

The Prognostic Potential of Growth Differentiation Factor-15 on Bleeding Events and Patient Outcome after Cardiac Surgery – A prospective cohort study

Kazem N, Hammer A, Koller L, Hofer F, Steinlechner B, Laufer G, Hengstenberg C, Wojta J, Sulzgruber P, Niessner A

Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Austria

Department of Cardiac Surgery, Medical University of Vienna, Austria

Division of Cardiac Thoracic Vascular Anaesthesia, Department of Anesthesiology, Medical University of Vienna, Austria

Background

GDF-15 (growth/differentiation factor 15) is induced by myocardial stretch, volume overload, inflammation and oxidative stress. Its expression is tightly linked with cardiovascular events as well as the risk for major bleeding and all-cause mortality. The present study aimed to elucidate the prognostic potential of GDF-15 in patients after cardiac surgery.

Patients and Methods

504 patients undergoing elective cardiac valve and/or coronary artery bypass graft surgery were prospectively enrolled. GDF-15 levels were measured prior surgery to evaluate the impact on bleeding events, thromboembolic events and mortality.

Results

Preoperative GDF-15 was associated with the primary endpoint of intra- and postoperative red blood cell transfusion (for bleeding risk factors adjusted [adj] OR [odds ratio] per 1-SD [standard deviation] of 1.62 [95%CI:1.31-2.00]; $p<0.001$). Higher concentrations of GDF-15 were observed in patients reaching the secondary endpoint of major or clinically relevant minor bleeding (for bleeding risk factors adj. OR per 1-SD of 1.70 [95%CI:1.05-2.75]; $p=0.030$) during the 1st postoperative year, but not for thromboembolic events. GDF-15 was a predictor for cardiovascular mortality (for comorbidities adj. HR [hazard ratio] per 1-SD of 1.67 [95%CI:1.23-2.27]; $p=0.001$) and all-cause mortality (for comorbidities adj. HR per 1-SD of 1.55 [95%CI:1.19-2.01]; $p=0.001$). A combined risk model of GDF-15 and EuroSCORE II outperformed the EuroSCORE II alone for long-term survival (c-index: 0.75 [95%CI: 0.70-0.80], $p=0.046$; net reclassification improvement: 33.6%, $p<0.001$).

	Overall (n=504)	Tertile 1 (n=168)	Tertiles of GDF-15		
		Tertile 1 (n=168)	Tertile 2 (n=168)	Tertile 3 (n=168)	p-value
Clinical Presentation					
Age, years (IQR)	69.8 (60.6-75.6)	65.2 (54.3-72.4)	71.9 (62.6-77.0)	71.9 (64.9-77.1)	<0.001
Gender (male), n (%)	335 (70.4)	121 (72.0)	118 (70.2)	116 (69.0)	0.834
Body mass index, kg/m ² (IQR)	27.3 (24.3-30.2)	26.7 (24.2-29.5)	27.7 (24.3-30.4)	27.7 (24.3-30.8)	0.220
Type of Surgery					0.003
Valve replacement, n (%)	216 (42.9)	86 (51.2)	71 (42.3)	59 (35.1)	
CABG, n (%)	162 (32.1)	52 (31.0)	59 (35.1)	51 (30.4)	
Valve replacement and CABG, n (%)	126 (25.0)	30 (17.9)	38 (22.6)	58 (34.5)	
NYHA-Class, n (%)					0.116
I	26 (5.2)	7 (4.2)	8 (4.8)	11 (6.5)	
II	126 (25.0)	46 (27.4)	38 (22.6)	42 (25.0)	
III	120 (23.8)	35 (20.8)	32 (19.0)	53 (31.5)	
VI	18 (3.6)	1 (0.6)	9 (5.4)	8 (4.8)	
LVEF, % (IQR)	60 (54.2-60.0)	60.0 (54.2-60.0)	60.0 (54.2-60.0)	60.0 (50.0-60.0)	0.008
LA diameter, mm (IQR)	56.2 (50.0-60.0)	56.2 (45.0-60.0)	55.0 (50.0-60.0)	56.2 (50.0-65.0)	0.137
CHA ₂ DS ₂ /VASC-Score (IQR)	4 (3-5)	3 (2-4)	3 (3-5)	5 (4-5)	<0.001
EuroSCORE II (IQR)	2.3 (1.2-4.4)	1.6 (0.9-2.6)	2.0 (1.2-3.5)	4.0 (2.1-8.7)	<0.001
Comorbidities					
Previous MI, n (%)	133 (26.4)	28 (16.7)	46 (27.4)	59 (35.1)	0.001
Hypertension, n (%)	406 (80.6)	122 (72.6)	136 (81.0)	148 (88.1)	0.002
Diabetes mellitus, n (%)	144 (28.6)	20 (11.9)	42 (25.0)	82 (48.8)	<0.001
Hypercholesterolemia, n (%)	317 (62.9)	99 (58.9)	114 (67.9)	104 (61.9)	0.226
Chronic kidney disease, n (%)	93 (18.5)	13 (7.7)	17 (10.1)	63 (37.5)	<0.001
Congestive heart failure, n (%)	290 (57.5)	89 (53.0)	87 (51.8)	114 (67.9)	0.004
COPD, n (%)	69 (13.7)	23 (13.7)	14 (8.3)	32 (19.0)	0.017
Current smoker, n (%)	61 (12.1)	20 (11.9)	22 (13.1)	19 (11.3)	0.878
History of bleeding events, n (%)	9 (1.8)	6 (3.6)	2 (1.2)	1 (0.6)	0.093
Laboratory measures at admission					
GDF-15, ng/L (IQR)	1274.1 (775.4-1889.8)	651.7 (517.9-776.3)	1274.1 (1089.2-1396.9)	2295.5 (1879.3-3343.1)	
Hemoglobin, g/dl (IQR)	13.1 (11.8-14.3)	13.5 (12.7-14.7)	13.1 (11.9-14.3)	12.5 (11.1-13.7)	<0.001
Hematocrit, % (IQR)	39.5 (36.0-42.1)	40.3 (38.5-43.0)	39.5 (35.9-41.7)	37.7 (33.9-40.9)	<0.001
Platelet count min., 1.000/ μ l (IQR)	222.5 (185.0-266.0)	224.5 (192.5-266.0)	221.0 (176.0-263.3)	222.0 (182.0-274.0)	0.558
NT-proBNP, pg/ml (IQR)	539.6 (210.4-1874.2)	339.8 (145.0-898.4)	512.8 (232.4-1285.8)	1198.0 (369.2-3249.5)	<0.001
Creatinine, mg/dl (IQR)	1.0 (0.8-1.2)	0.9 (0.7-1.0)	0.9 (0.8-1.1)	1.2 (0.9-1.5)	<0.001
hsCRP max. before surgery, mg/dl (IQR)	0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.2 (0.1-0.5)	0.3 (0.1-0.8)	<0.001

Table 1: Baseline characteristics stratified by GDF-15 tertiles. Categorical data are presented as counts and percentages and analyzed using Chi-square-test. Continuous data are presented as median and the respective interquartile range and analyzed using Kruskal Wallis Test. Correlations between continuous variables and GDF-15 tertiles were calculated using Spearman correlation coefficient.

Conflict of Interest: Nothing to declare.

Correspondence: niema.kazem@meduniwien.ac.at

Conclusion

Preoperative GDF-15 concentration is an independent predictor for intra- and postoperative major bleeding, major bleeding during the first year and for long-term cardiovascular or all-cause mortality after cardiac surgery.

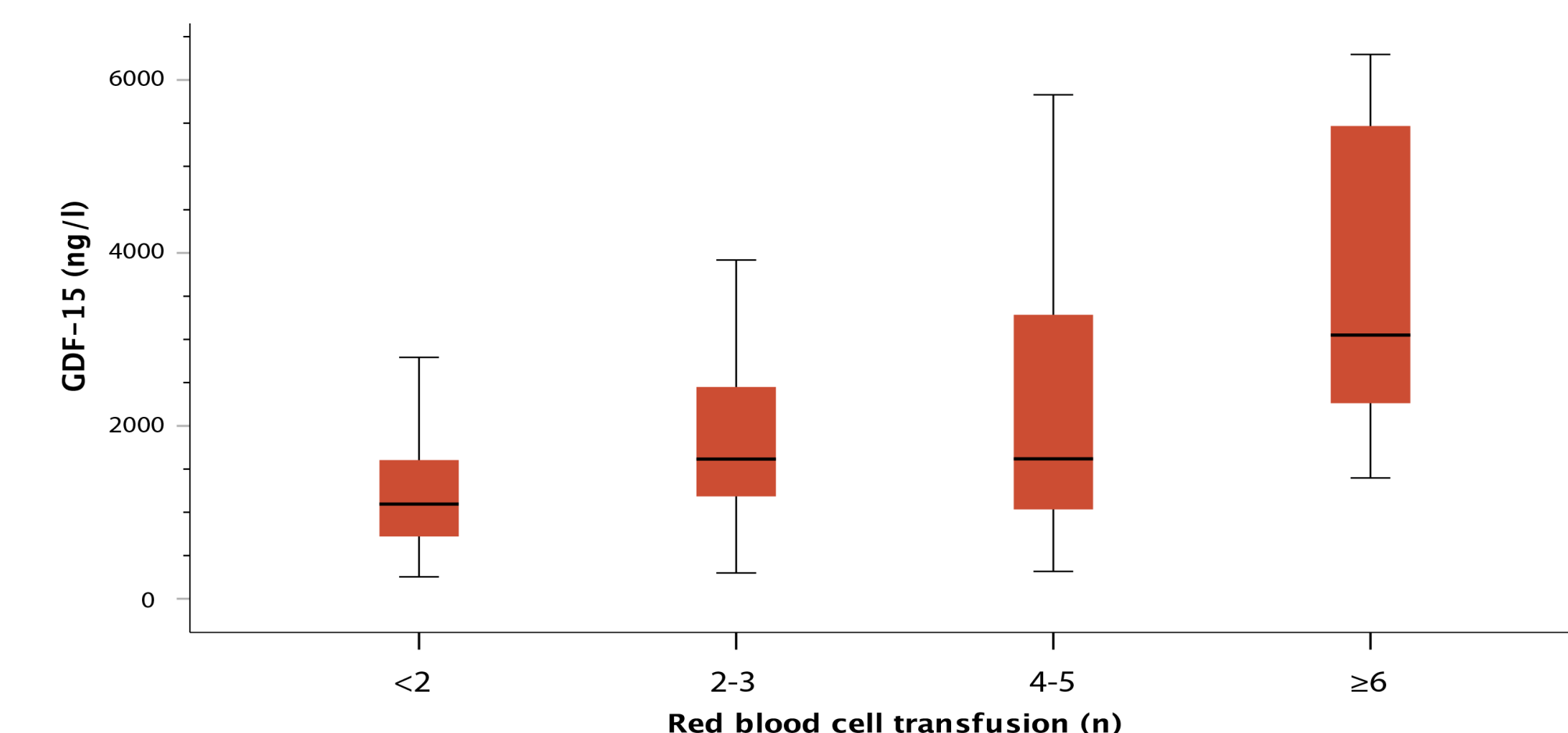


Figure 1: Boxplots for frequencies of intra- and postoperative red blood cell transfusions with preoperative GDF-15 levels.

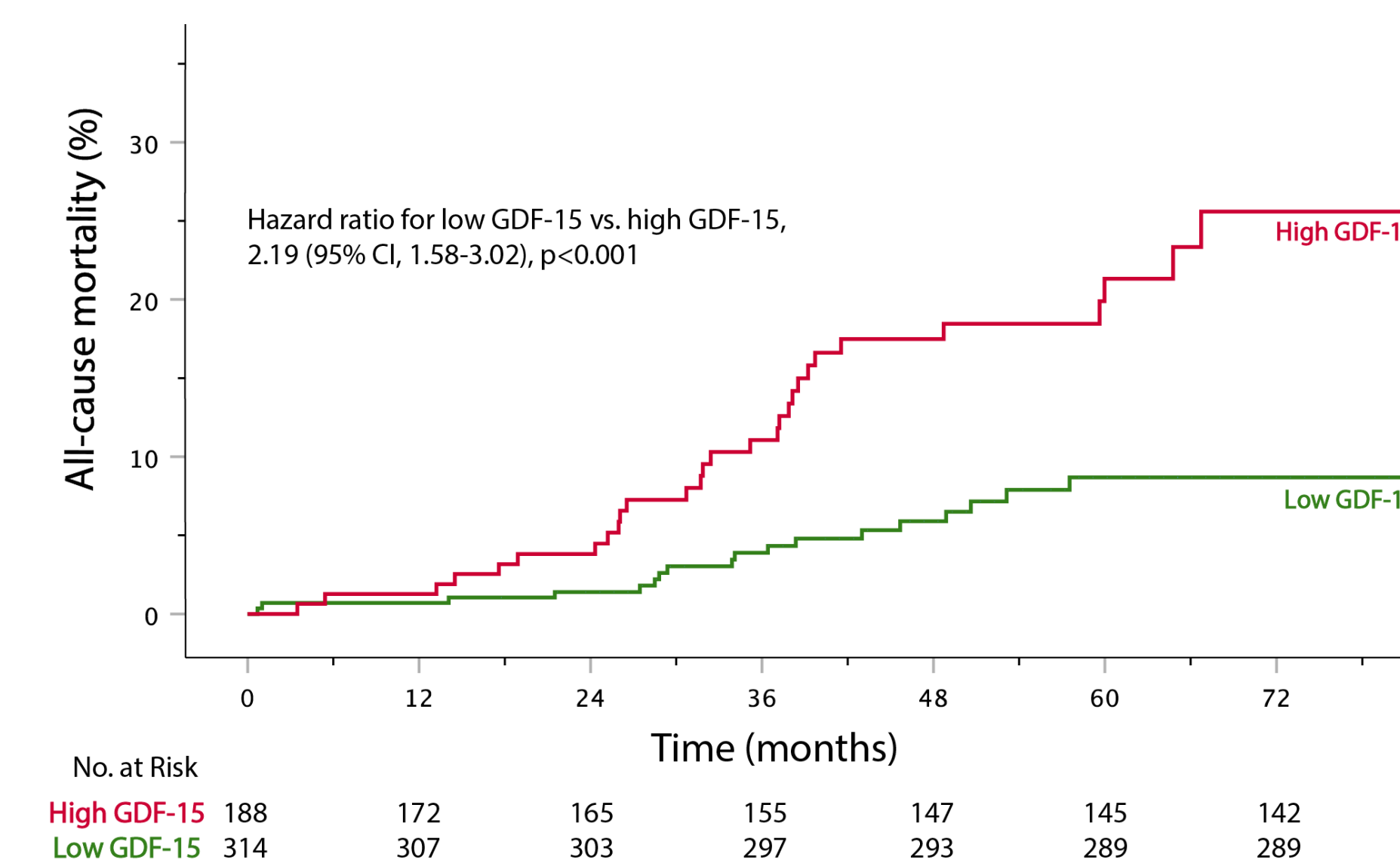


Figure 2: Kaplan-Maier curve for the cumulative probability of all-cause mortality. Hazard ratio per 1-SD for all-cause mortality comparing low pre-operative GDF-15 to high pre-operative GDF-15. p -value for log-rank test: <0.001