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Clinical paper

# Growth differentiation factor-15 predicts poor survival after cardiac arrest

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## Abstract

**Background:** Early prognostication in post-cardiac arrest (CA) patients remains challenging and biomarkers have evolved as helpful tools in risk assessment. The stress–response cytokine growth differentiation factor-15 (GDF-15) is dramatically up-regulated during various kinds of tissue injury and predicts outcome in many pathological conditions. We aimed to assess the predictive value of circulating GDF-15 in post-CA patients.

**Methods:** This prospective observational study included 128 consecutive patients (median age 60.3 years, 75.8% male) with return of spontaneous circulation after in- or out-of-hospital CA who were treated at a tertiary university hospital. GDF-15 serum levels were determined at admission.

**Results:** A total of 52 patients (40.6%) died during the 6-month follow-up. Median GDF-15 levels were significantly lower in survivors (1601 ng/L (interquartile range: 1114–2983 ng/L) than in non-survivors (3172 ng/L (1927–8340 ng/L); $p < 0.001$). GDF-15 levels were also significantly lower in patients with favourable neurological 6-month outcome (cerebral performance category (CPC) 1–2) than in those with poor neurological outcome (CPC 3–5; $p < 0.001$). GDF-15 significantly predicted 6-month mortality in univariate Cox regression analysis (hazard ratio (HR) per 1-standard deviation increase 1.76 [95% confidence interval (CI) 1.35–2.31; $p < 0.001$] and remained significant after multivariable adjustment (HR 1.57 [95% CI 1.19–2.07; $p = 0.001$]). Subgroup analysis revealed that the association between GDF-15 and 6-month outcome was present both in patients with in- and out-of-hospital CA.

**Conclusions:** GDF-15 predicts poor survival and neurological outcome in post-CA patients. GDF-15 may reflect the extent of hypoxic injury to the brain and other organs and might help to improve early risk stratification after CA.

**Keywords:** Cardiac arrest, Growth differentiation factor-15 (GDF-15), Biomarker, Cardiopulmonary resuscitation, Survival, Prognosis

## Introduction

Despite major advances in critical care medicine, long-term survival after initially successful resuscitation of cardiac arrest (CA) remains poor[1,2] and early risk stratification is still challenging. Therefore, the identification of novel prognostic parameters is warranted and might improve clinical decision-making in the future.

Growth differentiation factor-15 (GDF-15), also known as macrophage inhibitory cytokine-1, is an emerging biomarker which is

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https://doi.org/10.1016/j.resuscitation.2019.07.028
Received 12 April 2019; Received in revised form 8 July 2019; Accepted 26 July 2019
0300-9572/© 2019 Published by Elsevier B.V.

up-regulated during various kinds of tissue injury and is deemed to be involved in the regulation of the inflammatory and reparative response to injury in multiple disease states.[3–5] GDF-15 also seems to have the ability to promote cell survival as recently demonstrated for cardiomyocytes and neurons.[5–7] It is a member of the transforming growth factor-beta cytokine superfamily and has been shown to be a predictor of outcome in numerous pathologies such as stable ischaemic heart disease, acute myocardial infarction and heart failure.[4,5,8] Furthermore, GDF-15 was found to predict poor functional outcome after acute ischaemic stroke[9,10] and was reported to be up-regulated in animal models of acute hypoxic brain injury.[11] Although hypoxic injury of the brain and other organs is crucial for the outcome after CA, the role of GDF-15 in post-CA patients has not been investigated up to now.

The current study aimed to assess the prognostic value of circulating GDF-15 in post-CA patients with regard to 6-month survival.

## Methods

### *Study design, setting and population*

This study is a prospective observational single-center study. We included 128 consecutive patients with sustained return of spontaneous circulation (ROSC) after CA who were either admitted to the emergency department (ED) or the medical intensive care unit (ICU) of a tertiary university hospital (General Hospital of Vienna, Austria). Patients were either admitted directly after out-of-hospital CA or after in-hospital CA. Exclusion criteria were age less than 18 years and traumatic CA. The study was approved by the Ethical Committee of the Medical University of Vienna (approval reference number: 1101/2012) and complies with the Declaration of Helsinki. Written informed consent was obtained from all patients who regained consciousness. For unconscious patients the Ethical Committee waived the need for informed consent.

All CA patients were treated at the discretion of the treating physicians according to standard operating procedures and current guidelines. The treating physicians were not aware of GDF-15 levels and the participation in the study had no impact on the treatment of patients. Targeted temperature management (TTM, 33 degrees, 24 h) was performed using intravascular or surface cooling devices. TTM was not implemented in post-CA patients who regained consciousness, followed commands and showed purposeful movements directly after ROSC or had contraindications to TTM such as severe bleeding or haemodynamic instability during TTM unresponsive to volume resuscitation and vasopressor treatment.

The recorded pre-hospital and in-hospital parameters and patient baseline characteristics including Utstein variables are listed in Table 1. The Glasgow–Pittsburgh cerebral performance categories (CPC) were used to categorise the neurological status 6-months after CA (CPC 1–2: favourable neurological outcome; CPC 3–5: poor neurological outcome).[12] Severity of illness was assessed using the acute physiology and chronic health evaluation II (APACHE II) score. Patients were followed for 6 months. The study endpoint was survival at 6 months post CA.

### *Laboratory analysis*

Blood samples were collected on ED or ICU admission from the arterial line or central venous line. After immediate centrifugation (4 °C; 3000 RPM; 15 min), serum samples were stored at −80 °C until analysis. Serum levels of GDF-15 were analysed by ELISA (Quantikine, R&D Systems Inc., Minneapolis, Minnesota, USA). Intra- and inter-assay coefficients of variation for GDF-15 were ≤2.8% and ≤6%, respectively. The minimum detectable dose was 2.0 pg/mL. GDF-15 levels in healthy individuals and patients varied widely across studies, partly due to the use of different assays, and might therefore not be comparable between studies.[4] To give a rough overview, median GDF-15 levels in apparently healthy, elderly individuals were reported to be 762 (interquartile range (IQR): 600–959) ng/L,[13] in patients with stable coronary artery disease 1253 (IQR: 915–1827) ng/L[14] and 2166 (IQR: 1589–3057) ng/L,[15] in patients with atrial fibrillation 1383 (IQR: 977–2052) ng/L,[16] in heart failure patients 2705 (IQR: 1883–3994) ng/L[13] and 2040 (IQR:1426–3027) ng/L,[8] in patients with acute myocardial infarction 1635 (IQR: 1164–2309) ng/L,[17] in patients with acute myocardial infarction and cardiogenic shock 7662 ng/L (median),[18] in patients with ischemic stroke 1630 (IQR: 1055–2177) ng/L[9] and in patients with end-stage renal failure 7100 (range: 1400–34,400) ng/L,[19] respectively.

### *Statistical analysis*

Sample size calculation revealed that a sample size of 112 patients is required to detect a difference of 50% in GDF-15 serum levels between survivors and non-survivors when a mortality rate of 50% is assumed (80% power, 2-sided $\alpha = 0.05$). As the mortality rate was lower than expected, a total of 128 patients were finally included.

Continuous data are reported as median (IQR), since they were not normally distributed according to the Kolmogorov–Smirnov-Test and the Shapiro–Wilk-Test.

Spearman's rho correlation coefficient was used to assess associations between continuous variables. Differences between baseline variables and tertiles of GDF-15 were analysed using a test for linear association (Maentel–Haenszel-$\chi^2$ test). The Mann–Whitney-U test was used to compare GDF-15 serum levels between survivors and non-survivors and between patient with favourable and poor neurological outcome, respectively. The chi-square test was used to compare categorical variables between in-hospital and out-of-hospital CA patients. Univariable and multivariable Cox proportional hazard regression models were used to assess the influence of GDF-15 serum levels and other variables (as listed in Table 1) on 6-month all-cause mortality. Continuous data were log-transformed before entering regression analysis. Stepwise forward selection was used to select variables for the final multivariable model (criteria for entry: $p \leq 0.05$, criteria for removal $p \geq 0.1$). Interactions between GDF-15 and location of CA (in-hospital CA vs. out-of-hospital CA) were assessed by interaction terms. Kaplan–Meier curves (log-rank test) were used to display the crude cumulative survival of GDF-15 tertiles. A $p$-value ≤ 0.05 (two-sided) was considered statistically significant. SPSS 25.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses.

## Results

### *Baseline characteristics and associations with GDF-15*

The entire study cohort consisted of 128 consecutive patients with either out-of-hospital CA (83.6%, n = 107) or in-hospital CA (16.4%,

**Table 1 – Baseline characteristics.**

| | All | Tertiles of GDF-15 | | | Correlation | | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | | | |
| *n* | 128 | 43 | 42 | 43 | | | |
| GDF-15, median (IQR), ng/L | 2182 (1257–4661) | 1102 (795–1262) | 2182 (1778–2476) | 7150 (4228–10307) | *p* | r | *p* |
| Age, years | 60.3 (49.7–71.5) | 58.1 (48.9–67.5) | 59.5 (47.3–76.7) | 63.7 (52.5–71.8) | 0.049 | 0.21 | 0.016 |
| Male gender, *n* (%) | 97 (75.8) | 31 (72.1) | 31 (73.8) | 35 (81.4) | 0.316 | / | / |
| Body mass index, kg/m$^2$ | 26.4 (24.3–29.9) | 26.1 (23.4–30.0) | 26.6 (24.5–29.8) | 26.6 (24.5–30.7) | 0.603 | 0.08 | 0.350 |
| Location of CA | | | | | 0.004[a] | / | / |
| In-hospital CA, *n* (%) | 21 (16.4) | 1 (2.3) | 9 (21.4) | 11 (25.6) | / | / | / |
| Out-of-hospital CA, *n* (%) | 107 (83.6) | 42 (97.7) | 33 (78.6) | 32 (74.4) | / | / | / |
| | | | | | 0.783 | | |
| | | | | | 0.010 | | |
| Witnessed CA, *n* (%) | 104 (81.3) | 34 (79.1) | 37 (88.1) | 33 (76.7) | | / | / |
| Bystander-initiated CPR, n (%) | 99 (77.3) | 38 (88.4) | 33 (78.6) | 28 (65.1) | | / | / |
| Time from CA to ROSC, min | 27 (15–41) | 28 (16–40) | 21 (12–38) | 30 (16–50) | 0.538 | 0.05 | 0.600 |
| Initial rhythm shockable, *n* (%) | 87 (68.0) | 35 (81.4) | 26 (61.9) | 26 (60.5) | 0.038 | / | / |
| Adrenaline (epinephrine) dose, mg | 3 (1–4) | 3 (2–5) | 2 (1–3) | 3 (1–4) | 0.368 | −0.09 | 0.304 |
| Blood lactate level after CA, mmol/L | 7.9 (5.6–9.1) | 7.5 (5–9) | 7.8 (4.9–9.1) | 8.1 (6.0–9.7) | 0.098 | 0.14 | 0.113 |
| Mild therapeutic hypothermia, *n* (%) | 115 (89.8) | 43 (100) | 37 (88.1) | 35 (81.4) | 0.004 | / | / |
| Past medical history | | | | | / | / | / |
| Coronary artery disease, *n* (%) | 53 (41.4) | 16 (37.2) | 13 (31.0) | 24 (55.8) | 0.081 | / | / |
| Previous myocardial infarction, *n* (%) | 23 (18.0) | 6 (14) | 4 (9.5) | 13 (30.2) | 0.049 | / | / |
| Congestive heart failure, *n* (%) | 34 (26.6) | 5 (11.6) | 10 (23.8) | 19 (44.2) | 0.001 | / | / |
| Hypertension, *n* (%) | 57 (44.5) | 15 (34.9) | 22 (52.4) | 20 (46.5) | 0.280 | / | / |
| Diabetes mellitus, *n* (%) | 27 (21.1) | 0 (0) | 12 (28.6) | 15 (34.9) | <0.001 | / | / |
| COPD, *n* (%) | 22 (17.2) | 5 (11.6) | 7 (16.7) | 10 (23.3) | 0.155 | / | / |
| Serum creatinine level, mg/dL | 1.10 (0.87–1.32) | 1.12 (0.84–1.28) | 1.09 (0.85–1.28) | 1.25 (0.96–1.87) | 0.005 | 0.26 | 0.004 |
| APACHE II score | 25 (22–29) | 24 (22–29) | 25 (23–27) | 26 (23–33) | 0.373 | 0.17 | 0.064 |

Continuous data are reported as median (interquartile range (IQR)). Data were analysed using a test for linear association (Maentel–Haenszel-$\chi^2$ test). Additionally, the Spearman-Rho correlation coefficient was used to assess associations between GDF-15 and continuous variables (2 right columns). APACHE, acute physiology and chronic health evaluation; CA, cardiac arrest; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; GDF-15, growth differentiation factor 15; ROSC, return of spontaneous circulation.

[a] In-hospital CA vs. out-of-hospital CA.

n = 21) and sustained ROSC. Table 1 displays the demographic and clinical characteristics of the study population. Patients were predominantly male (75.8%, n = 97) with a median age of 60.3 years (interquartile range (IQR): 49.7–71.5 years).

Median GDF-15 serum levels at admission were 2182 ng/L (IQR: 1257–4661 ng/L). GDF-15 was significantly associated with age (r = 0.21; $p = 0.016$) and serum creatinine levels (r = 0.26; $p = 0.004$, Table 1). Furthermore, GDF-15 levels were higher in patients with diabetes mellitus, heart failure and a history of myocardial infarction and were lower in patients with a shockable initial cardiac rhythm, bystander-initiated CPR, out-of-hospital CA and in patients treated with mild therapeutic hypothermia (all $p < 0.05$, Table 1). Compared to the out-of-hospital CA patients, the in-hospital CA patients were older (72 years vs. 59 years, $p < 0.001$), had a higher rate of heart failure (48% vs. 22%, $p = 0.017$) and a borderline significant higher rate of previous myocardial infarction (33% vs. 15%, $p = 0.061$) and arterial hypertension (62% vs. 41%, $p = 0.080$).

### *GDF-15 serum levels and six-month outcome*

All-cause mortality at six months post CA was 40.6% (52 out of 128 patients). Patients who died within the first six months after CA showed significantly higher GDF-15 serum levels (3172 ng/L (IQR: 1927–8340 ng/L) than the surviving patients (1601 ng/L (IQR: 1114–2983 ng/L); $p < 0.001$; Fig. 1a). With regard to neurological 6-month outcome, 48.4% of patients (62 out of 128) had a favourable neurological outcome (CPC 1 or 2), whilst 51.6% (66 out of 128 patients) had a poor neurological outcome (CPC 3–5). GDF-15 levels were significantly higher (2713 ng/L (IQR: 1558–7525 ng/L)) in patients with poor neurological outcome than in those with favourable neurological outcome (1578 ng/L (IQR: 1124–2903 ng/L); $p < 0.001$; Fig. 1b).

In univariable Cox regression analysis, GDF-15 was a significant predictor of 6-month all-cause mortality with a hazard ratio (HR) per one standard deviation (1-SD) increase of 1.76 [95% confidence interval (CI) 1.35–2.31; $p < 0.001$] (Table 2). This association remained significant after multivariable adjustment (HR per 1-SD increase 1.57 [95% CI 1.19–2.07; $p = 0.001$] (Table 2). Fig. 2 shows Kaplan Meier survival curves of tertiles of GDF-15. The hazard of death for the 3rd tertile of GDF-15 was 4.7 times higher than that for the 1st tertile of GDF-15 [95% CI 2.1–10.3; $p < 0.001$]. Additionally, we created a cut-off for GDF-15 with high specificity set at 90% (GDF-15 ≥ 7230 ng/L), which might be helpful to predict 6-month mortality with a high degree of confidence. Due to the high specificity, the sensitivity at this cut-off was only 25%.

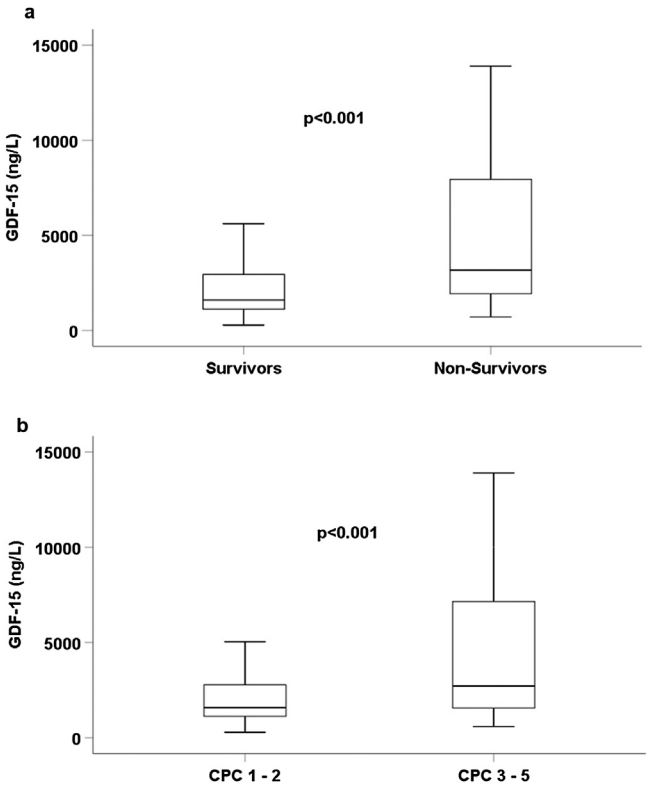


**Fig. 1 – Box plots showing serum levels of growth differentiation factor-15 (GDF-15) in patients with cardiac arrest and return of spontaneous circulation: (a) according to 6-month survival and (b) according to neurological outcome at six months (good neurological outcome as defined by cerebral performance category (CPC) 1 or 2 vs. poor neurological outcome as defined by CPC 3–5). *P*-values derived from Mann–Whitney-U test. Outliers not shown.**

Subgroup analysis revealed that GDF-15 predicted all-cause mortality both in patients with out-of-hospital CA (HR per 1-SD increase 1.57 [95% CI 1.16–2.12; $p = 0.003$]) and in-hospital CA (HR per 1-SD increase 2.05 [95% CI 1.13–3.74; $p = 0.019$]). The predictive value of GDF-15 did not significantly differ between these subgroups as assessed by interaction terms ($p = 0.507$).

## Discussion

The present study is the first study to describe a significant univariable and multivariable association between GDF-15 and survival in post-CA patients. High GDF-15 levels were associated with a poor 6-month survival both in patients with out-of-hospital and in-hospital CA. Moreover, GDF-15 levels were significantly higher in patients with a poor neurological outcome as compared to those with favourable neurological outcome.

On the basis of pre-existing clinical and experimental data showing GDF-15 up-regulation after other forms of brain injury,[9–11,20] elevated GDF-15 after CA might simply be a surrogate marker for the extent of brain damage gained during CA. Lesioned neurons, microglial cells and choroid plexus have been reported to be the source of GDF-15 production in experimental brain injury models.[11,20,21] In keeping with the present findings after CA, high GDF-15 levels were associated with stroke severity and poor functional 3-month outcome in patients with acute ischaemic stroke.[9,10] According to previous studies, GDF-15 is also linked to subclinical vascular brain damage and other neurodegenerative processes[22] as well as to worsening of cognitive function and dementia.[23] In line with these data, the present study found a significant difference in GDF-15 levels between patients with favourable and poor neurological 6-month outcome.

However, the present study cannot answer the question, as to whether circulating GDF-15 after CA is derived from the injured brain or from other organ systems which equally suffer from hypoxia and hypoperfusion and also contribute to the patient`s outcome.[24] Aside from the brain, the stress–response cytokine GDF-15 is dramatically up-regulated during injury of various other organ systems including the heart, liver, lungs and kidneys[3,4,6,11,25] and was linked to patients` outcome in multiple pathological states.[4,5,8–10,17,25–28] Its up-regulation is triggered by various stressor signals such as hypoxia, ischaemia/reperfusion, inflammation and oxidative stress,[3–5] all of which play a role in CA and might influence the prognosis of patients.[29] The lack of organ specificity of GDF-15 as a rather general marker of tissue injury, might even increase its value in risk prediction after CA as the level of circulating GDF-15 might reflect the summation of all CA-induced tissue lesions in the body. This fact might distinguish GDF-15 from other predictive biomarkers, such as neuron-specific enolase, which is more specific for neurological injury.[24] Although no single biomarker will have enough diagnostic power to determine clinical decisions alone, GDF-15 and other biomarkers might be essential components of a multimodal risk stratification approach in post-CA patients, where early prognostication is still very challenging. Advantages of GDF-15 and other biomarkers over other established diagnostic tools, such as EEG and clinical examination, include quantitative results and likely independence from the effect of sedatives.[24] Furthermore, GDF-15 can easily and quickly been assessed and might provide very early prognostic information (within 24 h), earlier than other established diagnostic tools.[24] A refinement of early risk prediction and more exact information about the extent of organ damage might help clinicians to optimize the post-resuscitation management of patients and provide guidance for clinical decision-making. This might include decisions concerning the patient`s suitability for advanced treatment options such as coronary interventions, extracorporeal mechanical life support and heart surgery, and might help to avoid inappropriate treatment. Furthermore, better risk stratification could help to define appropriate treatment goals, to provide adequate information to the family members and to reach a decisions on withdrawal of life-sustaining treatment. However, future large-sized studies have to evaluate the role of GDF-15 in a multimodal risk assessment approach.

The present findings might also help to better understand the underlying processes in CA. Increased insight into the biological function of GDF-15, its signaling pathways and neurotropic effects may offer the opportunity to discover novel treatment targets for future therapeutic interventions in post-CA patients. In view of the previously described neuro-protective and cardio-protective effects of GDF-15, its up-regulation after CA might therefore be

**Table 2 – Predictors of 6-month survival in univariable and multivariable Cox regression analysis.**

| | Univariable | | Final multivariable model | |
|---|---|---|---|---|
| | HR (95% CI) | *p* | HR (95% CI) | *p* |
| GDF-15[a] | 1.76 (1.35–2.31) | <0.001 | 1.57 (1.19–2.07) | 0.001 |
| Age[a] | 1.77 (1.23–2.55) | 0.002 | | |
| Male gender | 1.59 (0.88–2.86) | 0.124 | | |
| Body mass index[a] | 1.38 (1.07–1.79) | 0.015 | | |
| Location of CA[b] | 0.42 (0.23–0.78) | 0.006 | | |
| Witnessed CA | 0.50 (0.27–0.91) | 0.023 | 0.50 (0.27–0.92) | 0.027 |
| Bystander-initiated CPR | 0.65 (0.36-1.18) | 0.154 | | |
| Time from CA to ROSC[a] | 1.46 (1.06–2.0) | 0.020 | | |
| Initial rhythm shockable | 0.19 (0.11–0.33) | <0.001 | 0.18 (0.10–0.33) | <0.001 |
| Adrenaline dose[a] | 1.24 (0.93–1.63) | 0.144 | | |
| Blood lactate level after CA[a] | 1.88 (1.34–2.62) | <0.001 | 1.59 (1.12–2.26) | 0.009 |
| Mild therapeutic hypothermia | 0.83 (0.35–1.94) | 0.661 | | |
| Coronary artery disease | 0.97 (0.56–1.69) | 0.921 | | |
| Previous myocardial infarction | 1.99 (1.08–3.69) | 0.028 | | |
| Congestive heart failure | 2.42 (1.40–4.21) | 0.002 | | |
| Hypertension | 1.10 (0.64–1.90) | 0.730 | | |
| Diabetes mellitus | 1.64 (0.90–2.99) | 0.107 | | |
| COPD | 2.33 (1.27–4.25) | 0.006 | | |
| Serum creatinine[a] | 1.47 (1.17–1.86) | 0.001 | | |
| APACHE II score[a] | 2.04 (1.35–3.07) | 0.001 | | |

The final multivariable models was created using stepwise forward selection (criterion for entry: $p=0.05$; criterion for removal: $p=0.1$). Four variables were selected (right column).
APACHE, acute physiology and chronic health evaluation; CA, cardiac arrest; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; GDF-15, growth differentiation factor 15; ROSC, return of spontaneous circulation.
[a] HR per 1-SD increase (continuous variables).
[b] In-hospital CA vs. out-of-hospital CA.

an attempt to protect the brain and other organs from further damage. Currently, the modulation of GDF-15 via application of recombinant GDF-15, cytokine-induced GDF induction and use of anti-GDF-15 antibodies is studied in many pathological conditions, both in vitro and in vivo.[30–33] Although there are promising preliminary results, large interventional trials assessing the therapeutic potential of GDF-15 modulation are still missing.

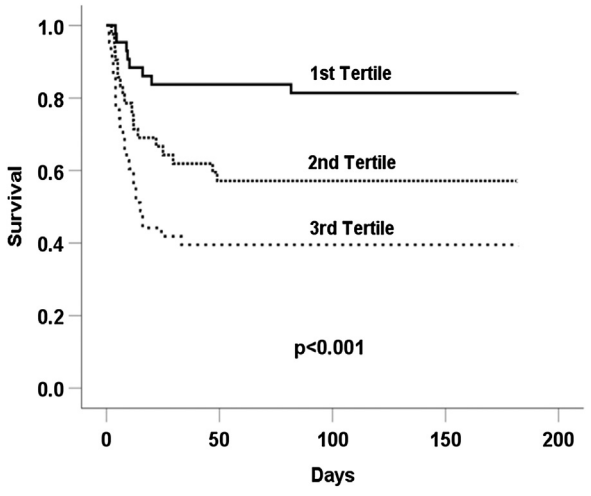


**Fig. 2 – Kaplan-Meier plot showing the probability of survival after cardiac arrest with initially successful resuscitation according to tertiles of growth differentiation factor-15 (GDF-15).**

### *Study limitations*

The present study is a prospective single-center study and includes both patients with in- and out-of-hospital CA. However, the predictive value of GDF-15 was present in both subgroups. As the present trial is an observational study, we can only describe the association between GDF-15 and mortality, but cannot prove a cause-and-effect relationship. Since we did not measure GDF-15 levels before CA, we cannot exclude that, at least in some of the patients, GDF-15 levels have already been elevated before the CA due to pre-existing comorbidities.[4] Therefore, the GDF-15 levels after CA might not only reflect CA-related ischemic injury, but also the presence of pre-existing comorbidities. The higher frequency of cardiovascular comorbidities might also be an explanation for the higher GDF-15 levels in patients with in-hospital CA than in those with out-of-hospital CA. Additionally, the study was not powered to compare GDF-15 levels between patients with good neurological outcome (CPC 1–2) and the surviving patients with poor neurological outcome (CPC 3–4).

## Conclusions

Circulating GDF-15 has independent value for predicting survival in post-CA patients and might reflect the extent of hypoxic organ

damage acquired during CA. Implementation of GDF-15 in multimodal risk stratification models might help to identify patients with poor outcome and might improve clinical decision-making. Future large-sized clinical studies are warranted to validate the present findings, to establish appropriate cut off values and to explore the exact role of GDF-15 in patients with in-hospital or out-of-hospital CA.

## Conflicts of interest

None.

## Sources of funding

This work was supported by the Association for the Promotion of Research in Arteriosclerosis, Thrombosis and Vascular Biology (Vienna, Austria) and by the Ludwig Boltzmann Cluster for Cardiovascular Research (Vienna, Austria). The sponsors had no involvement in the following processes: study design, collection, analysis and interpretation of data, writing of the manuscript and the decision to submit the manuscript for publication.

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