The gut hormone GLP-2 is associated with cardiovascular risk in patients with myocardial infarction

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Short title: GLP-2 associates with cardiovascular risk

Abstract

Background: GLP-1 and GLP-2 (glucagon-like peptide-1/2) are gut hormones co-secreted upon food intake. While GLP-1 regulates postprandial glucose metabolism and improves cardiovascular prognosis in patients with diabetes, GLP-2 enhances intestinal nutrient absorption and is clinically used in patients with short bowel syndrome. The relevance of GLP-2 for cardiovascular disease is unknown.
Objectives: To assess the predictive capacity of GLP-2 for cardiovascular prognosis in patients with myocardial infarction.
Methods: Total GLP-2 levels were assessed at time of admission in 918 patients with myocardial infarction. The primary outcome of the study was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (3-P-MACE) with a median follow-up of 311 days.
Results: Kaplan-Meier survival plots and univariable cox regression analyses found GLP-2 values to be associated with an increased risk for 3-P-MACE (logarithmized GLP-2 values HR: 2.87; 95% CI: 1.75 - 4.68; p<.0001). Further adjustment for age, sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, family history of cardiovascular disease, hs-Troponin T, NT-proBNP and hs-CRP levels did not affect the significant association of GLP-2 with poor prognosis. ROC curve analyses illustrated that GLP-2 is a strong indicator for cardiovascular events and proved to be comparable to established risk markers. Adjustment of the GRACE risk estimate by addition of GLP-2 increased the area under the receiver-operating characteristic curve.
Conclusions: In patients admitted with acute myocardial infarction, GLP-2 levels are associated with adverse cardiovascular prognosis. This suggests a strong, as of yet not appreciated crosstalk between the heart and the gut and warrants further exploration.

Condensed Abstract

GLP-1 and GLP-2 are gut hormones co-secreted upon food intake. While GLP-1 has been found to improve cardiovascular prognosis in patients with diabetes, the role of GLP-2 for cardiovascular disease is unknown. Here we found admission GLP-2 levels to be strongly associated with cardiovascular outcome and mortality in 918 patients with acute myocardial infarction. GLP-2 proved to be comparable to established risk markers and added additional value to the GRACE risk score. Future studies are needed to further explore this crosstalk between the heart and the gut with the possibility of new treatment avenues for cardiovascular disease.

Keywords: GLP-2; gut hormone; cardiovascular risk; myocardial infarction; GRACE score.

Abbreviations: GLP-2 (Glucagon-like peptide 2), GRACE (Global Registry of Acute Coronary Events), NT-proBNP (N-terminal brain natriuretic peptide), STEMI (ST-elevation myocardial infarction), NSTEMI (non-ST-elevation myocardial infarction), 3-P-MACE (3-point major adverse cardiovascular events: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), PTCA: Percutaneous transluminal coronary angioplasty, CABG: Coronary artery bypass grafting.

Introduction

Patients presenting with STEMI (ST segment elevation myocardial infarction) and NSTEMI (non-ST segment elevation myocardial infarction) present a heterogeneous population and differ in terms of clinical symptoms and short as well as long-term prognosis. Early risk stratification is essential to identify patients requiring immediate or early coronary angiography (1). While immediate revascularization is mandatory in patients with STEMI, patients with NSTEMI can be stratified by symptoms and comorbidities to receive coronary angiography within 24 or 72 hours. Clinical risk scores like the Global Registry of Acute Coronary Events (GRACE) score and the TIMI risk score are currently used to assess the individual risk and to determine triage and therapeutic decision making in patients with myocardial infarction (2,3).

GLP-1 and GLP-2 (glucagon-like peptide-1/2) are intestinal hormones that are co-secreted from L-cells in response to food intake (4-6). GLP-1 is known to induce postprandial insulin secretion and glucose lowering, thus making GLP-1 an attractive therapeutic target for the treatment of diabetes (7). Recently four large clinical trials found treatment with GLP-1 receptor agonists to improve cardiovascular prognosis in high-risk patients with diabetes (8-11). In contrast, GLP-2 has no insulinotropic effect, but improves intestinal integrity leading to the preservation of gut mucosal structure and gut barrier function with augmentation of nutritional absorption. GLP-2 agonists are clinically used for the treatment of patients with short bowel syndrome (5). Interestingly, GLP-2 has been found to provide cardioprotective effects in isolated ischemic rat hearts (12) but hitherto, the relevance of GLP-2 for the cardiovascular system in patients remains largely unexplored. The

aim of this study was to assess the predictive value of GLP-2 for cardiovascular prognosis in patients with myocardial infarction.

Methods

Study population and follow-up

We recruited 918 patients (mean age ± SD = 67±13 years; men 73%) with acute myocardial infarction (35% STEMI, 65% NSTEMI) at the time of hospital admission. All patients gave written informed consent. In case a patient reported another hospital admission for cardiovascular reasons during the study interval, hospital discharge reports were evaluated for a diagnosis of a cardiovascular event or death. Individual patient risk stratification, treatment and management decisions were left to the discretion of the attending physician. Patients who were lost during follow-up were treated as censored observations in the Cox regression model . For each patient of the cohort the time until the occurrence of an event or until loss-to follow-up was documented. The study follow-up was performed by using hospital records, questionnaires, phone calls and death certificates. The study complies with the Declaration of Helsinki and the locally appointed ethics committee approved the research protocol. The GRACE risk score has been described elsewhere (3). Briefly, the GRACE score is derived from eight variables that are available at hospital admission (age, heart rate, systolic blood pressure, serum creatinine concentration, Killip class, cardiac arrest, presence of ST-segment deviation, and elevated cardiac enzymes/markers). At the moment of hospital admission, the respective values for these variables were entered into the GRACE risk calculator (available at http://www.outcomes-umassmed.org/grace).

Laboratory parameters

Blood samples were drawn in the Chest Pain Unit (CPU) before medical treatment was initiated in the CPU and prior angiography. Serum samples were obtained by venipuncture at the time of admission and stored at -80°C. Serum creatinine, hs-Troponin T (cTnT) and hs-CRP concentrations were measured with the 4th generation Roche Diagnostics assay on an Elecsys 2010 platform. Cardiac Troponin T values ≥0.03 mg/L were regarded as an indicator of myocardial necrosis. NT-proBNP levels were measured by an immunoassay on an Elecsys 2010 instrument (Roche Diagnostics). Total GLP-2 levels were determined by using a commercial ELISA kit (Millipore). Readjudication of the diagnosis myocardial infarction and its type was performed by two independent cardiologists based on all available clinical data including angiography and imaging (including echocardiography, MRI if available). This study is based on a retrospective analysis from frozen serum samples. Additional clinical characteristics/parameters were also assessed retrospectively from the routine clinical documentation system.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or median with lower and upper quartile (Q1 – Q3) in case of skewed data. The skewness of data was examined visually through boxplots and histograms. Categorical outcomes are given as absolute and relative frequencies (%). For descriptive purposes, baseline characteristics and Kaplan-Meier curves are shown in dependence of the median GLP-2 levels (cut-off value 4.4 ng/mL). All further analyses refer to the continuously measured GLP-2 levels at admission.

The association between baseline characteristics and GLP-2 levels (separated by median) was assessed using the chi -square test for nominal characteristics and using an unpaired t-test or a

Mann–Whitney U test in the case of continuous characteristics. Kaplan-Meier cumulative event curves were used to display survival outcomes in dependence of the median GLP-2 value. Median follow-up times were computed separately for the combined triple endpoint (3-P-MACE) and for all-cause mortality by the reverse Kaplan-Meier method. Univariable and multivariable Cox regression models were applied to investigate the association of logarithmized GLP-2 levels and survival outcomes. Skewed data were logarithmically transformed to improve model stability. The proportional hazards assumption was checked graphically using Schoenfeld residuals. Time-dependent ROC curves were estimated to indicate the predictive ability of GLP-2 levels for survival outcomes. The performance of GLP-2 in the entire collective was compared to other clinically relevant markers (serum creatinine, hs-Troponin T, NT-proBNP and hs-CRP) by means of the area under the curve (AUC). We furthermore computed time-dependent ROC curves to illustrate the ability of the GRACE score alone and in combination with GLP-2 to predict cardiovascular outcomes. All ROC curves were estimated using the inverse probability of censoring weighting (IPWC) method of Cumulative/Dynamic time-dependent ROC curves by Uno et al. (13). The level of significance was set at 5%. No adjustments were made for multiple comparisons. Statistical analyses were performed using SAS software version 9.4 (PROC PHREG; SAS Institute, Cary NC, USA) and R, version 3.5.1 (14), packages timeROC(15) and survival (16).

Results

Admission GLP-2 levels in patients with acute myocardial infarction

The study population, clinical and laboratory baseline characteristics and biomarker concentrations according to GLP-2 levels (dichotomized by the median with 4.4 ng/mL as cut-off value) are shown in Table 1. GLP-2 levels displayed a statistically significant correlation with cardiovascular risk factors (including smoking and diabetes mellitus), pre-existing cardiovascular disease (myocardial

infarction, coronary intervention and coronary bypass surgery) and markers of heart failure and inflammation, as indicated by the levels of NT-proBNP and hs-CRP. Furthermore, GLP-2 levels were positively associated with the GRACE risk score. Most of the patients at the lowest estimated cardiovascular risk based on the GRACE risk score after myocardial infarction (low GRACE score) had low GLP-2 levels (< 4.4 ng/mL), while the majority of patients at a high GRACE risk score showed high GLP-2 levels (≥ 4.4 ng/mL). Admission GLP-2 levels were not significantly associated with hypertension, hypercholesterolemia, family history of cardiovascular disease and hs-Troponin T values (Table 1).

GLP-2 levels are associated with adverse cardiovascular outcome and mortality

Among 918 patients enrolled, the combined endpoint of first occurrence of non-fatal myocardial infarction or non-fatal stroke or cardiovascular death (3-P-MACE) occurred in 61 patients (7 %) (28 patients with non-fatal myocardial infarction, 4 patients with non-fatal stroke and 29 patients with cardiovascular death) while 67 patients (7%) died during a median follow-up of 311 days (Table 2).

Kaplan-Meier survival plots (separated by the median of GLP-2 with a cut-off value of 4.4 ng/mL) and univariable cox regression analyses (based on logarithmized continuous GLP-2 levels) found higher GLP-2 values to be associated with a significantly increased risk for the combined triple endpoint (3-P-MACE) of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death (HR of logarithmized GLP-2 values: 2.87; 95% CI: 1.75 - 4.68; p<.0001) as well as cardiovascular death (HR of logarithmized GLP-2 values: 3.90; 95% CI: 1.93 - 7.87; p=0.0001) and all-cause mortality (HR of logarithmized GLP-2 values: 2.75; 95% CI: 1.72 - 4.40; p<.0001) as shown in Figure 1 and Table 2. Multivariable Cox regression analyses based on continuous GLP-2 levels are shown in Table 3 and Table S1. Adjustment for age and sex (multivariable model 1) and further

adjustment for smoking, hypertension, hypercholesterolemia, diabetes and family history of cardiovascular disease (multivariable model 2) did not affect the significant association of GLP-2 and the increased risk for the combined triple endpoint (3-P-MACE). We extended model 2 to further adjustment for hs-Troponin T, NT-proBNP and hs-CRP in an additional multivariable Cox regression analysis (multivariable model 3). In this model the association between GLP-2 and the combined triple endpoint (3-P-MACE) remained significant with a p-value of 0.0053 (HR: 2.96; 95% CI: 1.38 - 6.34) (Table 3).

In the multivariable Cox regression model in Table S1 we adjusted untargeted for all baseline variables from Table 1 with a p-value <0.25 in the univariable Cox regression analysis (*1. combined triple endpoint (3P-MACE):* age, hypertension, hypercholesterolemia, diabetes mellitus, family history of cardiovascular disease, myocardial infarction, PTCA, CABG, myocardial infarction subtype (NSTEMI/STEMI) and logarithmized values of serum creatinine, NT-proBNP and hs-CRP; *2. all-cause mortality:* age, hypertension, diabetes mellitus, family history of cardiovascular disease, myocardial infarction, myocardial infarction subtype (NSTEMI/STEMI) and logarithmized values of serum creatinine, hs-Troponin T, NT-proBNP and hs-CRP). In this model the association between GLP-2 levels and the combined triple endpoint (3-P-MACE) still showed a non-significant trend (HR: 1.76; 95% CI: 0.75 - 4.15; p=0.1960) (Table S1).

Time-dependent receiver operating characteristic curve analyses illustrated that GLP-2 is a strong indicator for cardiovascular prognosis in patients with myocardial infarction and comparable to established biomarkers (area under the receiver-operating characteristic curve of the combined triple endpoint (3-P-MACE) at 6 months; GLP-2: 0.72; hs-Troponin T: 0.56; NT-proBNP: 0.70; hs-CRP: 0.62; serum creatinine: 0.75) (Figures S1 and S2). Adjustment of the GRACE risk estimate by GLP-2 increased the area under the receiver-operating characteristic curve for the

combined triple endpoint after 1 month from 0.76 (GRACE) to 0.82 (GRACE + GLP-2) and after 6 months from 0.70 (GRACE) to 0.76 (GRACE + GLP-2).

Discussion

In this study we identified the gut-derived hormone GLP-2 to be strongly associated with cardiovascular events (3-P MACE) and death in patients with acute myocardial infarction, which remained significant in complex statistical models including the adjustment for age, sex, cardiovascular risk factors and well-established risk indicators (hs-Troponin T, NT-proBNP and hs-CRP). This suggests a yet unappreciated crosstalk between the cardiovascular system and the gut. Surprisingly we found GLP-2 to have comparable prognostic power as established biomarkers like hs-Troponin T or NT-proBNP which are directly released from the injured heart. In contrast, the driving force for gut-derived GLP-2 secretion currently remains unknown in this context but may involve an inter-organ cross-talk between the infarcted myocardium and the gut. Relevant factors involved might include inflammatory, metabolic and/or hemodynamic mediators among others which will require additional investigations. Relevance of inflammatory parameters is suggested by co-manifestation of high GLP-2 and hs-CRP levels in the same patients in our cohort. GLP-2 is known to be co-secreted with GLP-1 from enteroendocrine L-cells of the gut following food intake (4,5). As GLP-1 is also released in response to inflammatory stimuli, this might hold similar relevance for GLP-2. We have recently found circulating GLP-1 levels to be associated with cardiovascular risk in patients with acute coronary syndrome (17).

GLP-1 is known to induce postprandial insulin secretion and glucose lowering and is clinically used for the treatment of patients with diabetes mellitus (as GLP-1 receptor agonists) (4). Beyond its glucoregulatory function GLP-1 exerts pleiotropic protective effects in various organs including

vaso- and cardioprotection in terms of cardiovascular disease (4,18-21). Recently four large clinical trials could show that treatment with GLP-1 receptor agonists improve cardiovascular prognosis in high-risk patients with diabetes (8-11).

In contrast to GLP-1, GLP-2 has no direct effect on pancreatic insulin secretion and regulation of blood glucose and its role for cardiovascular disease is unknown (5). Physiologically, GLP-2 acts as an intestinal growth factor with important functional relevance for the preservation of gut mucosal structure, gut barrier function and nutritional absorption (22-24). Thus, the GLP-2 receptor agonist teduglutide is clinically established for the treatment of short bowel syndrome (induced by surgical gut resection) (25). The relevance of intestinal integrity and gut barrier function for patients with acute myocardial infarction is incompletely understood. Impairment of myocardial function as a consequence of acute ischemia can lead to visceral congestion, mucosal lesion and subsequently to the translocation of bacteria and microbiota-derived mediators (26,27). Release of GLP-2 might therefore provide a protective counter regulatory stimulus aiming to preserve gut integrity under stressed conditions. The strong prognostic capacity of this system suggests disease modulating relevance. Patients with high GLP-2 levels might thereby face the strongest prevalence of intestinal congestion, which would explain their worse prognosis. Additional studies investigating the regulation of GLP-2 in patients with heart failure under consideration of left and right ventricular function, hemodynamics and fluid status will help to better understand the relevance of intestinal congestion as a relevant factor for the release of GLP-2. The cross-sectional design of the study is not sufficient to draw any conclusions on causality.

Future preclinical studies and human clinical trials are needed to foster our understanding of the gut - heart crosstalk thereby characterizing the role of GLP-2 in detail for cardiovascular disease including atherosclerosis, myocardial infarction and heart failure.

As shown before, biomarkers including hs-Troponin T, NT-proBNP and hsCRP as well as risk scores like the GRACE score are powerful tools for risk stratification in patients with myocardial infarction. The combination of these established biomarkers with the GRACE score can enhance risk discrimination (28). We found GLP-2 levels to be comparable to these established biomarkers in terms of cardiovascular risk prediction in patients with acute myocardial infarction. Thus circulating GLP-2 levels used alone or in combination with other biomarkers or risk scores might improve risk stratification and clinical decision making in patients with acute coronary syndrome. Consequently adjustment of the GRACE risk estimate by addition of GLP-2 increased the area under the receiver-operating characteristic curve indicating enhanced risk discrimination.

Study limitations:

This study has several strengths and limitations. We observe a strong association of GLP-2 levels with cardiovascular outcome and mortality in patients with myocardial infarction, which remained significant in complex statistical models and proved to be comparable to established biomarkers. However, this observation does not imply causality, which cannot be assessed in the performed observational cross sectional study design with limited duration and limited number of events. Additional mechanistic and larger prospective studies with repeated GLP-2 measurements are necessary to further evaluate clinical applicability of GLP-2 as a novel biomarker and potential therapeutical target in patients with acute myocardial infarction.

In conclusion, we identified the gut-derived incretin hormone GLP-2 as a strong biomarker for cardiovascular outcome and mortality which proved to be comparable to the established risk markers hs-CRP, hs-Troponin T, and NT-proBNP. Furthermore, admission GLP-2 levels added additional value to the GRACE risk score. Future studies are needed to investigate whether GLP-

2 could improve therapeutic decision making in NSTEMI/STEMI patients and be identified as a potential therapeutical target for cardiovascular disease.

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Figure legends:

Figure 1: GLP-2 levels are associated with adverse cardiovascular prognosis. (a) Kaplan-Meier cumulative event curves for the 3-P-MACE endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) with patients separated by the median value of GLP-2. **(b)** Kaplan-Meier cumulative event curves for all-cause mortality with patients separated by the median value of GLP-2.

Supplemental figure legends:

Figure S1: Time-dependent ROC-curves for the 3-P-MACE endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in all patients. The diagnostic ability of GLP-2 is compared to serum creatinine, hs-Troponin T, NT-proBNP and hs-CRP at 1 week, 2 weeks, 1 month and 6 months.

Figure S2: Time-dependent ROC-curves for all-cause mortality in all patients. The diagnostic ability of GLP-2 is compared to serum creatinine, hs-Troponin T, NT-proBNP and hs-CRP at 1 week, 2 weeks, 1 month and 6 months.

Figure S3: Time-dependent ROC-curves for the 3-P-MACE endpoint (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in all patients. The diagnostic ability of GLP-2, and the GRACE risk score alone and in combination is compared at 1 month and 6 months.

Table 1 Baseline characteristics

Characteristics	All patients (n=918)	Median of GLP-2 (ng/mL) [a]		p-value [b]
		< 4.4 (n=436)	≥ 4.4 (n=438)	
Demographics				
Age, years	66.9 ± 12.7	64.6 ± 12.3	69.4 ± 12.5	< 0.0001
Sex (male)	672 (73.20%)	311 (71.33%)	332 (75.80%)	0.1341
Cardiovascular risk factors				
Smoker	498 (59.36%)	265 (65.76%)	210 (53.16%)	0.0003
Hypertension	664 (75.37%)	304 (73.25%)	332 (78.49%)	0.0765
Hypercholesterolemia	452 (58.17%)	200 (55.56%)	233 (61.15%)	0.1222
Diabetes mellitus	223 (25.40%)	75 (17.99%)	138 (33.09%)	< 0.0001
GRACE score	149.1 ± 31.2	142.8 ± 30.8	155.8 ± 30.5	< 0.0001
GRACE category				
Low, ≤108	67 (7.30%)	43 (9.86%)	20 (4.57%)	
Medium, 108 - 140	314 (34.20%)	176 (40.37%)	123 (28.08%)	
High, >140	537 (58.50%)	217 (49.77%)	295 (67.35%)	
Previous cardiovascular disease				
Family history of CVD	305 (40.24%)	144 (39.78%)	143 (39.83%)	0.9882
Myocardial infarction	218 (24.86%)	82 (19.71%)	129 (30.64%)	0.0003
PTCA	244 (27.92%)	94 (22.60%)	142 (34.13%)	0.0002
CABG	92 (10.40%)	34 (8.11%)	54 (12.74%)	0.0282
Myocardial infarction subtype				
NSTEMI	597 (65.03%)	277 (63.53%)	299 (68.26%)	0.1400
STEMI	321 (34.97%)	159 (36.47%)	139 (31.74%)	
Risk markers at baseline				
hs-Troponin T (ng/mL)	146.3 (46.45 - 492.6)	130.1 (46 - 424.3)	165.4 (48 - 544.9)	0.1351
NT-proBNP (pg/mL)	663.6 (184.5 - 2271)	449.1 (151.2 - 1404)	1121 (287.4 - 3541)	< 0.0001
hs-CRP (mg/L)	4.28 (1.70 - 15.26)	3.5 (1.4 - 9)	5.5 (2.3 - 31)	< 0.0001
Serum creatinine (mg/dL)	0.93 (0.78 - 1.15)	0.8 (0.7 - 1.0)	1.0 (0.9 - 1.3)	< 0.0001

Continuous variables are expressed as mean ± SD or median (Q1 – Q3) in case of skewed data. Categorical variables are shown as absolute and relative frequencies.

[a] Forty-four patients with missing GLP-2 measurements.

[b] p-value of an unpaired t-test (Mann-Whitney U test) in the case of (skewed) continuous characteristics or p-value of the chi-square test in the case of nominal characteristics.

Table 2 Univariable Cox regression for log(GLP-2)

Survival Outcome	No. events	Estimated hazard ratio (95% CI)	p-value
3-P-MACE endpoint	61	2.865 (1.754, 4.680)	<.0001
All-cause mortality	67	2.753 (1.723, 4.398)	<.0001
Cardiovascular mortality	29	3.899 (1.933, 7.866)	0.0001
Non-fatal myocardial infarction	28	1.830 (0.891, 3.761)	0.1000
Non-fatal stroke	4	5.730 (0.831, 39.498)	0.0763

Table 3 Multivariable Cox regression for log(GLP-2)

	Model 1		Model 2		Model 3	
Survival Outcome	Estimated hazard ratio (95% CI)	p-value	Estimated hazard ratio (95% CI)	p-value	Estimated hazard ratio (95% CI)	p-value
3-P-MACE endpoint	2.552 (1.537, 4.235)	0.0003	2.663 (1.333, 5.319)	0.0055	2.958 (1.381, 6.338)	0.0053
All-cause mortality	2.177 (1.342, 3.534)	0.0016	1.821 (0.938, 3.535)	0.0767	1.875 (0.929, 3.785)	0.0792

Model 1 was adjusted for age and sex.
Model 2 was adjusted for age, sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, family history of cardiovascular disease.
Model 3 was adjusted for age, sex, smoking, hypertension, hypercholesterolemia, diabetes mellitus, family history of cardiovascular disease and logarithmized values of hs-Troponin T, NT-proBNP and hs-CRP.

Combined triple endpoint (3-P-MACE)

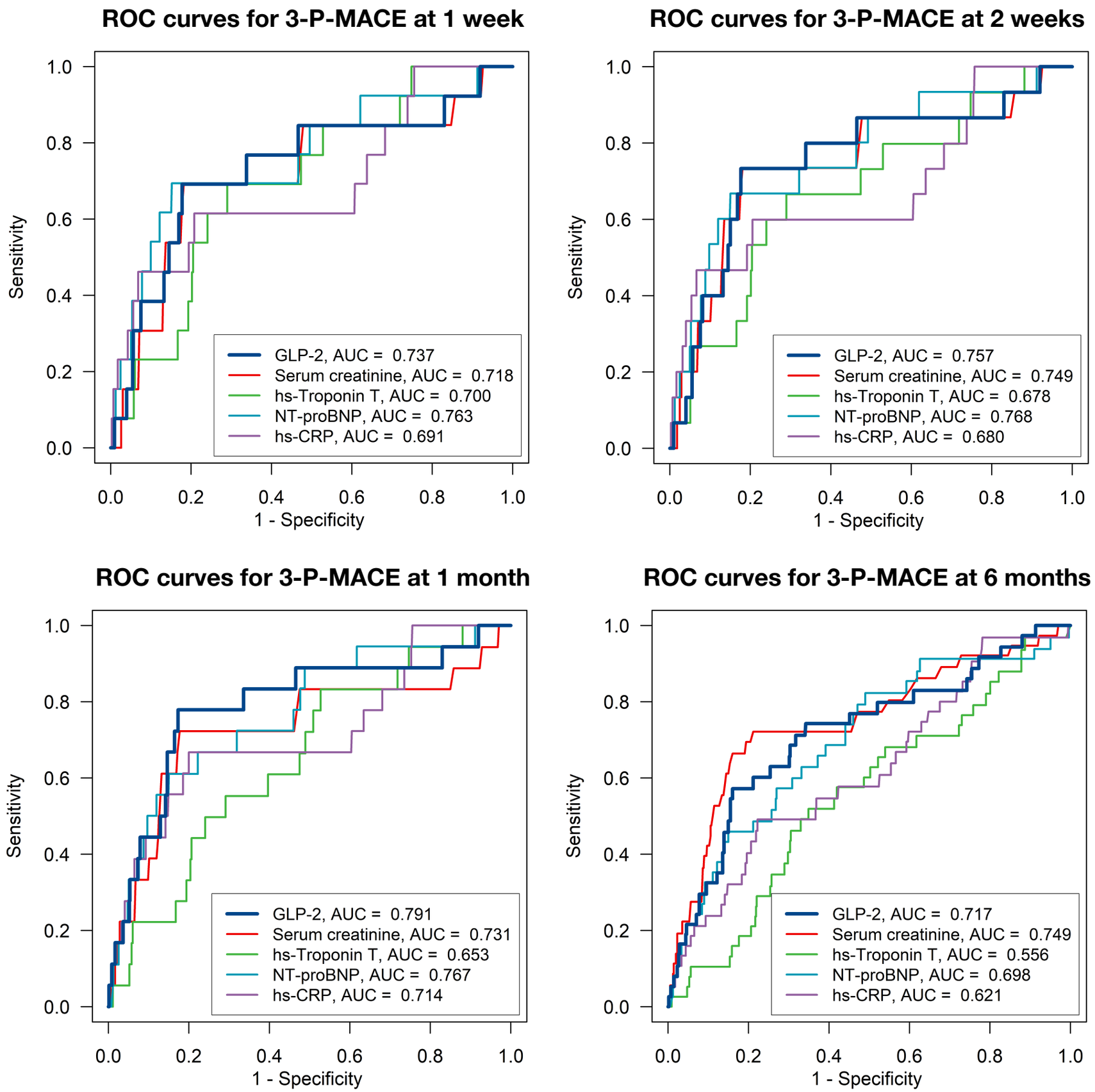

Figure S1

All-cause mortality

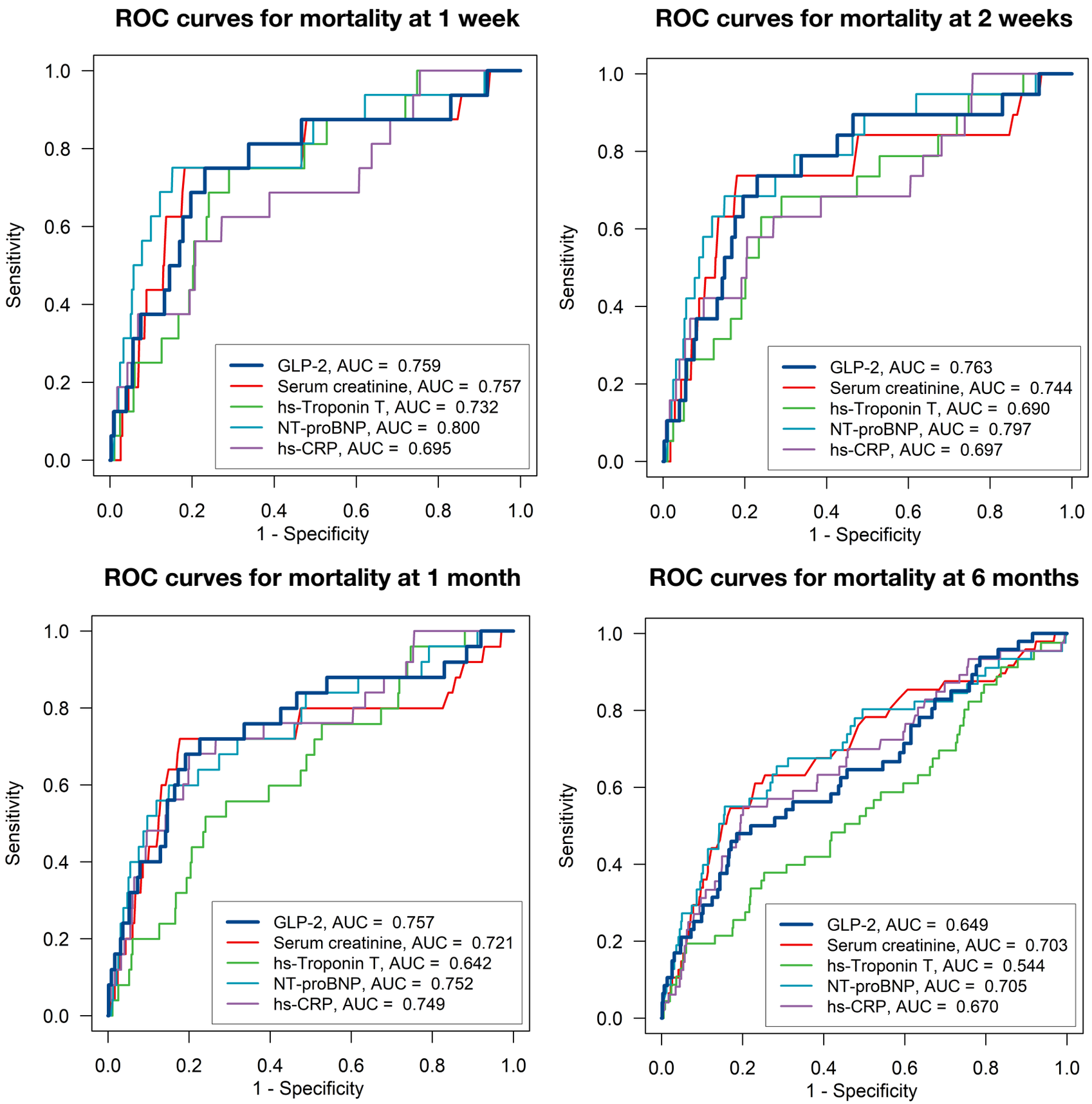

Figure S2

GRACE - Combined triple endpoint (3-P-MACE)

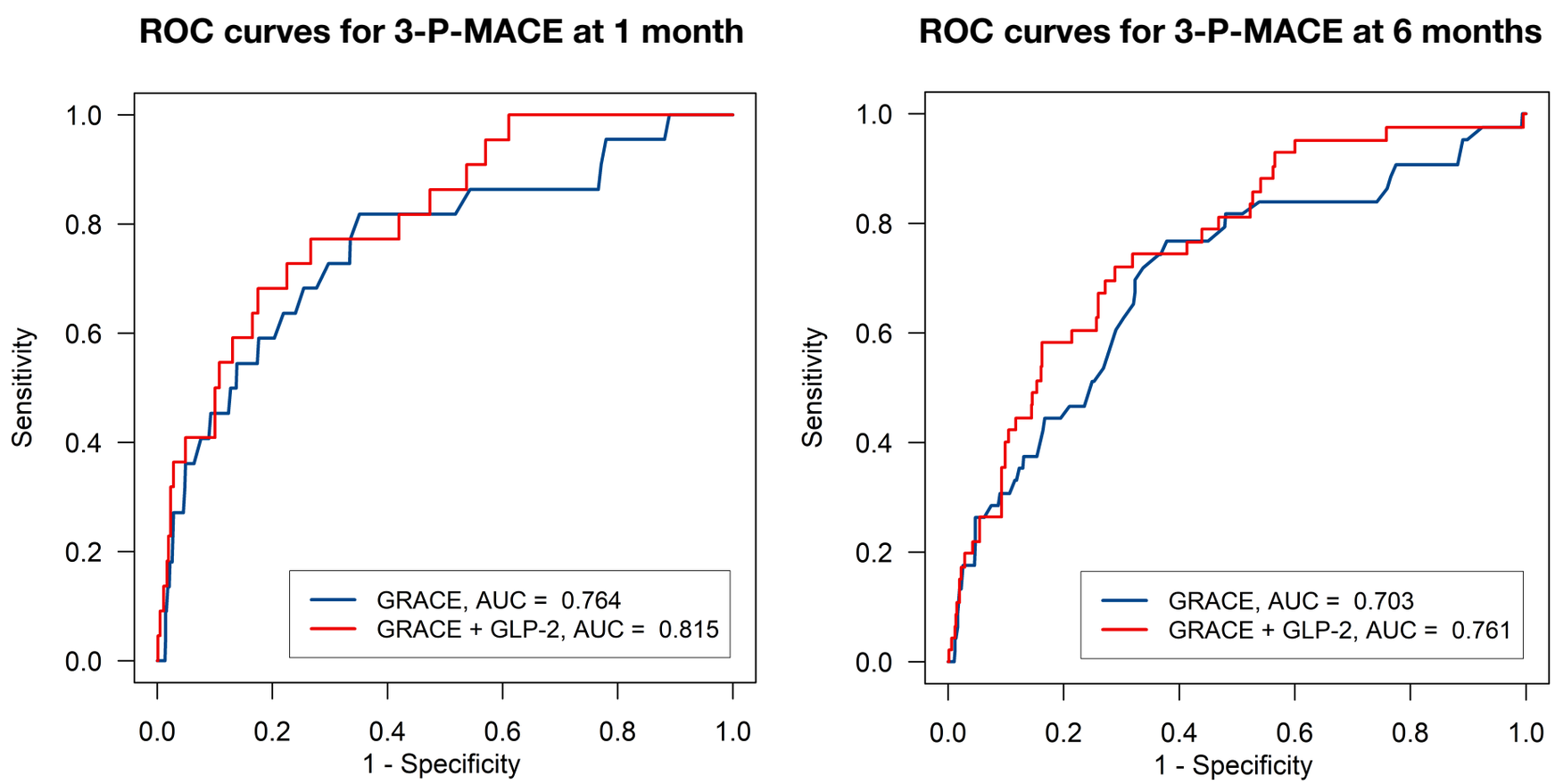

Figure S3

Table S1 Multivariable Cox regression for log(GLP-2) after variable selection.

Survival Outcome	Estimated hazard ratio (95% CI)	p-value
3-P-MACE endpoint	1.760 (0.747, 4.147)	0.1960
All-cause mortality	1.045 (0.508, 2.151)	0.9044

The multivariable model was adjusted for all baseline variables from Table 1 (except for GRACE-Score, GRACE–Category) with a p-value < 0.25 in the univariable cox regression analysis for the respective survival outcome. For the 3-P-MACE endpoint, these were age, hypertension, hypercholesterolemia, diabetes mellitus, family history of cardiovascular disease, myocardial infarction, PTCA, CABG, myocardial infarction subtype (NSTEMI/STEMI) and logarithmized values of serum creatinine, NT-proBNP and hs-CRP. For all-cause mortality, these were age, hypertension, diabetes mellitus, family history of cardiovascular disease, myocardial infarction, myocardial infarction subtype (NSTEMI/STEMI) and logarithmized values of serum creatinine, hs-Troponin T, NT-proBNP and hs-CRP.

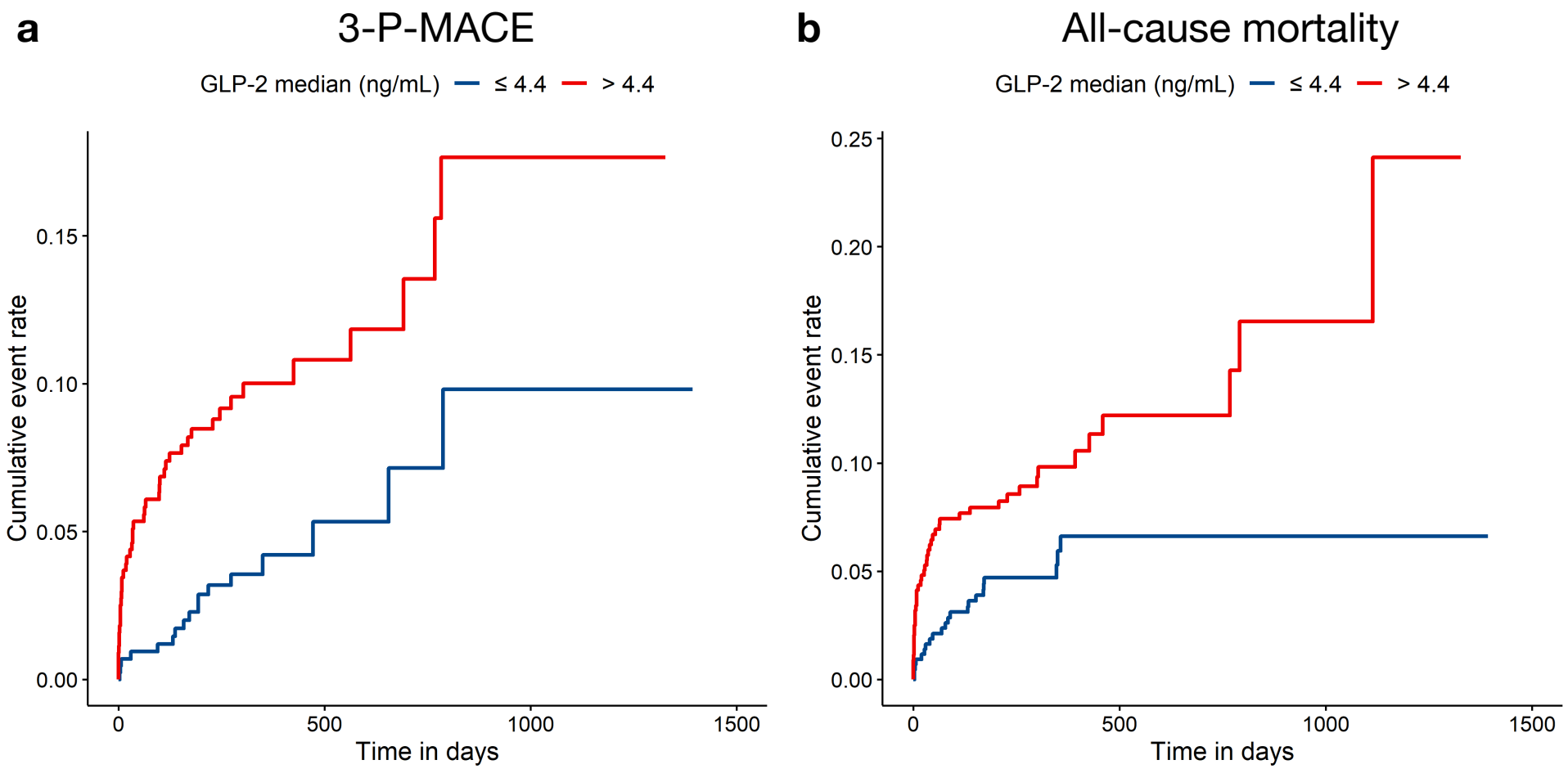
a
3-P-MACE
GLP-2 median (ng/mL)
≤ 4.4
> 4.4
Cumulative event rate
0.00
0.05
0.10
0.15
0
500
1000
1500
Time in days
b
All-cause mortality
GLP-2 median (ng/mL)
≤ 4.4
> 4.4
Cumulative event rate
0.00
0.05
0.10
0.15
0.20
0.25
0
500
1000
1500
Time in days

Figure 1