ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 2527–2534
Published online 2 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13377

ORIGINAL RESEARCH ARTICLE

Dynamics of growth differentiation factor 15 in acute heart failure

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Abstract

Aims Risk stratification in acute heart failure (HF) patients can help to decide therapies and time for discharge. The potential of growth differentiation factor 15 (GDF-15) in HF has been previously shown. We aimed to study the importance of GDF-15-level variations in acute HF patients.

Methods and results We retrospectively evaluated a cohort of patients hospitalized due to acute HF. GDF-15 was measured both at admission and on the discharge day. Patients were followed-up during a 3 year period. The endpoint under analysis was all-cause mortality. GDF-15 variation is equal to [(admission GDF-15 − discharge GDF-15)/admission GDF-15] × 100. Variation was categorized in levels of increase or decrease of GDF-15. Patients were cross-classified according to admission and discharge GDF-15 cut-off points. A Cox regression analysis was used to assess the prognostic impact of GDF-15 variation and the impact of both admission and discharge GDF-15 according to the cross-classification. We studied a group of 249 patients with high co-morbidity burden. Eighty-one patients died at 1 year and 147 within 3 years. There was a modest decrease in GDF-15 during hospitalization from a median value of 4087 to 3671 ng/mL (P = 0.02). No association existed between GDF-15 variation and mortality. In multivariate analysis, patients with admission GDF-15 $\geq$ 3500 ng/mL and discharge GDF-15 $\geq$ 3000 ng/mL had a significantly higher 1 year death risk when compared with the remaining—hazard ratio = 2.59 (95% confidence interval: 1.41–4.76)—and a 3 year 1.76 (95% confidence interval: 1.08–2.87) higher death risk compared with those with both values below the cut-off.

Conclusions Growth differentiation factor 15 decreased during an acute HF hospitalization, but its variation had no prognostic implications. The knowledge of both admission and discharge GDF-15 added meaningful information to patients' risk stratification.

Keywords Heart failure; Growth differentiation factor 15; Prognosis

Received: 9 January 2021; Revised: 21 March 2021; Accepted: 8 April 2021
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Introduction

Acute heart failure (HF) risk stratification is a cornerstone of patient management as it can help to decide the appropriateness and timing of therapies.[1–3] However, the performance of prognostic models or methods remains unsatisfactory in acute HF patients. The number of potential biomarkers that could improve risk stratification in acute HF has been exponentially emerging over recent years.[4–8]

Growth differentiation factor 15 (GDF-15) is currently one of the most attractive biomarkers that provides strong prognostic information.[9,10] GDF-15 is a member of the transforming growth factor-β superfamily and was identified in a broad range of cells.[11–14] GDF-15 is produced in response to several stimuli like inflammation, oxidative stress, tissue

hypoxia, and injury.[14] GDF-15 concentrations have been shown to increase significantly in a large number of pathological conditions, including renal dysfunction, diabetes, and sepsis.[15–18]

In models of HF and acute myocardial infarction, cardiomyocytes can be stimulated to produce GDF-15. GDF-15 is also produced in atherosclerotic plaques.[16,19] In HF patients, the production of GDF-15 is not well understood because, despite elevated levels, its production location does not seem to be on cardiomyocites.[20,21] Clinical studies found GDF-15 to be associated with all-cause death in chronic HF patients.[12,14] Circulating levels of GDF-15 have been shown to increase in chronic HF with reduced ejection fraction and to be predictive of cardiovascular outcomes.[22,23] Also, in the acute HF setting, its association with mortality has been previously suggested.[12,24–26]

However, although GDF-15 values decrease transiently with serelaxin in patients with acute HF,[27] the meaning of variations in GDF-15 levels in HF patients has never been explored. We aimed to study if dynamic changes in GDF-15 during hospital admissions due to acute HF portend prognostic implications.

Methods

We prospectively included consecutive patients in an acute HF registry. The registry took place in the Internal Medicine Department of Centro Hospitalar Universitário São João, Porto, Portugal. All patients hospitalized with the primary diagnosis of acute HF—*de novo* and worsening chronic HF—were eligible for inclusion in the registry. Exclusion criteria were patients in whom an acute coronary syndrome was the cause of decompensation, patients with normal echocardiogram, and patients whose symptoms were attributable to causes other than HF. An echocardiogram was performed to all patients during hospitalization. Systolic dysfunction was considered severe when left ventricular ejection fraction was $<30\%$, moderate when ejection fraction was between 30% and 39%, and mild between 40% and 49%. Patients with left ventricular ejection fraction $\geq 50\%$ were considered as having preserved systolic function. The 2008 European Society of Cardiology guidelines were used for the diagnosis of HF.[28] The physicians treating the patients were aware of the ongoing registry, but all the patient's treatment strategy, discharge, and discharge medication were a decision of the attending physician only. A complete physical examination both at admission and in the discharge day was performed to all patients, and a venous blood sample was also collected on the admission and in the discharge day. Blood was collected in serum separating tubes; samples were immediately centrifuged (4500 rotation per minute for 15 min) and then stored at $-75°C$ within 2 h. B-type natriuretic peptide (BNP) determination is a routine laboratory procedure in our hospital; an Abbott chemiluminescent microparticle immunoassay (two-step immunoassay) (Abbott, Wiesbaden, Germany) is used. Haemoglobin was obtained using an automated blood counter Sysmex® XE-5000 (Sysmex Europe GmbH, Norderstedt, Germany). Serum creatinine was measured using conventional methods with an Olympus AU5400® automated clinical chemistry analyzer Beckman Coulter® (Beckman Coulter Ireland Inc, Clare, Ireland).

The registry's protocol conformed to the ethical guidelines of the Declaration of Helsinki, and it was approved by the local ethics committee.

In order to study if dynamic changes of GDF-15 had prognostic implications in acute HF, we retrospectively analysed a subgroup of patients in whom enough serum was stored for GDF-15 measurement at both admission and discharge. The plasma concentrations of GDF-15 were determined by electrochemiluminescence immunoassay on the Roche Cobas e411 (Roche Diagnostics GmbH).

Patients were followed-up for a 3 year period. The endpoint under analysis was all-cause mortality. Vital status was ascertained by consulting hospital registries and by telephone contact with the patients or their relatives. When no information was obtained, we consulted the Registo Nacional de Utentes; Registo Nacional de Utentes is a national platform that provides information on patient mortality. No patient was lost to follow-up.

Statistical analysis

Admission and discharge GDF-15 were compared using a Wilcoxon signed-rank test. Correlation between admission and discharge GDF-15 was tested using a Spearman correlation coefficient. Receiver operating characteristic (ROC) curves were calculated to study the association of admission and discharge GDF-15 and of the GDF-15 variation with mortality. The ROC curves were used to choose good cut-off points of admission and discharge GDF-15 to accurately predict 1 and 3 year mortality.

Growth differentiation factor 15 variation was categorized to four groups: GDF-15 decrease $\geq 30\%$, GDF-15 decrease $<30\%$, GDF-15 increase $<30\%$, and GDF-15 increase $\geq 30\%$. Kaplan–Meier method was used to calculate the survival curves of the four groups created.

Based on the cut-off values of admission and discharge GDF-15 suggested by the ROC curves, 3500 and 3000 ng/mL, respectively, patients were cross-classified in four groups: patients with admission GDF-15 $<$ 3500 ng/mL and discharge GDF-15 $<$ 3000 ng/mL; patients with admission GDF-15 $<$ 3500 ng/mL and discharge GDF-15 $\geq$ 3000 ng/mL; patients with admission GDF-15 $\geq$ 3500 ng/mL and discharge GDF-15 $<$ 3000 ng/mL; and patients with admission GDF-15 $\geq$ 3500 ng/mL and discharge GDF-15 $\geq$ 3000 ng/mL.

Survival curves according to the four groups created were determined by the Kaplan–Meier method. A multivariate Cox regression analysis was used to access the independent prognostic impact of admission and discharge GDF-15. The four groups of admission and discharge GDF-15 were rearranged based on the Kaplan–Meier curves. For 1 year prognostic analysis, patients with admission GDF-15 $\geq$ 3500 ng/mL and discharge GDF-15 $\geq$ 3000 ng/mL were compared with the remaining. For the 3 year prognostic analysis, the variable was dummy coded: reference category: patients with both admission and discharge GDF-15 below the cut-off, and the other two categories would be those with only one of the measurements above the cut-off and those with both measurements above the cut-off. Multivariate models were built accounting for potential confounders and variables known to be prognostic associated. Variables taken into consideration for adjustment were age, New York Heart Association and systolic blood pressure at admission, diabetes *mellitus*, arterial hypertension and atrial fibrillation history, ischaemic heart disease, discharge BNP, high-sensitivity troponin T and C-reactive protein, a BNP decrease of >30% during hospitalization, renal dysfunction and anaemia at discharge, systolic dysfunction, and evidence-based therapy according to updated guidelines by the time patients were hospital admitted.

Table 1 Patients' characteristics

Characteristics	*N* = 249
Gender: male/female, *n* (%)	134 (53.8)/115 (46.2)
Age (years), mean (SD)	74 (13)
Left ventricular ejection fraction	
Preserved	76 (30.5)
Mild dysfunction	23 (9.2)
Moderate dysfunction	34 (13.4)
Severe dysfunction	116 (46.6)
NYHA class at admission	
II	5 (2.0)
III	98 (39.4)
IV	143 (57.4)
Systolic blood pressure at admission (mmHg), mean (SD)	136 (30)
Heart rate at admission (b.p.m.), mean (SD)	89 (22)
Co-morbidities	
Diabetes mellitus, *n* (%)	133 (53.4)
Arterial hypertension history, *n* (%)	190 (76.3)
Chronic kidney disease, *n* (%)	57 (22.9)
Smoking status	
Never smoker, *n* (%)	144 (57.8)
Former smoker, *n* (%)	83 (33.3)
Current smoker, *n* (%)	22 (8.8)
Atrial fibrillation history, *n* (%)	101 (40.6)
Ischaemic heart failure, *n* (%)	137 (55.0)
Laboratory parameters	
Admission haemoglobin (g/dL), mean (SD)	11.9 (2.0)
Discharge haemoglobin (g/dL), mean (SD)	12.2 (2.0)
Admission creatinine (mg/dL), mean (SD)	1.58 (0.73)
Discharge creatinine (mg/dL), mean (SD)	1.52 (0.69)
Admission CRP (mg/L), median (IQR)	22.4 (9.0–54.9)
Discharge CRP (mg/L), median (SD)	11.4 (5.6–24.9)
Admission high-sensitivity troponin T (ng/L), median (IQR)	47.9 (30.9–76.6)
Discharge high-sensitivity troponin T (ng/L), median (IQR)	41.8 (27.3–71.9)
Admission BNP (pg/mL), median (IQR)	1534.5 (926.7–2766.3)
Discharge BNP (pg/mL), median (IQR)	727.1 (302.3–1383.6)
Admission GDF-15 (ng/mL), median (IQR)	4087.0 (2606.0–6376.5)
Discharge GDF-15 (ng/mL), median (IQR)	3671.0 (2365.0–4662.5)
GDF-15 variation (%), median (IQR)	5.9 (−23.7 to 29.4)
Medication	
Discharge BB, *n* (%)	197 (79.1)
ACEi and/or ARB, *n* (%)	200 (80.3)
MRA, *n* (%)	67 (26.9)
Furosemide, *n* (%)	233 (93.6)
Outcome	
1 year all-cause mortality	81 (32.5)
3 year all-cause mortality	147 (59.0)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; BNP, B-type natriuretic peptide; CRP, C-reactive protein; GDF-15, growth differentiation factor 15; IQR, inter-quartile range; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD, standard deviation.

Results

We studied 249 patients hospitalized with the primary diagnosis of acute HF with GDF-15 levels measured at the admission and discharge day. It was a group of old patients with high co-morbidity burden; both men and women and patients with preserved and reduced ejection fraction were well represented. More than half of the patients were admitted in New York Heart Association Class IV, and natriuretic peptide system was highly activated. Median (inter-quartile range) length of hospital stay was of 7 (5–11) days. Eighty-one patients died at 1 year of follow-up, and 147 patients died within 3 years. Patients' characteristics are depicted in *Table 1*.

Admission and discharge GDF-15 presented a greatly skewed and right tailed distribution. Median values of admission and discharge GFD15 were 4087 and 3671 ng/mL, respectively. There was a modest however statistically significant decrease in GDF-15 during hospital stay (P = 0.02, Wilcoxon signed-rank test) and admission and discharge GDF-15 showed a strong and positive correlation (ρ = 0.71, $P < 0.001$) has depicted in *Figure 1*. The GDF-15 variation was also highly skewed distributed: median (inter-quartile range): 5.9 (−23.7 to 29.4) %. Mortality rates at 1 and 3 years of follow-up were 32.5% and 59.0%, respectively. *Figure 2* shows the ROC curves of the association of admission GDF-15, discharge GDF-15, and GDF-15 variation with 1 and 3 year all-cause mortality. Both admission and discharge GDF-15 were associated with all-cause death at 1 and 3 years. However, no association was found between GDF-15 variation and mortality at both 1 and 3 years (*Figure 3*). Survival curves are similar in patients with decreases or increases above and below 30% of GDF-15 during hospital stay. Following the ROC curves, we propose admission GDF-15 of 3500 ng/mL and discharge GDF-15 of 3000 ng/mL as good cut-off points for 1 and 3 year mortality prediction. Sensitivity, specificity, and predictive values for each cut-off are shown in *Table 2*. When patients were cross-classified according to admission and discharge GDF-15 categorized based on the cut-offs derived from the ROC curves, four groups were created. Survival curves according to these four groups at 1 and 3 years of follow-up are depicted in *Figure 4*. At 1 year of follow-up, patients with both GDF-15 values

Figure 1 Scattered dot of the correlation between admission and discharge growth differentiation factor 15 (GDF-15). A strong positive correlation exists between admission and discharge GDF-15 levels in acute heart failure patients.

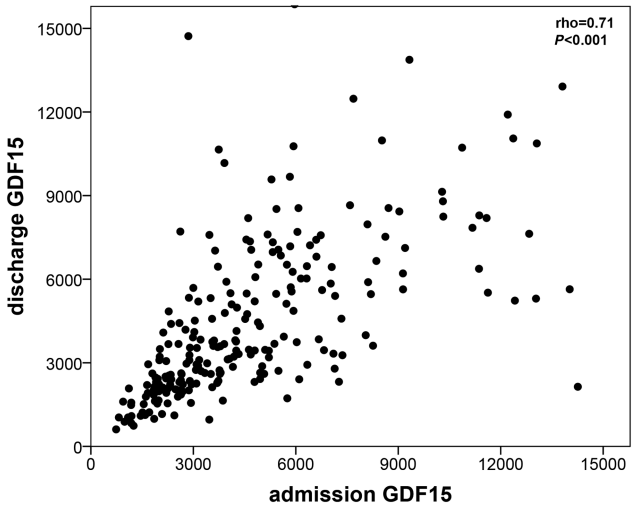
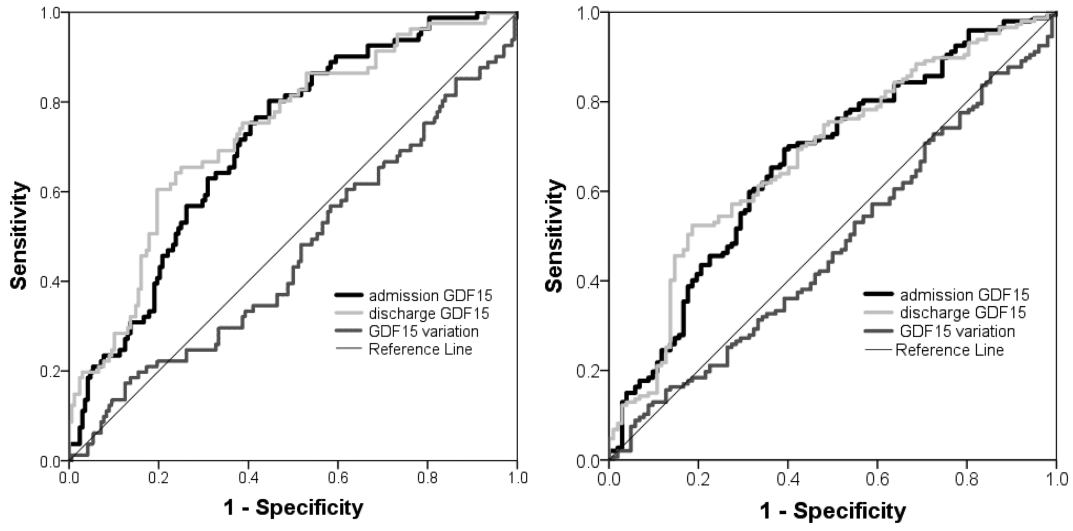
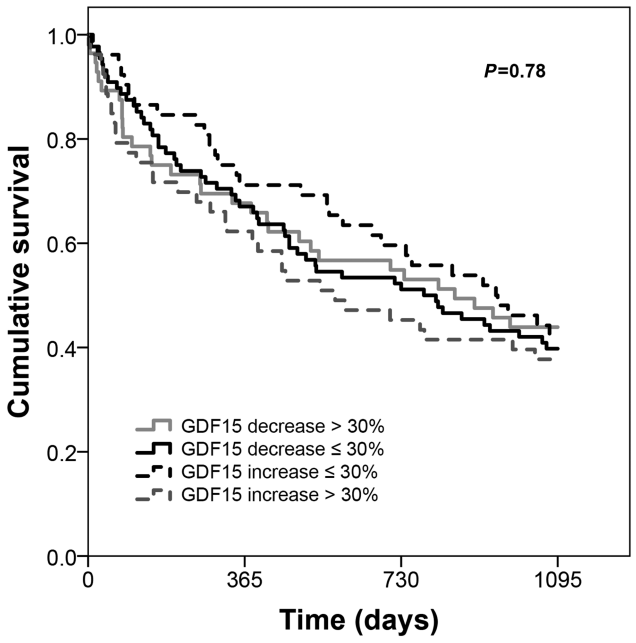


Figure 2 Receiver operating characteristic curves of the association of admission and discharge growth differentiation factor 15 (GDF-15) and of the GDF-15 variation with 1 year (left) and 3 year (right) mortality.



above the cut-off had a clear survival disadvantage when compared with all the other groups. Cut-offs discriminated three groups with distinct survival at 3 years: patients with admission GDF-15 ≥ 3500 ng/mL and discharge GDF-15 ≥ 3000 ng/mL had the worst survival, while patients with admission GDF-15 < 3500 ng/mL and discharge GDF-15 < 3000 ng/mL had the best 3 year survival. The remaining patients gathered in a group with intermediate medium-term prognosis. Patients with admission GDF-15 ≥ 3500 ng/mL and discharge GDF-15 ≥ 3000 ng/mL had a multivariate-adjusted 2.59 [95% confidence interval (CI): 1.41–4.76] higher risk of 1 year all-cause death than the remaining patients. When considering a medium-term 3 year prognosis, patients with admission GDF-15 ≥ 3500 ng/mL and discharge GDF-15 ≥ 3000 ng/mL had a multivariate-adjusted 1.76 (95% CI: 1.08–2.87) higher 3 year death risk than those with admission GDF-15 < 3500 ng/mL and discharge GDF-15 < 3000 ng/mL. *Table 3* shows crude and multivariate-adjusted hazard ratio of 1 and 3 year mortality according to groups of admission and discharge GDF-15. Patients with admission levels of GDF-15 ≥ 3500 ng/mL or discharge ≥3000 ng/mL had a non-significant 39% higher 3 year mortality than those with both values below the defined cut-offs. Patients with admission and discharge GDF-15 values above the cut-off values showed a 1.52 (95% CI: 1.01–2.30, *P* = 0.04) higher risk of death than all the remaining patients and a non-significant 40% increase in 3 year death risk compared with those with only one of the values above the cut-off. When GDF-15 variation along hospital stay was also accounted for in the multivariate model, results were similar (data not shown).

Figure 3 Kaplan–Meier curves according to growth differentiation factor 15 (GDF-15) variation. GDF-15 variation during hospitalization due to acute heart failure is not prognostic associated.



Discussion

Growth differentiation factor variation during hospitalization due to acute HF showed no prognostic impact; however, both admission and discharge GDF-15 levels were associated with mortality at 1 and 3 years. Patients with admission GDF-15 < 3500 ng/mL or discharge GDF-15 < 3000 ng/mL presented 85% probability of being alive at 1 year of follow-up. On the other hand, patients with admission GDF-15 above the cut-off showed a 69% probability of being dead up to 3 years, and those with discharge GDF-15 ≥ 3000 ng/mL had the same probability of fatal outcome at 3 years. Furthermore, the gathered knowledge of admission and discharge GDF-15 could add predictive information beyond known prognostic determinants in acute HF. Patients with admission GDF-15 higher than 3500 ng/mL and discharge GDF-15 ≥ 3000 ng/mL had over 2.5-fold higher death risk at 1 year, while the risk was nearly two-fold higher by 3 years when compared with patients with both values below the cut-off. In the medium-term 3 year follow-up, patients with both GDF-15 at admission<3500 ng/mL and discharge GDF-15 < 3000 ng/mL were the group of patients with the best prognosis. The remaining patients presented an intermediate outcome.

Our results bring relevant insights on the dynamics of GDF-15 in acute HF, reassuring previous observations suggesting that GDF-15 levels are strong prognostic markers in acute HF[10,12,14,24–27] and proving that its prognostic value is similar in the beginning of an acute HF episode and at hospital discharge.

In healthy individuals, GDF-15 is weakly expressed in tissues. However, under pathological conditions, GDF-15 can be produced by many cardiovascular and non-cardiovascular

Table 2 Sensitivity, specificity, VPP, and VPN of admission and discharge GDF-15 in acute HF mortality prediction

		Sensitivity	Specificity	VPP	VPN
1 year mortality	Admission GDF-15 3500 ng/mL	81.5	49.4	43.7	84.7
	Discharge GDF-15 3000 ng/mL	82.7	48.8	43.7	85.4
3 year mortality	Admission GDF-15 3500 ng/mL	70.7	53.9	68.8	56.1
	Discharge GDF-15 3000 ng/mL	72.1	53.9	69.2	57.3

GDF-15, growth differentiation factor 15; HF, heart failure; VPN, negative predictive value; VPP, positive predictive value.

Figure 4 Kaplan–Meier survival curves of groups of patients cross-classified according to cut-off points of admission and discharge growth differentiation factor 15 (GDF-15). Group 1: admission GDF-15 < 3500 ng/mL and discharge GDF-15 < 3000 ng/mL (*n* = 72, 28.9); Group 2: admission GDF-15 < 3500 ng/mL and discharge GDF-15 ≥ 3000 ng/mL (*n* = 26, 10.4%); Group 3: admission GDF-15 ≥ 3500 ng/mL and discharge GDF-15 < 3000 ng/mL (*n* = 25, 10.0%); and Group 4: admission GDF-15 ≥ 3500 ng/mL and discharge GDF-15 ≥ 3000 ng/mL (126, 50.6%). One year follow-up (left) and 3 year follow-up (right).

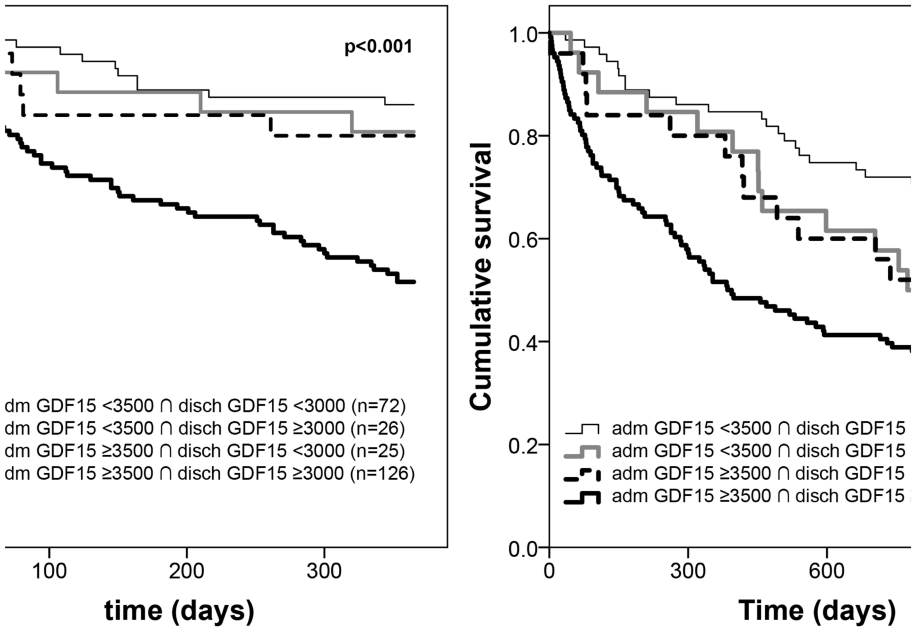


Table 3 Crude and multivariate-adjusted hazard ratio of 1 and 3 year mortality according to admission and discharge GDF-15

	1 year mortality	*P*-value
admGDF-15 ≥ 3500 ∩ dischGDF-15 ≥ 3000 vs. others (crude)	3.70 (2.23–6.13)	<0.001
admGDF-15 ≥ 3500 ∩ dischGDF-15 ≥ 3000 vs. others (mv adjusted[a])	2.59 (1.41–4.76)	0.002
	3 year mortality	*P*-value
admGDF-15 < 3500 ∩ dischGDF-15 < 3000	1	
admGDF-15 ≥ 3500 or dischGDF-15 ≥ 3000	1.49 (0.88–2.51)	0.14
admGDF-15 ≥ 3500 ∩ dischGDF-15 ≥ 3000 (crude)	2.68 (1.76–4.08)	<0.001
admGDF-15 < 3500 ∩ dischGDF-15 < 3000	1	
admGDF-15 ≥ 3500 or dischGDF-15 ≥ 3.000	1.39 (0.78–2.49)	0.26
admGDF-15 ≥ 3500 ∩ dischGDF-15 ≥ 3000 (mv adjusted[a])	1.76 (1.08–2.87)	0.02

adm, admission; disch, discharge; GDF-15, growth differentiation factor 15; mv, multivariable.
[a]Multivariate adjustment accounting for age, New York Heart Association class in the emergency department, systolic blood pressure in the emergency department, diabetes mellitus, arterial hypertension history, atrial fibrillation, ischaemic heart failure, B-type natriuretic peptide decrease >30% during hospitalization, discharge B-type natriuretic peptide, high-sensitivity troponin T and C-reactive protein, renal dysfunction at discharge, anaemia at discharge, severe systolic dysfunction, and evidence-based therapy (beta-blocker, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blocker, and mineralocorticoid receptor antagonist).

cell types.[14] GDF-15 is not cardiac specific; instead, it reflects the sum of cardiac, peripheral, and systemic abnormalities, related to co-morbidities, ageing, and even lifestyle.[11–14] GDF-15 levels mirror a number of systems and events that are activated in HF—neurohumoral, oxidative stress, hypoxia, and inflammation—and there is evidence that therapies used in acute HF have limited effect in the modulation of these systems.[29,30] Until now, only serelaxin has been shown to decrease GDF-15 in the acute setting, and this decrease in GDF-15 levels had no impact in outcome.[31]

Compared with chronic HF populations in whom increasing levels of GDF-15 over time have been reported irrespective of HF therapy,[30] in our study, we observed a small decrease in GDF-15 during the acute episode. This may suggest that, in an acute HF setting, an at least modest GDF-15 modulation by evidence-based therapy may exist or, more likely, that the control of the decompensating factor is perhaps responsible for this GDF-15 reduction. In chronic HF, there is now evidence that GDF-15 dynamics is prognostic related: variations of GDF-15 are associated with outcome in HF patients

with reduced ejection fraction. A mortality increase of 19% has been observed per each 20% increase in GDF-15.[30] Despite these observations in chronic HF, no association between GDF-15 variations and evidence-based therapies in HF such as angiotensin receptor–neprilysin inhibitors or angiotensin II receptor blockers has been detected.[29,30]

The reasons and mechanisms underlying the association between GDF-15 and outcome are still poorly understood. On the one hand, higher GDF-15 levels have been linked to significant left ventricular remodelling,[32] and on the other hand, left ventricular dilatation has been shown to be a predictor of increasing levels of GDF-15.[33] The short time interval between measurements of GDF-15 in our study can be a possible reason for the lack of association of GDF-15 variations with prognosis, because significant ventricular remodelling and cardiac structural adaptations are not expected to occur in such a small period as the one corresponding to an HF hospitalization.

Previous reports of the prognostic impact of GDF-15 in HF have shown different conclusions with respect to its potential value in HF patients' risk stratification. It is consensual knowledge that biomarkers are important tools that can help clinicians in the management of HF; however, no single biomarker can answer all prognostic uncertainties. Our results showing an independent prognostic value of GDF-15 in acute HF, measured at hospital admission, at hospital discharge, or both, strongly support a role for this biomarker in the acute setting.

The study has some limitations to note. First, it had a retrospective design and was single centred with inherent problems, namely, concerning data availability and conclusions generalizability. Second, the small sample size is also a setback; nevertheless, patients were followed for a long enough period to gather an adequate number of events to perform a multivariate analysis with adjustment for main confounders. Third, physicians responsible for HF patients were aware of the registry, and this might have influenced treatment approach. Fourth, patients were prospectively recruited between 2009 and 2010, and GDF-15 measurements were performed in 2018. Blood samples were immediately processed and stored at −7°C; however, the time elapsed between storage and analysis makes it impossible to totally guarantee the integrity of the samples. The admission and discharge GDF-15-level distribution show a reliable right tail skewed distribution, similar to many biomarkers, and measurements are consistent with values described in the literature.

Despite the described limitations, this is the first study that specifically addresses the performance of GDF-15 during hospital admission due to acute HF and the prognostic impact of its dynamics. GDF-15 variation showed no prognostic impact; however, the gathered knowledge of GDF-15 at admission and discharge adds meaningful information to patients' risk stratification.

Acknowledgement

We thank Roche Diagnostics for providing GDF-15 determinations.

Conflict of interest

None declared.

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