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C-terminal fragment of IGFBP-4 is independently associated with mortality in patients hospitalized due to acute heart failure

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Introduction

Insulin-like growth factor binding protein-4 (IGFBP-4) fragments are products of proteolytic cleavage mediated by pregnancy-associated plasma protein A (PAPP-A, Fig.1). IGFBP-4 fragments have been proposed as biomarkers of major adverse cardiovascular events risk in patients with acute coronary syndrome. In addition, IGFBP-4 fragments have been shown to predict cardiac and all-cause mortality in patients with type 1 diabetes.

Recently carboxy-terminal fragment of IGFBP-4 (CT-IGFBP-4) was shown to provide incremental prognostic information on cardiovascular events and mortality in patients with ST-elevation myocardial infarction. As progressive heart failure (HF) is a major cause of morbidity and mortality following acute myocardial infarction, we suggest that CT-IGFBP-4 could also be utilized as a biomarker for prognosis of HF outcomes.

The purpose of the study: To evaluate the prognostic value of CT-IGFBP-4 for all-cause mortality in emergency patients with acute HF.

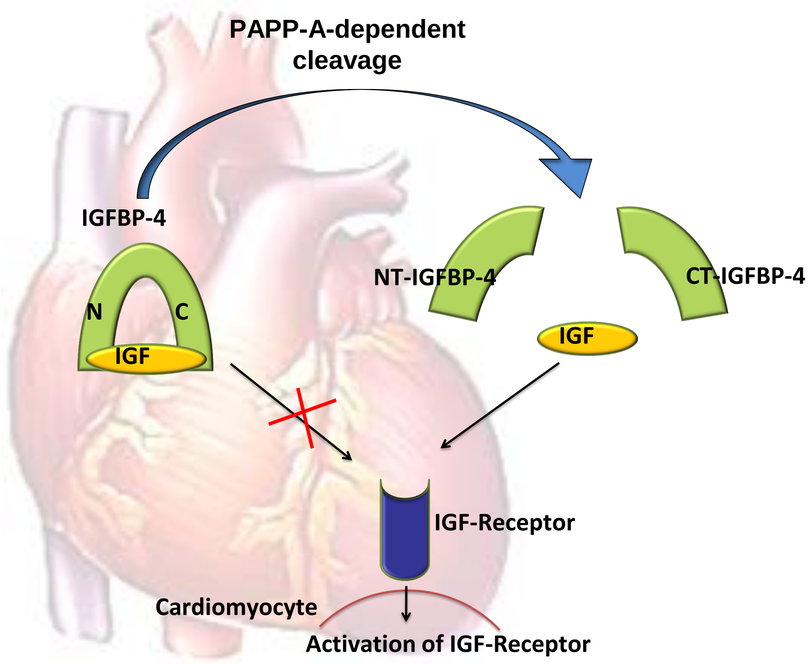

FIGURE 1. The **scheme of PAPP-A-dependent cleavage of IGFBP-4.** The cleavage leads to two proteolytic fragments formation. The fragments are released in the circulation.

Materials and Methods

CT-IGFBP-4 was measured at admission in Li-heparin plasma samples of 156 emergency patients with acute HF. A specific immunoassay utilizing monoclonal antibodies recognizing proteolytic neo-epitopes of CTIGFBP-4 was used. Cross-reaction of the immunoassay with intact IGFBP-4 was less than 2%. One year all-cause mortality was recorded. ROC curve and Cox proportional hazard ratio analysis were performed to evaluate prognostic value of CT-IGFBP-4.

Immunoassays: Monoclonal antibodies (mAbs) IBP163, IBP182 conjugated with horseradish peroxidase (HRP), recombinant human CT-IGFBP-4 calibrator were from HyTest Ltd. In the sandwich immunoassay for CT-IGFBP-4 measurement, MAb IBP163 (specific to proteolytic neoepitope of CT-IGFBP-4) was used as a capture antibody and MAb IBP182HRP (recognizing both full-length IGFBP-4 and CT- IGFBP-4) was used as a detection antibody. The sandwich immunoassay IBP163-IBP182HRP has <2% cross-reactivity to IGFBP-4 and NT-IGFBP-4; linear range 0.3–6.0 µg/L; analytical limit of detection 0.15 µg/L; within-assay imprecision CV <6.0%; total imprecision CV <9.7%. Recovery of the assay was 82%, 86%, and 87% for 300, 100, and 30 µg/L CT-IGFBP-4, respectively.

Patients: 156 patients were recruited. At baseline, demographic and past medical history data were collected. Lithium-heparin plasma samples were taken on admission. Patients were followed from the day of discharge for one year and mortality data were obtained from Finnish National Population Registry. The endpoint of the study was all-cause mortality.

Results

During one year of follow-up 52 (33.3%) patients died. 52% of deaths (27 of 52 cases) occurred during the first month of observation. The concentration range of CT-IGFBP-4 of the study cohort was 9.4–1121 ng/mL. CT-IGFBP-4 was significantly elevated in non-survivors at both one month (p=0.0003) and one year (p=0.0018) periods, Fig. 2.

CT-IGFBP-4 predicted all-cause mortality at one month and one year follow-up periods: the areas under the ROC curves were **0.753** and **0.727**, respectively, Fig. 3. The optimal cut-off value of CT-IGFBP-4 for predicting all-cause mortality was 92.5 ng/mL that corresponded to 81% sensitivity and 58% specificity. On the basis of defined cut-off values Kaplan-Meier analysis of survival was performed, Fig. 4.

Also the Cox hazard analysis revealed CT-IGFBP-4 as a predictive factor of one month and one year mortality. The unadjusted hazard ratio (HR) for CT-IGFBP-4≥92.5 ng/mL for one month and for one year of follow-up are presented at Table. 1. After adjustment for multiple clinical and echocardiographic variables CT-IGFBP-4 was an independent risk biomarker for one month and one year mortality.

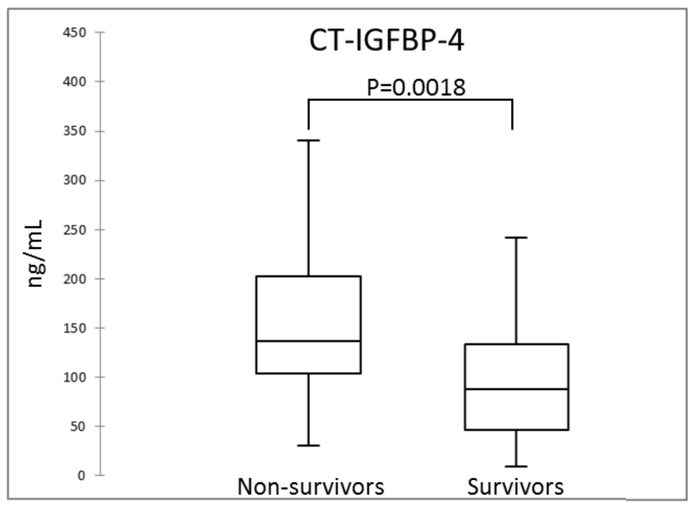

FIGURE 2. CT-IGFBP-4 concentrations at admission in 1-year survivors and non-survivors with acute HF. Central line represents median, box represents interquartile range, and whiskers represent fifth and 95th percentile.

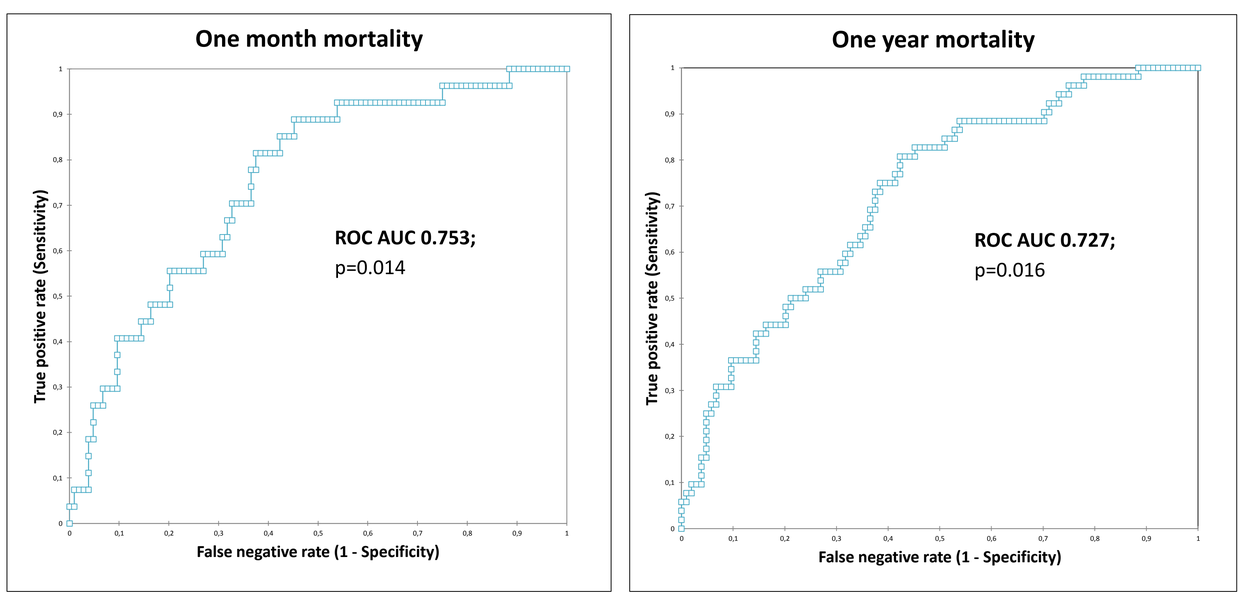

FIGURE 3. ROC analysis of CT-IGFBP-4 prognostic value.

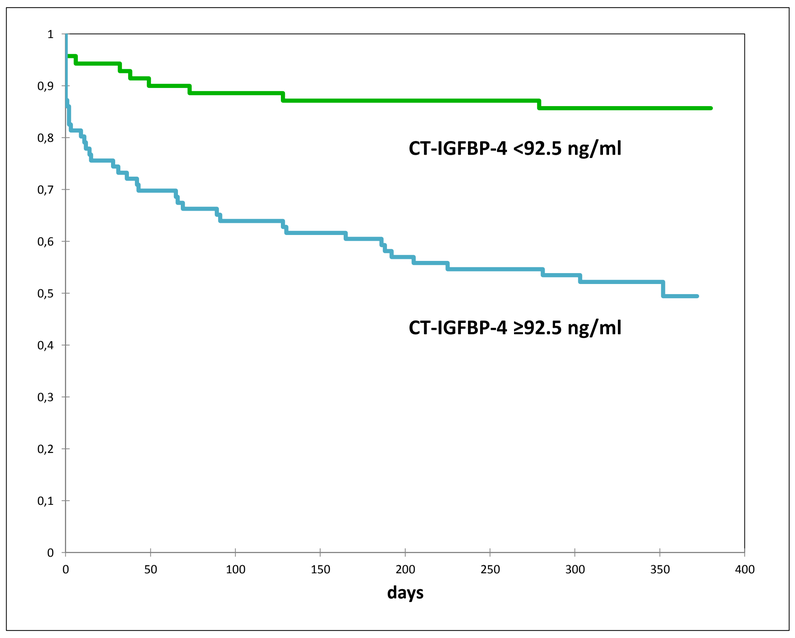

FIGURE 4. Kaplan-Meier survival curve for patients according CT-IGFBP-4 levels.

	One month mortality		*One year mortality*	
	Hazard ratio, Univariate	**Hazard ratio, Multivariate***	**Hazard ratio, Univariate**	**Hazard ratio, Multivariate***
CT-IGFBP-4≥92.5 ng/ml	**6.15 (2.12-17.79; p=0.0008)**	**5.39 (2.11-13.76; p=0.0004)**	**4.20 (2.11-8.39; p< 0.0001)**	**3.26 (1.63-6.51; p=0.0008)**

TABLE 1. Adjusted HR (95% CI) for all-cause mortality within one year and one month follow-up by NTproBNP, CT-IGFBP-4, and hsCRP levels. *- multivariate analysis included age, sex, early diagnosed HF, coronary artery disease, hypertension, chronic kidney failure, history of diabetes, hypercholesterolaemia, EF ≥ 45, heart rate, Hb, plasma sodium, and other clinical variables.

Conclusions

CT-IGFBP-4 independently predicts all-cause mortality in patients with acute HF at one month and one year follow-up.

The ability of CT-IGFBP-4 to predict mortality in patients with acute heart failure suggests that PAPP-A/IGFBP-4 can be involved in the pathogenesis of HF.

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