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Prognostic value of alkaline phosphatase in patients with acute coronary syndromes

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ABSTRACT

Objectives: The objective of the study was to investigate the association between alkaline phosphatase (AP) activity and prognosis of patients with acute coronary syndrome (ACS).

Design and methods: The study included 2134 patients with ACS undergoing percutaneous coronary intervention. All included patients had baseline AP measurements available. The receiver operating characteristic curve analysis showed that the best cut-off of AP for mortality prediction was 98.0 U/L. Using this cut-off, patients were divided into two groups: a group with AP > 98.0 U/L (n = 493) and a group with AP ≤ 98.0 U/L (n = 1641). The primary endpoint was 3-year mortality.

Results: Overall, there were 229 deaths over the follow-up: 90 deaths among patients with an AP > 98.0 U/L and 139 deaths among patients with an AP ≤ 98.0 U/L (Kaplan-Meier estimates of 3-year total mortality, 19.5% and 9.3%, respectively; adjusted hazard ratio [HR] = 1.37, 95% confidence interval [CI] 1.10–1.70, P = 0.004 for each unit higher log AP). Cardiac deaths occurred in 157 patients: 66 deaths among patients with an AP > 98.0 U/L and 91 deaths among patients with an AP ≤ 98.0 U/L (Kaplan-Meier estimates of 3-year cardiac mortality, 14.3% and 6.0%, respectively; adjusted HR = 1.32 [1.02–1.70], P = 0.033, for each unit higher log AP). The C-statistic of the multivariable model with baseline variables was 0.836 [0.807–0.866] and it increased to 0.842 [0.814–0.874] after inclusion of AP (P = 0.045).

Conclusions: In patients presenting with an ACS and treated with percutaneous coronary intervention, elevated AP activity is associated with increased risk of subsequent mortality.

1. Introduction

Although the risk prediction for future adverse events in patients presenting with acute coronary syndromes (ACS) has been greatly improved, research is still needed to identify reliable biomarkers that can predict the patient's prognosis following an ACS. Alkaline phosphatase (AP) – an enzyme involved in bone mineralization – has recently garnered interest for its association with cardiovascular disease or as a risk marker for mortality in population-based cohorts [1] or patients with coronary artery disease (CAD) [1,2]. The rationale for investigating AP in patients with ACS stems from the association of AP with a number of well-defined factors predisposing to ACS, including conventional cardiovascular risk factors, systemic inflammation and metabolic syndrome [3–5], vitamin D deficiency [6], coronary artery calcium [2] and liver disease [7]. All these factors have been found to predispose to atherosclerotic plaque instability or to predict prognosis in patients with ACS. Despite this evidence, no study so far has investigated the association of AP with mortality in patients with ACS. The aim of this study was to assess the association between AP and prognosis in patients presenting with an ACS.

2. Methods

2.1. Study patients

We investigated a retrospective cohort of 2134 consecutive patients investigated at 2 university hospitals in Munich, Germany (between 2000 and 2011) who presented with ACS and were treated with percutaneous coronary intervention (PCI). Characteristics of the source sample were reported in a prior publication from our institution [8]. To

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be included in the study, patients had to have an ACS diagnosed by clinical and angiographic criteria and baseline AP measurements available. Patients with acute infections, malignancies, known liver or bone disease, excessive alcohol consumption, chronic kidney failure with dialysis on admission or cardiogenic shock were excluded. Patients with elevated aminotransferase levels (alanine aminotransferase activity > 50 U/L) were also excluded even in the absence of clinical liver disease. Overall, there were 846 patients with unstable angina, 346 patients with non-ST-segment elevation myocardial infarction (NSTEMI) and 942 patients with STEMI. Unstable angina was diagnosed according to the Braunwald's criteria [9]. NSTEMI was diagnosed in the presence of clinical and electrocardiographic criteria similar to those of unstable angina plus elevation of cardiac troponin T exceeding the upper limit of normal. Conventional troponin T assay (upper limit of normal 0.03 μg/L) was used until October 2009 and high-sensitivity cardiac troponin T assay (upper limit of normal 0.014 μg/L) was used thereafter. STEMI was diagnosed in the presence of chest pain lasting > 20 min associated with ST-segment elevation of ≥ 0.1 mV in ≥ 2 limb leads or ≥ 0.2 mV in ≥ 2 contiguous precordial leads or complete left bundle branch block of new onset. The study conforms to the Declaration of Helsinki.

2.2. Definitions and therapy

Arterial hypertension, hypercholesterolemia, diabetes and smoking are defined according to the standard criteria. CAD was confirmed by coronary angiography in all patients. Angiographic criteria included documentation of coronary stenosis ≥ 50% lumen narrowing in at least 1 of the main coronary arteries or culprit lesions, defined as an acute occlusion or intraluminal filling defects [or thrombus], ulcerated plaques with contrast-filled pocket protruding into plaque with or without delayed contrast wash-out, extra-luminal contrast, dissection or intraluminal flaps [10]. Left ventricular ejection fraction was calculated using the area length method on left ventricular angiograms. Coronary calcium was graded angiographically as follows: none, no radiopacity; mild, faint radiopacities noted during the cardiac cycles; moderate, dense radioapcities noted only during the cardiac cycle; severe, dense radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen [11]. All angiographic analyses were performed in the core angiographic laboratory by personnel blinded to patients' clinical data. Body mass index was calculated using the patient's weight and height measured during the hospital stay. Estimated glomerular filtration rate was calculated using the Cockcroft–Gault equation.

Coronary angiography and PCI were performed according to the standard practice. Patients were pre-treated with clopidogrel (loading dose 600 mg) and aspirin (325–500 mg) and unfractionated heparin or bivalirudin were used for peri-procedural anticoagulation. Chronic antithrombotic therapy at discharge included aspirin (80–325 mg/day continuously) and a P2Y12 receptor inhibitor (usually clopidogrel 75 mg/day) for at least 12 months. Other drugs were prescribed at the discretion of the patient's treating physician.

2.3. Laboratory measurements

Blood for AP measurement was taken on admission (before angiography). Activity of AP was measured in lithium-heparin plasma samples by a standardized, colorimetric enzyme-assay on the automatized cobas c 501® system from Roche Diagnostics GmbH (Mannheim, Germany) according to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method [12]. The imprecision of the method is indicated by coefficients of variation between 0.9% and 2.4% for between-days comparison using assay controls and human serum samples, as provided by manufacturer. Measuring range of the method is 5–1200 U/L. Reference ranges are 40–130 U/L for adult men and 35–105 U/L for adult women. Sensitive C-reactive protein (CRP) was measured using a fully automated latex-enhanced immunoturbidometric assay on a Cobas Integra analyser (Roche Diagnostics, Mannheim, Germany). The assay has an analytical sensitivity of 0.085 mg/L and a measuring range of up to 160 mg/L. The upper limit of the reference range in healthy adults is 5 mg/L. Serum creatinine was measured using a kinetic colorimetric assay based on the compensated Jaffe method. Other laboratory measurements were performed using standard methods. Laboratory personnel who performed laboratory measurements were unaware of the patients' clinical data.

2.4. Study endpoints

The primary endpoint was 3-year total mortality. Secondary endpoits included: cardiac mortality, nonfatal myocardial infarction or stroke. Data on deaths were obtained from the hospital records, death certificates, insurance companies and registration of address office or phone contact with the patient's relatives or referring physician. Cardiac deaths were defined according to the Academic Research Consortium criteria [13]. Nonfatal myocardial infarction was diagnosed in the presence of clinical symptoms associated with electrocardiographic changes (new abnormal Q waves in ≥ 2 adjacent limb leads or ≥ 2 contiguous precordial leads) or biomarker elevation (creatine kinase myocardial band activity elevation > 2 times [> 3 times within the first 48 h after a PCI procedure] the upper limit of normal). Stroke was diagnosed in the presence of a focal deficit lasting for > 24 h that was confirmed by brain imaging tests.

The follow-up included a telephone interview at 1 month, a clinic visit at 6 months and yearly telephone interviews thereafter. The follow-up information was collected and the events were adjudicated by personnel unaware of laboratory or clinical data.

2.5. Statistical analysis

Data are presented as mean with standard deviation, median with 25th to 75th percentiles or counts and proportions (%). The normality of data distribution was assessed using the one-sample Kolmogorov-Smirnov test. Discrete data are presented as counts and proportions (%) or Kaplan-Meier estimates (survival data). Continuous data were compared with the *t*-test or Wilcoxon rank-sum test depending on the distribution pattern. Discrete data were compared with the chi-square test. The receiver operating characteristic curve analysis was performed to define the best AP cutoff regarding prediction of mortality. Survival analysis was performed using the Kaplan-Meier method and the differences in survival were compared using the univariable Cox proportional hazards model. Multivariable analysis was performed using the Cox proportional hazards model. Multicollinearity was assessed by calculating the variance inflation factor (VIF) for each variable. A VIF between 5 and 10 indicates high correlation between the variables. Glucose, alanine aminotransferase, creatinine and glucated hemoglobin were excluded from analysis because they showed a VIF > 5. All the remaining variables of Table 1 were entered into the model. AP, CRP and troponin T were entered into the model after logarithmic transformation (due to skewed distribution) and the hazard ratios were calculated per unit increment in the logarithmic scale of the respective biomarkers. The C statistic and integrated discrimination improvement (IDI) were calculated to assess whether the risk prediction for mortality is improved by adding AP to the multivariable Cox proportional hazards model containing the same variables as the model for mortality. The bootstrapping method (400 samples) was used to calculate the 95% confidence interval of the C-statistic and IDI, which allowed comparison of C-statistics (or IDIs) of the models without and with AP. All analyses were performed using the R 2.15.1 Statistical Package (The R foundation for Statistical Computing, Vienna, Austria). A two-sided $P < 0.05$ was considered statistically significant.