 42 (26.8) | 19 (22.4) | 25 (21.6) | 0.560 |
| NSTEMI | 220 (61.5) | 93 (59.2) | 49 (57.7) | 78 (67.2) | 0.288 |
| Unstable angina | 52 (14.5) | 22 (14.0) | 17 (20.0) | 13 (11.2) | 0.211 |

Data represent the number (percentage) or median (interquartile range). eGFR indicates estimated glomerular filtration rate; LVEF: left ventricle ejection fraction; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction.

along with other 92 biomarkers in a proximity extension assay chip. However, there were not an absolute quantification of GDF-15 and the incremental prognostic value was analysed in combination with other biomarkers [38]. In a recent investigation by Rueda et al. [39] where only patients with STEMI were admitted and followed for a median of 3.1 years, the addition of GDF-15 to a clinical model did not increase discrimination or reclassification. Therefore, our study that includes all types of ACS and longer follow-up provides relevant information about GDF-15 prognostic value.

After an ACS GDF-15 has been associated, not only with all-cause death, but also with major adverse cardiovascular events. In previous studies higher GDF-15 value has been related to a combine endpoint of mortality or new MI [23,24,36]. In that line our study, for the first time, demonstrated that higher GDF-15 values were associated independently with long-term all-cause death, new MI or heart failure. Regarding the GDF-15 association with the incidence of new MI there are contradictory observations. In a meta-analysis, Zang et al. reported a significant correlation of GDF-15 with the recurrence of MI only for

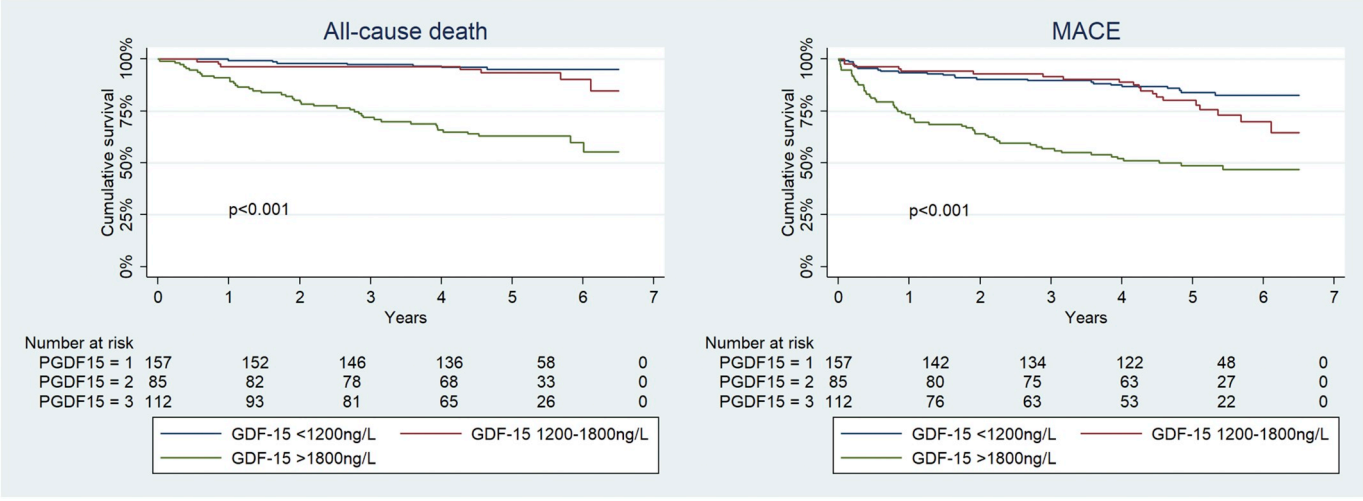


**Fig. 1.** All-cause death and major adverse cardiovascular events (all-cause death, non-fatal myocardial infarction and heart failure) cumulative survival.

**Table 3**
Hazard ratios associated with all-cause death in univariate and multivariate Cox regression analysis.

| Variables | Univariate Cox regression | | Multivariate Cox regression | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-Value | HR (95% CI) | P-Value |
| Age | 1.09 (1.06–1.12) | < 0.001 | 1.06 (1.02–1.09) | 0.001 |
| Diabetes mellitus | 2.11 (1.25–3.56) | 0.005 | – | – |
| Hypercholesterolemia | 1.94 (1.07–3.51) | 0.028 | – | – |
| Chronic kidney disease | 4.59 (2.46–8.54) | < 0.001 | – | – |
| Previous myocardial infarction | 2.67 (1.57–4.53) | < 0.001 | 1.74 (1.00–3.01) | 0.048 |
| Intermediate or high GRACE score | 5.22 (2.24–12.18) | < 0.001 | – | – |
| Significant three vessels stenosis | 2.03 (1.17–3.50) | 0.011 | – | – |
| LVEF < 40% | 4.67 (2.49–8.76) | < 0.001 | 3.25 (1.70–7.22) | < 0.001 |
| GDF-151200–1800 ng/L | 1.90 (0.67–5.41) | 0.231 | – | – |
| GDF-15 > 1800 ng/L | 10.63 (4.77–23.69) | < 0.001 | 4.09 (1.57–10.71) | 0.004 |

GRACE: Global Registry of Acute Coronary Events score; HR: hazard ratio; CI: confidence interval; LVEF: left ventricle ejection fraction; GDF-15: growth differentiation factor-15.

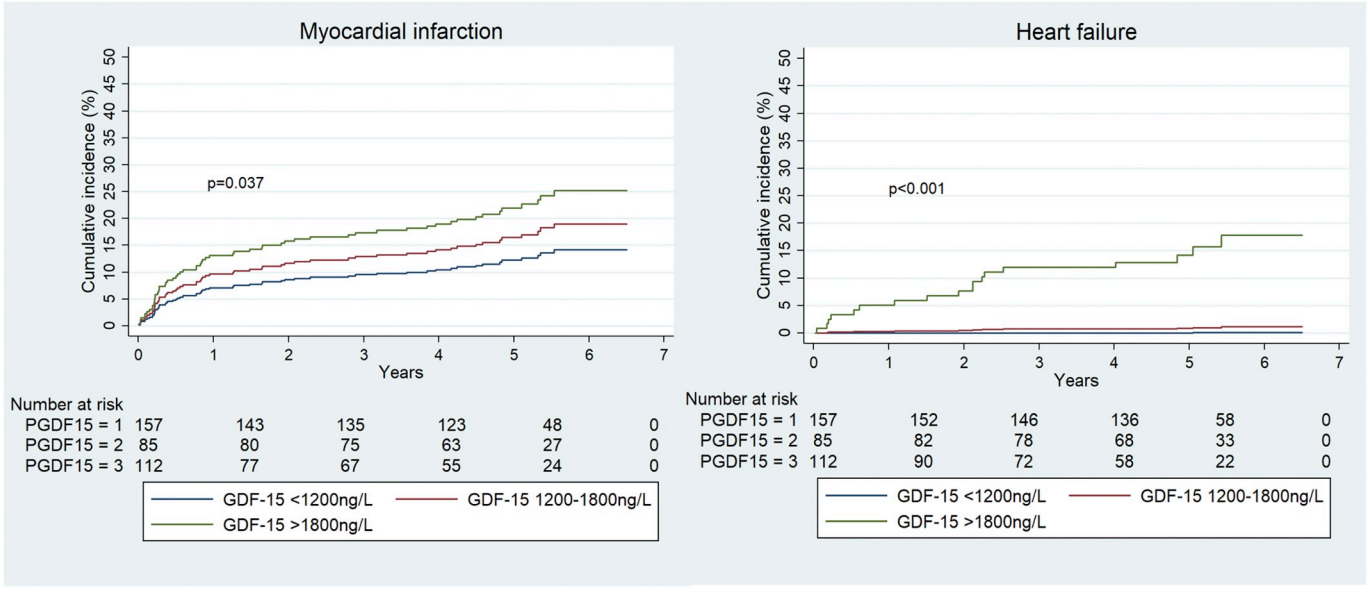


**Fig. 2.** Cumulative incidence of readmission for myocardial infarction and heart failure.

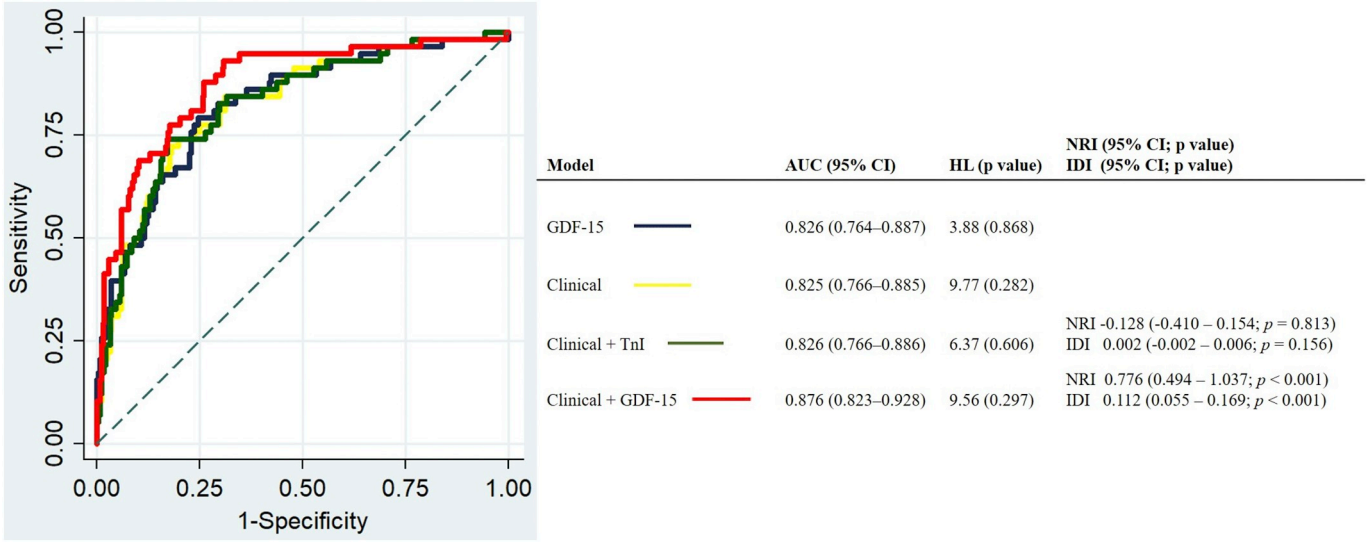


**Fig. 3.** ROC curves, NRI and IDI for predicting all-cause death of GDF-15 alone, the clinical model alone and with TnI or GDF-15. The clinical model includes age, medical history of MI, GRACE score and LVEF < 40% at discharge. AUC indicates area under the curve; CI: confidence interval; HL: Hosmer-Lemeshow; ROC: receiver operating characteristic; NRI: net reclassification improvement; IDI: integrated discrimination improvement; GDF-15: GDF-15: growth differentiation factor-15 and TnI: cardiac troponin I.

follow-up periods longer than one year [40]. Nevertheless, like in our work, such a clear independent relation has not been found in studies with follow-up periods longer than one year [23,24,36]. On the other hand, our study also found that GDF-15 measured during an ACS correlates excellently with the incidence of heart failure although this event was not frequently observed in our population. Similar findings have been reported despite they were on patients with significant shorter follow-up periods [21,41]. Therefore, GDF-15 could identify those patients with higher risk of developing heart failure and help to address therapies to prevent or delay its occurrence.

### 4.1. Limitations

Our study had the following limitations. It is a unicentric observational study with a relatively small sample size. GDF-15 was measured only once at the time of coronary angiography during admission, so we are unaware if the kinetics of GDF-15 or the time between symptoms onset and sample extraction could improve or worsen the observed results. On the other hand, we are aware that heart failure HR could be overestimated due to the low number of events. However, most of those events were related to GDF-15 levels above 1800 ng/L and therefore in our population study GDF-15 correlates excellently with the incidence of heart failure. Although a multivariable analysis was performed potential impact of residual confounding may be present due to the nature of a retrospective observational study. Finally, after hospital discharge and during follow-up, treatment of patients was unknown and their influence on the outcomes cannot be identified.

## 5. Conclusions

Altogether our study demonstrated that a single determination of GDF-15 in the setting of an ACS is associated with long-term all-cause death, heart failure and a composite endpoint of MACE. In addition, GDF-15 provides incremental prognostic value beyond traditional risks factors in the long-term. Therefore, GDF-15 appears to be a very interesting prognosis biomarker in ACS. Additional research on GDF-15 are needed as support in therapeutic management and decision making.

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