Neutrophil gelatinase-associated lipocalin (NGAL) for the prediction of acute kidney injury in chronic kidney disease patients treated with primary percutaneous coronary intervention

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1. Introduction

Deterioration of renal function resulting in acute kidney injury (AKI) is a significant complication associated with adverse outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) [1,2]. Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein stored in granules of mature neutrophils and is found to be released by renal tubular cells following acute tubular damage. Laboratory measurements can detect NGAL elevation within a few hours following tubular insult and were found to predict acute kidney injury (AKI) earlier, when compared to serum creatinine (sCr), in various patient populations including cardiac surgery, contrast administration and septic shock [3–9]. Recent studies have also reported altered NGAL levels in patients with baseline chronic kidney disease (CKD) [10–12], suggesting the possibility that NGAL production from tubular cells may also reflect the entity of active renal damage that underlies the chronic impairment condition.

To the best of our knowledge, no study to date has investigated the utility of plasma NGAL assessment to predict the incidence of AKI following primary PCI in patients suffering from chronic renal failure. Accordingly, we aimed to assess the possible predictive ability of plasma NGAL levels to identify acute deteriorations in renal function following primary PCI in STEMI patients with pre-existing renal failure.

Keywords:
NGAL
AKI
STEMI
PCI

Abstract

Introduction: Elevated plasma levels of neutrophil gelatinase-associated lipocalin (NGAL) is a marker of tubular damage and aid in the early identification of acute kidney injury (AKI). We evaluated NGAL levels for identification of AKI superimposed on chronic kidney disease (CKD) vs. “de novo” AKI among ST elevation myocardial infarction (STEMI) patients undergoing primary coronary intervention (PCI).

Methods: 217 STEMI patients treated with PCI were prospectively included, 34 (16%) had baseline CKD. Plasma NGAL levels were drawn 24 h following PCI. Receiver-operator characteristic (ROC) methods were used to identify optimal sensitivity and specificity for the observed NGAL range in AKI patients with and without CKD.

Results: Overall AKI incidence was 13%. NGAL levels were significantly higher for patients with AKI compared to no-AKI, irrespective of CKD. Different optimal cutoff value for NGAL to predict AKI were found for patients with CKD (133 ng/ml, sensitivity of 73% and specificity of 75%; AUC: 0.837, p < 0.001) and for non-CKD (104 ng/ml with sensitivity of 79% and specificity of 82%; AUC: 0.844, p < 0.001). In a multivariate logistic regression model, NGAL levels were independently associated with AKI in patients with and without CKD.

Conclusions: Elevated plasma NGAL levels identify patients who are at high-risk to develop AKI following primary PCI. Determining different cutoff values of plasma NGAL for de novo AKI and AKI superimposed on CKD may be necessary for accurate AKI diagnosis and risk stratification.

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2. Methods

2.1. Patients

In this prospective, observational, open label, single-center trial, we enrolled consecutive STEMI patients admitted to the Cardiac Intensive Care Unit (CICU) following primary PCI, between December 2017 and March 2020. The presence of CKD was based on past laboratory data and medical records, available for all included patients. Based on the availability of NGAL kits, the study population consisted of 217 STEMI patients undergoing primary PCI. STEMI diagnoses were established by a typical history of chest pain, diagnostic electrocardiographic changes and serial elevations of cardiac biomarkers in patient serum, consistent with current guidelines [13]. Critically ill patients were defined as mechanically ventilated or need for ionotropes/intra-aortic balloon counterpulsation insertion. Primary PCI was performed for patients presenting within 12 h following symptom onset and for patients presenting within 12–24 h from ischemic symptom onset who remained symptomatic upon hospital admission. Iodixanol was used as a contrast agent (Visipaque, GE Healthcare, Ireland) in all. Normal saline (0.9%) was administered intravenously at a rate of 1 ml/kg/h for 12 h following exposure to contrast material although for patients with overt heart failure, the hydration rate was reduced at the physician’s discretion. All patients underwent echocardiography to assess left ventricular function within 3 days of admission. The study protocol was approved by the local institutional ethics committee (institutional Board Review number TLCV-16-224).

2.2. Laboratory

Serum NGAL levels of venous blood were collected from all patients 24 h following admission to the CICU. Samples were centrifuged within 10 min using a cooled centrifuge, and plasma and serum were stored at –20 °C. NGAL levels were analyzed using NGAL rapid turbidimetric immunoassay (Bioporto Diagnostics, Copenhagen, Denmark).

The same venous blood samples were also used for sCr and high sensitivity C-reactive protein (CRP) level measurements, which were also tested repeatedly on a daily basis throughout hospitalization for all patients. CRP levels were analyzed quantitatively using the Bayer wide-range assay. Estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14]. CKD was defined by an eGFR < 60 ml/min/1.73 m² based on past laboratory reports. AKI was defined using the KDIGO criteria: A. Increase in serum creatinine by 0.3 mg/dl or more within 48 h. B. Increase in serum creatinine above 1.5 times baseline within 7 days [15].

2.3. Statistics

Categorical variables were expressed as frequencies and percentages. Distribution of continuous variables was assessed using histogram and quantile–quantile plots. Normally distributed continuous variables were described using mean and standard deviations (SD) and non-normally distributed variables using median and interquartile range (IQR). Chi square test was used to evaluate association between categorical variables. Continuous variables were compared using the independent sample t-test and the Mann–Whitney U test. Multivariate binary regression model was used to assess the association between plasma NGAL levels and the risk for AKI and to control for potential confounders. Initially, univariate regression was employed and variables with a p value < 0.1 were then included in the multivariate binary logistic regression model. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cutoff point of plasma NGAL levels (at which sensitivity and specificity would be maximal) for the prediction of AKI using the Youden index. Area under the curve (AUC) was calculated as measure of the accuracy of the tests. A two-tailed p value < 0.05 was considered significant for all analyses. All analyses were performed using the IBM SPSS 25.0 software (SPSS Inc., Chicago, IL version 25).

3. Results

Patients presenting with STEMI and treated with primary PCI, (mean age 64 ± 13, 82% men), 34 (16%) had baseline CKD. A total of 29 patients (13%) developed AKI during hospitalization. Median time to AKI diagnosis based on sCr criteria was 36 h. Compared to patients with no CKD, patients with CKD had a significantly higher rate of AKI (44% vs 8% respectively; p < 0.001). Baseline characteristics for patients with vs. without CKD according to AKI occurrence are presented in Table 1.

3.1. NGAL, CKD and AKI

Table 2 presents key laboratory findings according to the presence of baseline CKD and the occurrence of AKI. Fig. 1 demonstrates NGAL levels stratified by presence/absence of baseline CKD and the development of AKI. Patients who developed AKI demonstrated significantly higher plasma NGAL levels, both among patients without (82 ± 34 ng/ml vs 140 ± 80 ng/ml respectively; p = 0.001) and with CKD (104 ± 37 ng/ml vs 194 ± 93 ng/ml; p < 0.001).

Following multivariable logistic regression plasma NGAL was found to be independently associated with increased risk for AKI both for patients without (HR 1.03, 95% CI: 1.01–1.05; p = 0.01) and with CKD (HR 1.04, 95% CI: 1.01–1.08; p = 0.02). Hazard ratios with their corresponding 95% confidence intervals of the univariate and multivariate binary logistic regression for the development of AKI in patients with and without CKD are summarized in Table 3.

According to ROC curve analysis, the optimal cutoff value to predict AKI for patients without CKD was 105 ng/ml with sensitivity of 79% and specificity of 82% (AUC: 0.844, p < 0.001), whereas the optimal cutoff value for Patients with CKD was 133 ng/ml with sensitivity of 73% and specificity of 75% (AUC: 0.837, p < 0.001) (Fig. 2).

4. Discussion

We demonstrated for the first time that for STEMI patients, NGAL levels following primary PCI were independently associated both with de novo AKI and AKI superimposed on CKD.

AKI following PCI for STEMI patients is common, and even minute increases in sCr are associated with prolonged hospitalizations and unfavorable in-hospital and long-term outcomes [1,2,16,17]. The presence of CKD is also well established as a predictor of death and complications in the context of myocardial infarction [18,19], as these patients are often older and have many comorbidities. Furthermore, CKD is significantly associated with AKI occurrence following primary PCI [16,17]. In these particularly vulnerable patients, early detection of possible acute renal damage is therefore important.

Consensus criteria define deterioration of kidney function primarily by sCr elevation [15]. However, normal kidney function is usually characterized by a redundant capacity, such that as much as 50% of functional kidney mass can be impaired without sCr elevation [20]. Another limitation of sCr use as a biomarker of AKI is that creatinine half-life increases...
As AKI treatment is rather limited, the focus of management should lie in its prevention. Measurement of plasma NGAL levels can assist in stratification of those at high risk for further deterioration, as nearly 50% of patients with CKD demonstrated acute on chronic renal impairment. This type of patient profile is increasingly frequent among STEMI population, and for these high-risk patients, early diagnosis, and corresponding early initiation of therapy if necessary and avoiding or deferring the use of drugs that may be potentially nephrotoxic, such as nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors/ angiotensin-II receptor blockers.

In the current cohort patients developing AKI at a median time of 36 h following admission. When we classified the patients into four groups using AKI and pre-existing CKD, we demonstrated an elevated NGAL levels in patients with CKD(+)/AKI(−) compared to CKD(−)/AKI(−) as well as CKD(−)/AKI(+) compared to CKD(−)/AKI(−). While plasma NGAL levels were independently associated with AKI both in patients with and without CKD, we identified different cutoff values of plasma NGAL for diagnosis of de novo AKI and AKI superimposed on CKD. It appears thus, that plasma NGAL levels should be interpreted based on the existence of CKD.

In the present cohort CKD(+)/AKI(+) demonstrated highest troponin levels. While this may reflect the decreased left ventricular systolic function, which was lowest in this patient group, elevated levels may also reflect impairment of troponin clearance as major portion of this biomarker is removed from the circulation by the kidney.
higher risk for AKI [22,23]. It is possible thus, that elevated NGAL may reflect combined tubular injury and inflammatory response incited by the infarction. A recent trial demonstrated that early administration of statins significantly reduced the incidence of contrast nephropathy [24,25]. As statins are known to have pleiotropic and anti-inflammatory effects independent of their lipid-lowering function [25], early administration of high-dose, high-potency statins may blunt the acute inflammatory response elicited by the occurrence of STEMI as indicated in published guidelines [15].

Our study has notable limitations. This is a single center study with a modest sample size. No information was present on the reason for CKD. The small number of patients with CKD might be insufficient to determine the reliability and generalizability of plasma NGAL within this patient group. In addition, our study is based on measurements of plasma NGAL. The addition of urinary NGAL measurements to the analysis would have strengthened our conclusions. In patients with chronic renal insufficiency, urinary NGAL have did not appear to have any predictive value for the identification of those who will go on to develop AKI [26,27]. Based on this data, it would seem that in patients with chronic renal failure, plasma NGAL may be a better marker of AKI than urinary NGAL. As NGAL may derive from neutrophils and may reflect inflammatory disease state rather than renal damage, measurement of more specific renal biomarkers (e.g. kidney injury molecule 1), would be more specific for tubular damage. Utilization of normal saline may increase the risk of AKI due to its large chloride concentration.

Finally, AKI diagnosis based on serum creatinine might underestimate renal injury. The 10th Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) reported a combination of kidney functional (serum creatinine) and damage markers (new biomarkers including NGAL) to stratify patients with AKI [28]. Subclinical AKI can be diagnosed only using damage markers, such as NGAL, even when no change in serum creatinine is observed (structural AKI). Indeed, among STEMI patients, increased NGAL with no sCr elevation (NGAL-positive/sCr negative) was associated with adverse clinical outcomes [29,30].

Additional evaluation must be undertaken to clarify the role of plasma NGAL for detecting structural AKI that would be diagnosed independently from sCr values, and further investigations are needed before firm conclusions about clinical and financial implications of NGAL measurements can be drawn.
5. Conclusion

Elevated NGAL levels may identify high-risk population for AKI. Determining different cutoff values of postoperative plasma NGAL for de novo AKI and AKI superimposed on CKD is necessary for accurate AKI diagnosis. Further investigation is necessary to confirm these findings because the small number of patients.

Author contributions

Drs. Marder and rozenfeld contributed equally in study design, data gathering and writing. Drs. Zahler, Shtark, Goldiner, Fortis contributed in data gathering. Dr. Hochstadt contributed in data gathering and statistics. Dr. Loewenstein contributed in data gathering and editing. Drs. Keren and Shacham contributed in conceptualization, study design and editing. Dr. Lewit

Prof Banai reviewed and commented on the revised manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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