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Growth differentiation factor 15 and geriatric conditions in acute coronary syndrome

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ABSTRACT

Background: Growth differentiation factor 15 (GDF-15) is a marker of cell senescence. Age is a well-known determinant of GDF-15 levels, yet no study has analyzed the relationship between geriatric conditions and GDF-15. We hypothesize that geriatric conditions reflecting biological age might be stronger determinants of GDF-15 than chronological age in elderly patients with acute coronary syndrome.

Methods: A total of 208 patients (mean age = 78.3 ± 7.0 years) were included. Prior to discharge, a thorough geriatric assessment was performed and GDF-15 measured. Predictors of GDF-15 (transformed by its natural logarithm) were determined with linear regression. Furthermore, Cox regression was used for the analysis of all-cause mortality. The median follow-up was 728 days.

Results: Median GDF-15 concentration was 2432 pg/ml. In multivariate analysis, frailty (Fried score, $p = 0.001$), and comorbidity (Charlson index, $p = 0.003$) were independent determinants of lnGDF-15 while age was not significant ($p = 0.17$). Other covariates included in the model were male gender ($p = 0.017$), diabetes ($p = 0.169$), Killip class ≥2 ($p = 0.046$) and glomerular filtration rate ($p = 0.001$). The Fried score and Charlson index provided significant incremental value in the R^2 model (0.362 vs 0.447; $p = 0.0001$). A total of 66 (32%) patients died. LnGDF-15 was a significant mortality predictor (HR = 1.82, 95% CI 1.12–2.94, $p = 0.015$) along with the Fried score ($p = 0.013$) and the Charlson index ($p = 0.030$).

Conclusions: Geriatric conditions are strong determinants of GDF-15 levels on top of age in acute coronary syndromes. Furthermore, GDF-15 was associated with mortality independently of geriatric status. Geriatric assessment and GDF-15 are complementary tools.

1. Introduction

Growth differentiation factor 15 (GDF-15) is synthetized by a wide variety of cells in response to acute and chronic stressors such as cellular aging, cellular growth, oxidative stress, inflammation, hypoxia and oncogene activation [1]. In health GDF-15 is weakly expressed in human tissues, but under pathological conditions it can be produced by cardiovascular cells, both in the myocardium and atherosclerotic plaques, as well as by non-cardiovascular cells [2,3].

The factors determining circulating GDF-15 levels and the prognostic value of GDF-15 after acute coronary syndrome have been evaluated in several studies [1]. Age is a well-known determinant of GDF-15 blood concentrations. We speculate, however, that geriatric conditions reflecting biological age might be stronger determinants of GDF-15 than chronological age. To date, no study has analyzed the relationship between geriatric status and GDF-15.

The present study involved elderly patients with acute coronary syndrome in whom a thorough geriatric evaluation was performed,

Abbreviations: GFF-15, growth differentiation factor 15; OLS, ordinary least squares; HR, hazard ratio; CI, confidence intervals; FP, fractional polynomials.

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assessing frailty, functional independence, instrumental activities of daily living, cognitive impairment and comorbidities. The aims were to investigate the influence of geriatric status on top of age on GDF-15 levels, and how geriatric status influences the predictive capacity of GDF-15 for long-term mortality.

2. Patients and methods

2.1. Patient population

The study population included a total of 208 patients from 2 cohorts of elderly (mean age 78.3 ± 7.0 years) patients hospitalized for acute coronary syndrome at University Clinic Hospital in Valencia, Spain. The first cohort consisted of 342 consecutive patients (from October 1, 2010, to February 1, 2012), older than 65 years and survivors of acute coronary syndrome (either ST-segment elevation or non-ST-segment elevation acute coronary syndrome). A detailed description of this cohort is reported elsewhere [4,5]. Biomarker sample was available in 120 participants. The second cohort included patients from the "Randomized comparison between a strategy of intervention in frailty versus the usual care in frail patients after an acute myocardial infarction" trial (ClinicalTrials.gov ID: NCT02715453). The trial started in January 2016 and the first 88 patients recruited up to September 2017 were included in the current study in order to allow a clinical follow-up period of at least 1 year after biomarker determination. Inclusion criteria for the trial were survivors after an acute myocardial infarction (with or without ST segment elevation), older than 70 years and with pre-frailty (1–2 points) or frailty (≥3 points) according to Fried's scale assessed 24 h before hospital discharge [6]. This trial's recruitment period finished in October 2018.

The study was reviewed and approved by the Clinical Research Ethics Committee of the University Hospital Clinic in Valencia.

2.2. Geriatric assessment

On day of hospital discharge, 5 geriatric conditions were evaluated in all patients: 1) Frailty, using the Fried score; parameters were unintentional weight loss, physical activity, walk time, grip strength, and exhaustion [6]. 2) Functional independence, using the Barthel index [7]. 3) Instrumental activities of daily living, using the Lawton-Brody scale [8]. 4) Cognitive impairment, using the Pfeiffer questionnaire [9]. 5) Comorbid conditions, using the Charlson index [10]. Geriatric conditions were assessed by 2 nurses trained for the purpose using predefined standard instruments. In addition to the geriatric assessment, a number of variables were collected including clinical patient characteristics (age, gender, coronary risk factors, prior history of ischemic heart disease, prior hospitalization for heart failure, admission heart rate and blood pressure, and Killip class), electrocardiograms (ST-segment deviation, atrial fibrillation at admission), routine blood tests (high-sensitivity troponin T levels, admission hemoglobin level and glomerular filtration rate), and echocardiograms (left ventricular ejection fraction). The GRACE score for 6-month mortality was also calculated.

2.3. GDF-15 measurement

Blood samples were drawn before discharge, collected in EDTA tubes and centrifuged immediately. Plasma samples were frozen in aliquots, and stored at −70 °C until analyzed in the Biochemical Department of the University Clinic Hospital in València. GDF-15 was determined with the Elecsys GDF-15 immunoassay on the cobas e 801 analytical unit (Roche Diagnostic).

2.4. Outcomes

The primary end point was all-cause mortality. The follow-up period was considered to start at hospital discharge. Patients were followed

Table 1
Baseline patient characteristics across GDF-15 quartiles.

Variable	Q1	Q2	Q3	Q4	*p* value
Age (years)	75 ± 7	78 ± 7	80 ± 7	80 ± 6	0.001
Frailty (Fried score, points)	1.7 ± 1.3	2.3 ± 1.0	2.7 ± 1.1	2.9 ± 1.2	0.0001
Comorbidity (Charlson index, points)	0.8 ± 0.9	1.6 ± 1.3	2.4 ± 1.8	2.7 ± 1.6	0.0001
Cognitive impairment (Pfeiffer test, no. mistakes)	0.4 ± 0.9	0.4 ± 0.9	0.9 ± 1.5	1.1 ± 1.8	0.01
Functional independence (Barthel index, points)	97 ± 6	94 ± 9	93 ± 9	92 ± 12	0.03
Instrumental activities (Lawton-Brody test, points)	6.6 ± 1.6	5.5 ± 2.3	5.8 ± 2.1	4.6 ± 2.0	0.0001
Male gender	27 (52%)	30 (58%)	24 (46%)	33 (64%)	0.3
Current smoker	9 (17%)	4 (7.7%)	3 (5.8%)	5 (9.6%)	0.3
Hypertension	39 (75%)	45 (87%)	45 (87%)	45 (87%)	0.3
Hypercholesterolemia	29 (56%)	29 (56%)	28 (54%)	36 (69%)	0.4
Diabetes mellitus	15 (29%)	22 (42%)	31 (60%)	32 (62%)	0.002
Previous myocardial infarction	10 (19%)	17 (33%)	22 (42%)	25 (48%)	0.02
Previous percutaneous coronary intervention	10 (19%)	8 (15%)	13 (25%)	14 (27%)	0.5
Previous coronary artery bypass graft	2 (3.8%)	3 (5.8%)	4 (7.7%)	6 (11.5%)	0.5
Previous admission for acute heart failure	5 (9.6%)	4 (7.7%)	6 (11.5%)	12 (23%)	0.09
Previous stroke	1 (1.9%)	8 (15%)	9 (17%)	6 (12%)	0.07
Peripheral artery disease	0 (0%)	4 (7.7%)	6 (11.5%)	7 (13.5%)	0.07
Admission systolic blood pressure (mmHg)	140 ± 30	141 ± 29	139 ± 29	137 ± 29	0.9
Admission heart rate (beats/min)	79 ± 19	82 ± 18	81 ± 18	81 ± 20	0.9
Admission Killip class ≥2	7 (14%)	12 (23%)	15 (29%)	25 (48%)	0.001
ST-segment elevation	14 (27%)	11 (21%)	12 (23%)	6 (12%)	0.3
ST-segment depression	13 (25%)	14 (27%)	14 (27%)	15 (29%)	1.0
Left bundle branch block	8 (15%)	2 (3.8%)	4 (7.7%)	10 (19%)	0.06
Atrial fibrillation	3 (5.8%)	9 (17%)	5 (9.6%)	6 (11.5%)	0.3
Troponin elevation	48 (92%)	51 (98%)	50 (96%)	50 (96%)	0.6
Left ventricular ejection fraction at discharge (%)	55. ± 11	55 ± 13	54 ± 12	51 ± 13	0.3
Admission hemoglobin (g/dL)	13.7 ± 1.8	12.5 ± 1.9	12.1 ± 1.8	12.0 ± 2.1	0.0001
Admission glomerular filtration rate (ml/min/1.73 m^2)	66 ± 12	57 ± 14	49 ± 15	44 ± 17	0.0001
Invasive coronary angiography	48 (92%)	46 (89%)	47 (90%)	42 (81%)	0.3
In-hospital revascularization	26 (50%)	29 (56%)	30 (58%)	23 (44%)	0.5
GRACE score (points)	132 ± 27	138 ± 24	150 ± 35	147 ± 25	0.008
Mortality	6 (12%)	13 (25%)	20 (39%)	27 (52%)	0.0001

GDF-15: Growth differentiation factor 15.

until September 1, 2016 in the first cohort and until September 2018 in the second cohort. One patient from the first cohort and 2 patients from the second cohort were lost to follow-up. Median follow-up for the entire patient population was 728 days (range, 7–2103 days). Information on mortality was collected from the hospital files or outpatient department. In patients who did not return to the hospital or outpatient department, information was obtained by contacting the patient, the general physician, or the regional mortality registry. Cardiovascular death was defined as death due to a cardiovascular cause (such as acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular haemorrhage, and other cardiovascular causes). Death of unknown cause was classed as cardiovascular death.

2.5. Statistical analysis

Patient population was categorized according to GDF-15 quartiles. Continuous variables were expressed as mean ± 1 standard deviation or median [interquartile range] when appropriate. Discrete variables were summarized as frequency (percentages). Between-group comparisons were performed using Kruskal-Wallis test and chi-square test for continuous and discrete variables, respectively. Likewise, correlation between GDF-15 levels and geriatrics scores (Fried, Charlson, Pfeiffer, Barthel and Lawton-Brody scores) was assessed through Spearman's rank correlation coefficient (rho). A univariate association between GDF-15 quartiles with all-cause and cardiovascular mortality were depicted with Kaplan–Meier and the cumulative incidence function methods, respectively. Their overall differences were tested by the log-rank test and the Gray method, respectively.

We selected explanatory variables for the multivariable regression models with subject-matter knowledge as the main criterion. Starting with an initial (oversaturated) model, a backward elimination procedure was applied by excluding variables with *p*-values ≥0.25. Simultaneous to the process of backward elimination, a multivariable fractional polynomial transformation was applied to continuous variables whose functional form did not meet the linearity assumption. This dual selection process ensured a final parsimonious model with the minimum residual confounding [11].

Using this variables' selection strategy, two main multivariable regression models were performed:

1) Ordinary least squares (OLS) regression was used to determine the independent predictors of GDF-15. In order to ensure the normality assumption of residuals, GDF-15 was transformed by its natural logarithm. Due to high collinearity between chronological age and geriatric conditions, two OLS models were performed: 1) Age was modelled together with the block of clinical variables (OLS_1), and 2) age was replaced by geriatric conditions (OLS_2). For either model, the comparison of ΔR^2 between the base model (clinical variables) and the selected geriatric conditions was used as a metric of the incremental value provided by the later.

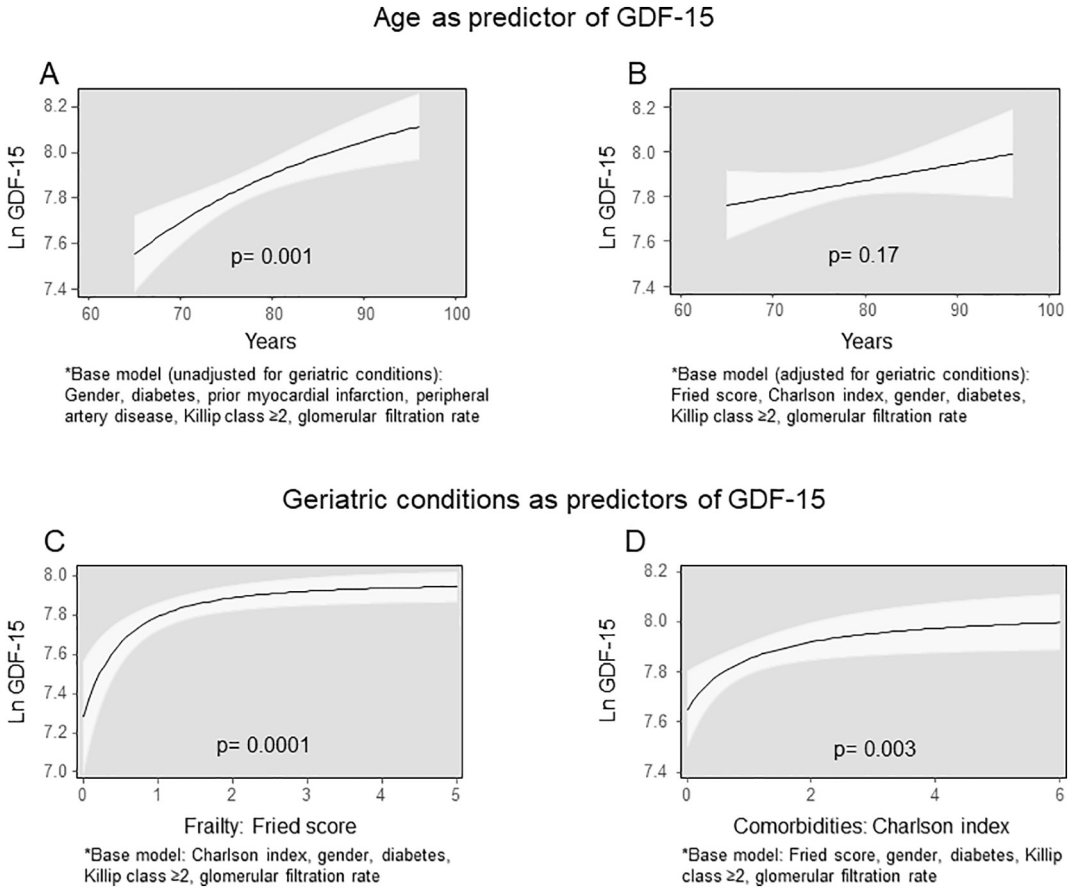


Fig. 1. Relationship between ln GDF-15, age and geriatric conditions (frailty and comorbidity). A: Age as independent predictor of lnGDF-15. Model adjusted for gender, diabetes, prior myocardial infarction, peripheral artery disease, Killip class ≥2 and glomerular filtration rate as covariates. Age provided significant incremental value in the R^2 of the model over the block of the other covariates: 0.379 vs 0.422; $\Delta R^2 = 0.043$ ($p = 0.001$). B: Age lost its statistical significance when modelled simultaneously with the geriatric conditions: R^2 over the block of the other covariates: 0.445 vs 0.451; $\Delta R^2 = 0.005$ ($p = 0.17$). C: Frailty (Fried score) as independent predictor of lnGDF-15. Model adjusted for Charlson index, glomerular filtration rate, male gender, diabetes and Killip class ≥2. Fried score added value over the base model: 0.401 vs 0.447 ($\Delta R^2 = 0.046$; $p = 0.001$). D: Comorbidities (Charlson index) as independent predictor of lnGDF-15. Model adjusted for Fried score, glomerular filtration rate, male gender, diabetes and Killip class ≥2. Charlson index added value over the base model: 0.423 vs 0.447 ($\Delta R^2 = 0.025$; $p = 0.003$).

2) Cox regression, was used to determine the independent association of GDF-15 and geriatric conditions with mortality. The proportional-hazards assumption, which was met, was tested by means of scaled Schoenfeld residuals and "log–log" plots. Together with the selected geriatric indices, GDF-15 was modelled with either the block of clinical variables (Cox_1) or the GRACE mortality score (Cox_2).

3. Results

3.1. Determinants of elevated GDF-15

Median GDF-15 concentration was 2432 pg/ml (1750 to 3746 interquartile range). Table 1 presents the baseline characteristics of the patient population across GDF-15 quartiles, in terms of age, geriatric conditions, clinical data, electrocardiogram, blood tests and left ventricular ejection fraction. A total of 185 (89%) patients underwent a coronary angiogram and 72 (39%) showed multivessel disease. There was a non-significant trend towards a high frequency of multivessel disease in the upper GDF-15 quartiles: 12 (25%), 18 (39%), 22 (47%) and 20 (47%), $p = 0.09$. On the other hand, GDF-15 levels did not correlate with peak high-sensitivity troponin T concentrations as a surrogate for infarct size (rho = 0.05, $p = 0.5$).

Regarding geriatric conditions, patients with high GDF-15 levels were older ($p = 0.001$) and had worse geriatric profiles in frailty ($p = 0.0001$), comorbidities ($p = 0.0001$), cognitive impairment ($p = 0.01$), functional independence ($p = 0.03$) and instrumental activities of daily living ($p = 0.02$). GDF-15 levels correlated with geriatric scores (Fried: rho = 0.33, $p = 0.0001$; Charlson: rho = 0.49, $p = 0.0001$; Pfeiffer: rho = 0.26, $p = 0.0001$; Barthel: rho = −0.23, $p = 0.001$; Lawton-Brody: rho = −0.34, $p = 0.0001$).

In OLS_1, age (years) was a powerful predictor of lnGDF-15 ($p = 0.001$) (Fig. 1A) independent of gender ($p = 0.110$), diabetes ($p < 0.001$), glomerular filtration rate (ml/min/1.73 m^2, $p = 0.001$), prior myocardial infarction ($p = 0.029$), peripheral artery disease ($p = 0.208$), and Killip class ≥2 ($p = 0.006$). In this model, age provided significant incremental value in the R^2 of the models over the block of the other covariates: 0.379 vs 0.422; $\Delta R^2 = 0.043$ ($p = 0.001$). In a sensitivity analysis (OLS_2), age lost statistical significance when modelled simultaneously with geriatric conditions ($p = 0.17$, Fig. 1B).

In OLS_2, Fried score (points, $p = 0.001$, Fig. 1C) and Charlson index (points, $p = 0.003$, Fig. 1D) were significant predictors of lnGDF-15, independent of gender ($p = 0.017$), diabetes ($p = 0.169$), glomerular filtration rate ($p = 0.001$) and Killip class ≥2 ($p = 0.046$). In this model, the Fried score and Charlson index provided significant incremental value in the R^2 of the models over the block of the other covariates: 0.362 vs 0.447; $\Delta R^2 = 0.086$ ($p = 0.001$).

3.2. Mortality

A total of 66 (32%) patients died during follow-up; in 42 (20%) patients, death was of cardiovascular origin. All-cause mortality rate increased progressively across the GDF-15 quartiles ($n = 6$, 12%; $n = 13$, 25%; $n = 20$, 39%; $n = 27$, 52%; omnibus p-value = 0.0001; Fig. 2). Likewise, the cumulative incidence function for GDF-15 quartiles shows a monotonic increase of risk for cardiovascular mortality (Gray test = 0.0012).

In the Cox_1 model (C-statistics = 0.795), lnGDF-15 was a significant mortality predictor (HR = 1.82, 95% CI = 1.12–2.94, $p = 0.015$) (Fig. 3, top). The other covariates independently associated in the model were: Fried score ($p = 0.013$), Charlson index ($p = 0.030$), Lawton-Brody scale (points, $p = 0.130$), glomerular filtration rate ($p = 0.018$), admission hemoglobin (g/dL, $p = 0.003$), admission systolic blood pressure (mmHg, $p = 0.034$), and prior coronary artery bypass graft ($p = 0.055$).

In the sensitivity analysis (Cox_2), where the GRACE score (points, HR = 3.15, 95% CI = 1.31–7.56, $p = 0.010$) was included instead of the block clinical variables, lnGDF-15 was also significantly associated with mortality (HR = 1.75, 95% CI = 1.09–2.81, $p = 0.019$; Fig. 3, bottom). In this model, the Fried score included with 2-degree fractional polynomials [FP (3 3)] ($p = 0.0033$), and Charlson index (HR = 1.27, 95% CI = 1.07–1.50, $p = 0.005$), were also significant.

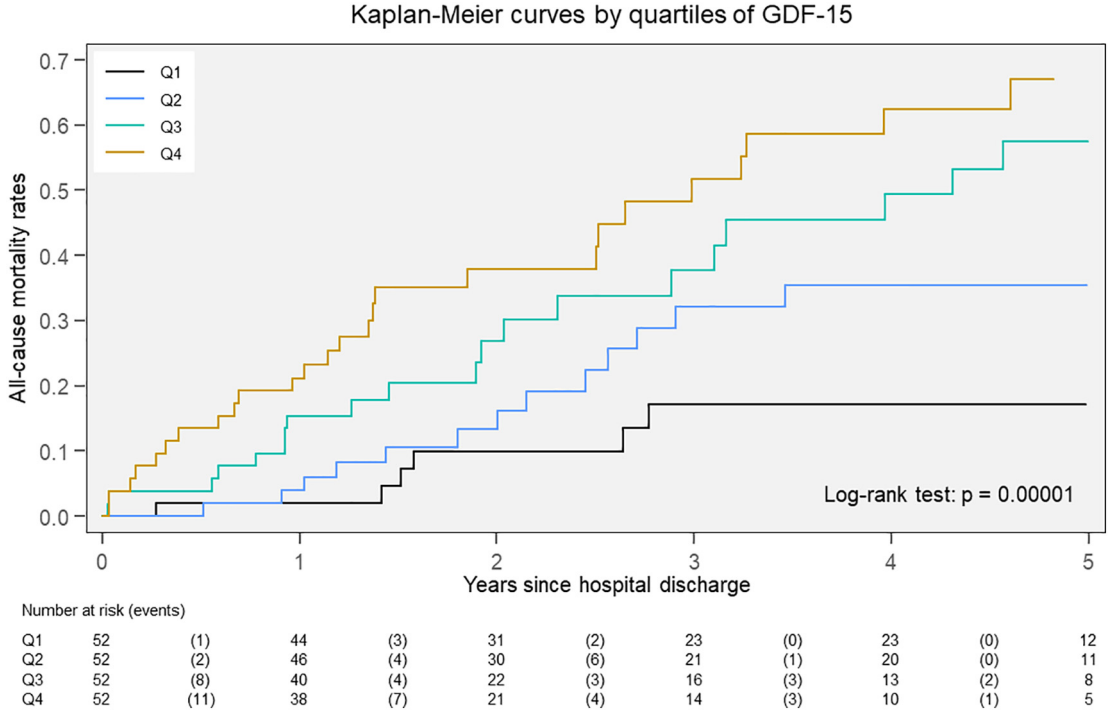


Fig. 2. Kaplan-Meier curve for all-cause mortality according to GDF-15 quartiles (Q). Mortality rate progressively increased from Q1 to Q4 (Q1: $n = 6$, 12%; Q2: $n = 13$, 25%; Q3: $n = 20$, 39%; Q4: $n = 27$, 52%; log-rank test, $p = 0.0001$).

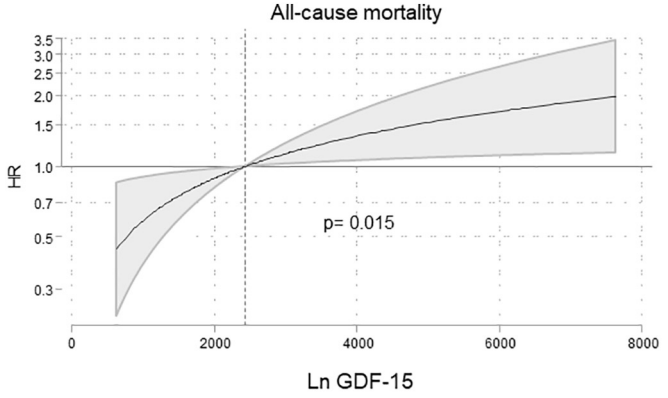
4. Discussion

To the best of our knowledge, this is the first study to investigate the relationship between circulating GDF-15 and biological age, as defined by geriatric status, in elderly patients with acute coronary syndrome. The main finding was that frailty and comorbid conditions were strong determinants of circulating GDF-15 levels on top of chronological age. Indeed, age was only a significant determinant if geriatric status was not considered. Furthermore, frailty, comorbidity and GDF-15 were independently associated with a higher mortality risk, indicating that the prognostic information provided by geriatric conditions and GDF-15 does not overlap.

4.1. Age and GDF-15

The multiple stressors potentially involved in triggering GDF-15 cell production explain the interindividual variation in GDF concentrations. Age is a well-known determinant of GDF-15 levels [12–14]. To date, however, no study has adjusted age for the geriatric conditions. Chronological age is only a rough estimate of senility; geriatric conditions reveal biological age and provide more solid prognostic information than age in acute coronary syndrome [5]. A close relationship between GDF-15 level as a marker of cell senescence and geriatric status, seems plausible. Our study confirmed this hypothesis since frailty and comorbidity indexes determined GDF-15 levels on top of age. This result suggests a potential role for GDF-15 as a marker of biological age.

Renal function was another strong determinant of GDF-15 levels. Previous studies have also found increased GDF-15 in patients with poorer renal function [12–15]. This association might be due to impaired GDF-15 clearance when renal function declines, or alternatively to the deleterious effect caused by GDF-15 itself through direct kidney or vascular damage [15]. Other determinants of blood GDF-15 levels, such as male gender and admission Killip class ≥2, were also found in other studies [12,13].



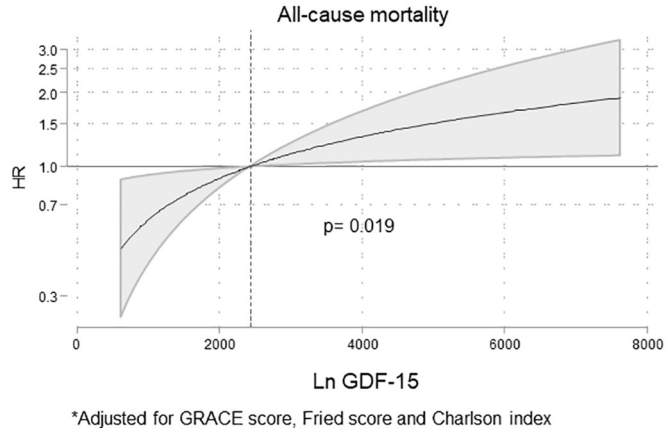


Fig. 3. Top: Independent association of GDF-15 with all-cause mortality. HR are depicted against the median value of GDF-15 (2432 pg/ml). Overall *p*-value for the trajectory = 0.0148. GDF-15 values truncated at its upper 95 percentiles. Analysis adjusted for the Fried score, Charlson index, Lawton Instrumental Activities of Daily Living Scale, admission systolic blood pressure, glomerular filtration rate, hemoglobin levels and previous coronary bypass surgery. Bottom: Independent association of GDF-15 with all-cause mortality. The GRACE score (HR = 3.15, 95% CI = 1.31–7.56, $p = 0.010$) was included instead of the block clinical variables. LnGDF-15 was significantly associated with mortality (HR = 1.75, 95% CI = 1.09–2.81, $p = 0.019$). In this model, Fried score and Charlson index were also significant.

4.2. GDF-15 and prognosis

Previous studies have shown the association between elevated GDF-15 and mortality in acute coronary syndromes [13,14,16–21]. The present study underscores the prognostic value of the biomarker beyond standard predictors and geriatric conditions. Indeed, the prognostic value of GDF-15 was not adjusted for geriatric status in previous studies. According to our findings, GDF-15 concentrations are not only a marker of biological age in acute coronary syndromes; in fact, GDF-15 is produced in the atherosclerotic plaques of the coronary arteries and in the myocardium after acute myocardial infarction [2,3]. On the other hand, frailty and comorbidity provided robust prognostic information additional to GDF-15 levels. In this sense, while not a substitute for thorough geriatric assessment, GDF-15 serves as a complementary tool and its role as a simple and practical surrogate for geriatric status could be considered.

4.3. Limitations

Several limitations deserve to be acknowledged. First, though independently associated with frailty, GDF-15 levels cannot be considered a pure marker of frailty status since they were also associated with comorbidities and other clinical characteristics. Second, this is a small study performed in a single center; these two factors might increase the possibility of selection bias limiting the generalization of these results to other populations. Third, there are limitations inherent to the observational nature of the design. Fourth, the lack of a universally accepted cut-off for dichotomization of markers, precluded further determination of the marker's diagnostic accuracy. However, modelling the marker in its continuum form provides the most solid evidence of its performance. On the other hand, strengths include the novelty of the results which, added to future additional evidence, could dictate the future role of this marker in daily clinical practice.

4.4. Conclusions

Geriatric conditions, such as frailty and comorbidities are strong determinants of GDF-15 levels in acute coronary syndromes. Furthermore, in this population GDF-15 was shown to be associated with mortality independently of geriatric status. Thus, geriatric assessment and GDF-15 seem to be complementary tools.

Author contributions

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Data acquisition, analysis, or interpretation: Sanchis, Bonanad, Ruescas, Valero, García-Blas.

Drafting of the manuscript: Sanchis, Núñez E, Núñez J.

Critical revision of the manuscript for important intellectual content: Sanchis, Núñez E, Núñez J, Ruiz, Ruescas.

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Declaration of Competing Interest

Roche provided the Elecsys GDF-15 immunoassay free of charge. Dr. Sanchis reports grants from Biotronik, Prosmedica and Bayer outside the submitted work. Dr. Núñez reports personal fees from Novartis, Vifor, Rovi, Boehringer Ingelheim and Novo Nordisk, outside the submitted work. The remaining authors have nothing to disclose.

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