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Urinary neutrophil gelatinase-associated lipocalin and cystatin C compared to the estimated glomerular filtration rate to predict risk in patients with suspected acute myocardial infarction

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ABSTRACT

Introduction: Impaired renal function, reflected by estimated glomerular filtration rate (eGFR) or cystatin C, is a strong risk predictor in the presence of acute myocardial infarction (AMI). Urinary neutrophil gelatinase-associated lipocalin (uNGAL) is an early marker of acute kidney injury. uNGAL might also be a good predictor of outcome in patients with cardiovascular disease. Aim of the present study was to evaluate the prognostic value of uNGAL compared to eGFR and cystatin C in patients with suspected AMI.
Methods: 1818 patients were enrolled with suspected AMI. Follow-up information on the combined endpoint of death or non-fatal myocardial infarction was obtained 6 months after enrolment and was available in 1804 patients. 63 events (3.5%) were registered.
Results: While cystatin C and eGFR were strong risk predictors for the primary endpoint even adjusted for several variables, uNGAL was not independently associated with outcome: When applied continuously uNGAL was associated with outcome but did not remain a statistically significant predictor after several adjustments (i.e. eGFR). By adding cystatin C or uNGAL to GRACE risk score variables, only cystatin C could improve the predictive value while uNGAL showed no improvement.
Conclusion: We could show that cystatin C is an independent risk predictor in patients with suspected AMI and cystatin C can add improvement to the commonly used GRACE risk score. In contrast uNGAL is not independently associated with outcome and seems not to add further prognostic information to GRACE risk score.

1. Introduction

Early and adequate risk stratification is essential in patients with suspected acute myocardial infarction (AMI). Within the last years impaired renal function has been established as a marker for mortality and cardiovascular events in patients with cardiovascular disease or AMI [1]. Furthermore, patients with acute kidney injury (AKI) in the context of AMI have an increased mortality risk with respect to short- and long-term outcome [2,3].

Quantification of renal function in clinical routine is mainly based on serum creatinine, age and sex using different formulas for estimation of the glomerular filtration rate (eGFR). Most widely used and recommend are the Modification of Diet in Renal Disease (MDRD) formula and the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula [4,5].

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Besides creatinine-based approaches, measurement of cystatin C allows to estimate renal function. Cystatin C levels are independent of muscle mass, which commonly confounds the estimation of glomerular filtration rate by creatinine. In addition, unlike creatinine, cystatin C is not secreted in the tubulus, an effect which causes overestimation of GFR by creatinine. Therefore, cystatin C is a better, albeit much more expensive measure of renal function [6].

Further, it was also shown that cystatin C outperforms creatinine based estimation of renal function as risk predictor in patients with cardiovascular disease. Cystatin C is associated with cardiovascular events and mortality in patients with acute and chronic heart failure, in patients with coronary artery disease and in patients with suspected AMI [7–10].

In 1994 a 25 kDa protein named neutrophil gelatinase-associated lipocalin (NGAL) was first described and – measured in urine (uNGAL) and plasma (pNGAL) – it became an important early marker to detect AKI [11–13]. NGAL is also expressed and measurable in several other tissues, e.g. atherosclerosis plaques, myocardial infarction tissue or in in cardiac tissue of patients undergoing heart transplantation or suffering from myocarditis [14–18]. NGAL measured in urine as well as in plasma can be used as early markers for kidney injury or renal impairment in patient with chronic heart failure (HF) [19,20].

Besides the relation to the renal function, the value of NGAL as a risk predictor in cardiovascular disease has been controversially discussed: NGAL is an independent risk factor in patients with chronic and acute HF [21–25] and NGAL was evaluated in suspected or confirmed coronary artery disease [16,26,27]. Data on uNGAL levels in the risk population of patients with suspected AMI is not available so far.

Against the background of the controversial discussion about the predictive power of NGAL in cardiovascular disease and the lack of data of NGAL levels in the setting of suspected AMI, the aim of the present study is to evaluate the prognostic utility of uNGAL compared to the well-known risk predictors cystatin C and eGFR in patients with suspected AMI.

2. Methods

2.1. Study sample

Between January 2007 and December 2008, a total of 1818 patients presented consecutively in stable conditions to the chest pain units (CPU) of 3 German study centers with suspected AMI and participated in the present study. Detailed information on the study setting was previously published [28]. Final diagnosis of AMI was adjudicated in 413 patients (22.7%).

In brief, all patients that were hemodynamically stable, older than 18 years and younger than 85 years of age with symptoms suggestive of AMI were eligible to participate. Exclusion criteria were trauma or major surgery within the last 4 weeks, pregnancy, intravenous drug abuse, and anemia (hemoglobin level below 10 g/dL). Data on cardiovascular risk factors were obtained as described earlier [28]. Participation was voluntary and each participating patient gave written informed consent at admission. The study was approved by the local ethics committees.

The final diagnosis AMI was adjudicated by two independent cardiologists using all available clinical findings, imaging and laboratory results including serial conventional troponin testing.

2.2. Outcome measures

Follow-up data was assessed 6 months after enrollment via standardized telephone interview and hospital or general practitioner charts. As outcome measure the combined endpoint of death (after study inclusion) or non-fatal myocardial infarction (excluding the initial event leading to study inclusion) within 6 months after enrollment was defined. This endpoint was reached by 63 (30 deaths, 33 non-fatal myocardial infarction) patients. Data on follow-up was available in 1804 patients (99.2%) (*Supplement Figure 1*).

2.3. Blood sampling and laboratory methods

Blood was obtained directly upon admission. Urine was collected as spot urine as early as possible after admission. Both were obtained before an e.g. invasive treatment. Routine laboratory parameters, including in-house troponin, C-reactive protein (CRP), creatinine, and creatinine kinase-MB were measured directly using standardized methods in the respective hospital laboratory. Additionally, blood and urine samples were centrifuged and frozen at 80 °C until further measurement.

Investigational cardiac troponin I was determined using a highly sensitive assay (hs-cTnI; ARCHITECT STAT hs Troponin I, Abbott Diagnostics) with assay range of 0–50,000 ng/L, limit of detection (LoD) of 1.9 ng/L and 99th percentile diagnostic cut-off of 30 ng/L. [IFCC List]. B-type natriuretic peptide (BNP), cystatin C and uNGAL were assayed in 2010 on the ARCHITECT i System (Abbott Diagnostics, Germany). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine, age, sex and race [5]. Data on cystatin C was available in 1722 patients, and on uNGAL in 1164 patients; eGFR could be calculated in 1802 patients.

All investigational biomarkers were measured in frozen by experienced technical assistants blinded to patient characteristics. Further, research staff involved in enrollment or follow-up as well as the respective treating physicians were unaware of the investigational biomarker data.

2.4. Statistical analyses

Variables with (near) normal distribution were characterized by arithmetic mean and SD, whereas skewed variables were described by median and interquartile range.

To evaluate the prognostic potential of uNGAL, cystatin C and eGFR, univariate and multivariate cox regression analyses were carried out with respect to the combined endpoint of death or non-fatal myocardial infarction.

Multivariate analyses were adjusted for sex, age, CRP, BNP, GRACE (global registry of acute coronary events) risk score excluding creatinine, troponin I, eGFR, final diagnosis, and cystatin C or uNGAL, as appropriate. Hazard ratios were derived for all variables as continuous variables and for cystatin C and uNGAL with respect to literature-based cut-offs as well as for cut-offs with the highest sum of specificity and sensitivity to detect an event (Youden's Index) in our cohort. For cystatin C the literature based cut-off was 0.95 mg/L [29], the Youden cut-off was 0.81 mg/L; for uNGAL the literature based cut-off was 107 μg/L [30] and the Youden cut-off was 10.2 μg/L. As these literature cut-offs do not directly relate to the used assays they might not be representative and should only be seen as comparators.

Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) [31] were used to assess the additional value of uNGAL and cystatin C for risk stratification in addition to the GRACE risk score.

Spearman's rank correlations coefficient was derived to analyze statistical dependence between biomarkers and different variables including sex, age, diabetes mellitus, dyslipidemia, arterial hypertension, family history of coronary artery disease (CAD), smoking, atrial fibrillation, congestive heart failure, valvular heart disease, Troponin I and BNP, serum creatinine, eGFR, CRP, final diagnosis, TIMI Risk Score [32], GRACE risk score [33].

Kaplan-Meier estimator was carried out to estimated event-free survival according to baseline levels of cystatin c, uNGAL and eGFR.

In addition to the analysis on the prognostic potential, cystatin C and uNGAL levels were compared according to final diagnosis of non-coronary chest pain (NCCP), AMI and unstable angina pectoris (UAP).

p-Values < 0.05 were considered significant. All analyses were carried out using the R 3.1.1 software package (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline data

Data of the cohort classified according to the occurrence of an event is presented as baseline Table 1. 63 (3.5%) of the analyzed 1804 patients with suspected AMI suffered an event. 413 patients had the final diagnosis AMI as underlying diagnosis leading to presentation and study enrollment. Patients with unfavorable outcome were more often male, more often suffered from cardiovascular risk factors and were more often initially diagnosed with AMI.

Data on eGFR was available in 1802 patients (61 events; AMI $n = 409$; UAP $n = 237$; NCCP $n = 1156$); 306 of these patients (17.0%) presented with an eGFR of <60 mL/min and were therefore classified as patients with CKD. 112 patients presented with an eGFR of <45 mL/min (6.2%) and 33 of <30 mL/min (1.8%).

Data on cystatin C was available in 1722 patients (58 events; AMI $n = 381$; UAP $n = 222$; NCCP $n = 1119$) and on uNGAL in 1164 patients (35 events; AMI $n = 246$; UAP $n = 158$; NCCP $n = 760$).

The biomarkers uNGAL ($p = 0.004$) and cystatin C ($p < 0.001$) were significantly higher in case of an event while eGFR was significantly lower ($p < 0.001$). Also, other laboratory parameters such as BNP, cardiac troponin I, and CRP were significantly elevated in case of an event (Table 1).

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