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Plasma NGAL predicts early acute kidney injury no earlier than s-creatinine or cystatin C in severely burned patients



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ABSTRACT

Introduction: Neutrophil gelatinase-associated lipocalin (NGAL) is a novel biomarker used in acute kidney injury (AKI) diagnostics. Studies on burn patients have highlighted it as a promising biomarker for early detection of AKI. This study was designed to discover whether plasma NGAL is as a biomarker superior to serum creatinine and cystatin C in detecting AKI in severely burned patients.

Methods: Nineteen subjects were enrolled from March 2013 to September 2014 in the Helsinki Burn Centre. Serum creatinine, cystatin C, and plasma NGAL were collected from the patients at admission and every 12 h during the first 48 h and thereafter daily until seven days following admission. AKI was defined by acute kidney injury network criteria.

Results: Nine (47%) developed AKI during their intensive care unit stay and two (11%) underwent renal replacement therapy. All biomarkers were significantly higher in the AKI group but serum creatinine- and cystatin C values reacted more rapidly to changes in kidney function than did plasma NGAL. Plasma NGAL tended to rise on average $72 \text{ h} \pm 29 \text{ h}$ (95% CI) later in patients with early AKI than did serum creatinine. Area-under-the-curve values calculated for each biomarker were 0.92 for serum creatinine, 0.87 for cystatin C, and 0.62 for plasma NGAL predicting AKI by the receiver-operating-characteristic method.

Conclusion: This study demonstrated serum creatinine and cystatin C as faster and more reliable biomarkers than plasma NGAL in detecting early AKI within one week of injury in patients with severe burns.

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1. Introduction

Acute kidney injury (AKI) is common in severely burned patients and is associated with high mortality. Risk factors for AKI are high total burned surface area (%TBSA), use of

nephrotoxic drugs, sepsis, and prolonged need for ventilation [1].

Serum creatinine (SCr) and urine output are the main means to diagnose AKI. More than 50% of renal function must be lost before elevated SCr levels in blood are detectable and levels depend on age, gender body mass, and ethnicity [2].

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Another test sometimes used in AKI diagnosis, involves cystatin C (CysC), a 13 kD protease inhibitor located in nucleated cells; that is freely filtered through human glomeruli, but it is not actively secreted into urine. Impairment of glomerular filtration rate (GFR) leads to its increased levels in plasma. Normal plasma concentrations neither depend on age, gender or muscle mass, and CysC may be a better indicator for kidney function than is SCr in patients with severe burns [3–5].

Of the other biomarkers studied so far, none has gained widespread use in AKI diagnostics [6].

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein bound to gelatinase from neutrophils. It is, in normal conditions, expressed in the human epithelia of kidney, stomach, colon, trachea, and lungs. Concentrations rise in inflammatory processes and after epithelial injury. Elevated concentrations of NGAL are detectable in patients with rheumatoid arthritis, chronic obstructive pulmonary disease, or severe peritonitis [7]. Professional swimmers constantly exposed to chlorinated water may also show high NGAL levels [8].

NGAL has been considered as an excellent biomarker predicting AKI after cardio-pulmonary bypass in children [9]. It can be rapidly measured from plasma or urine by using enzyme-linked immunosorbent assay (ELISA). The role of NGAL in burn related injuries has so far not been clearly defined and the purpose of this study was to evaluate whether plasma NGAL (p-NGAL) is superior in detecting AKI at an earlier phase than is CysC or SCr in severely burned patients.

2. Materials and methods

We enrolled 19 consecutive patients at Helsinki Burn Centre between March 2013 and September 2014, all with a %TBSA of at least 20%—or for those aged over 60, a lower 15%TBSA. Grading of AKI was based on acute kidney injury network (AKIN) criteria [10] (See Table 1). AKI was diagnosed when grade I AKIN criteria were fulfilled. Since SCr is one of the AKIN criteria it sets limitation to the interpretation of the results.

The following parameters were included: Age, gender body mass index (BMI), %TBSA, burn mechanism, need for intubation or ventilation, escharotomies, abbreviated burn severity index (ABSI) [11], sequential organ failure assessment score (SOFA) [12], co-morbidities, need for renal replacement therapy (RRT), duration of intensive care, and outcome. Measurements of SCr, CysC, and p-NGAL values continued from the week after arrival at 12-h intervals during the first 48 h and thereafter daily at 6–8 a.m. Measurements of SCr and urine output (UOP) continued through out the intensive care to detect AKI at any time point. SCr at arrival set the baseline for AKIN criteria determination.

SCr and CysC were analyzed by hospital laboratory services and p-NGAL by Triage[®], a point-of-care device (Alere Inc., Waltham, MA, USA). It detects p-NGAL values between 15 and 1300 ng/ml by an ELISA-based immunoassay. Quality control was run for each set of test kits by the manufacturer's orders. Cut-off points were chosen 100 $\mu\text{mol/l}$ (1.14 mg/dl) for SCr, 1.4 mg/l for CysC, and 400 ng/ml for p-NGAL, all generally accepted values indicating AKI.

Table 1 – AKIN classification of acute kidney injury (10).

Stage	Creatinine criteria	Urine output criteria
AKIN 1	Increase in serum creatinine at least 0.3 mg/dl (26.4 $\mu\text{mol/l}$) or increase at least to 150–200% (1.5- to 2-fold) from baseline.	Less than 0.5 ml/kg per hour for more than 6 h.
AKIN 2	Increase in serum creatinine more than 200–300% (2- to 3-fold) from baseline.	Less than 0.5 ml/kg per hour for more than 12 h.
AKIN 3	Increase in serum creatinine more than 300% (>3-fold) from baseline or serum creatinine at least 4.0 mg/dl (354 $\mu\text{mol/l}$) with an acute increase at least 0.5 mg/dl. (44 $\mu\text{mol/l}$).	Less than 0.3 ml/kg per hour for more than 24 h or anuria for 12 h or need for RRT.

AKIN, acute kidney injury network; RRT, renal replacement therapy.

Patients were resuscitated by our standard fluid protocol (Parkland formula, no colloids during the first 8 h, urine output target 0.5 ml/kg h). When necessary, vasoactive agents maintained adequate hemodynamics. Statistical analysis was run by IBM SPSS Statistics for Macintosh, Version 22.0 (Armonk, NY, USA, IBM Corp.). Student's t-test and chi-square test analysis were performed between groups when appropriate. Area under the curve (AUC) was defined for each biomarker by the receiver operating characteristics (ROC) method.

The Research Ethics Board at our institution approved the study protocol and informed consent was obtained from all subjects.

3. Results

The treatment in the ICU began on average 3.6 h (1.5–8 h) after burn injury. Nine patients (47%) developed AKI during their intensive care. Eight patients (42%) developed early AKI during the seven days' study time, all within five days after burn. Five patients were diagnosed by Scr criterion, three by UOP criterion and one patient fulfilled both criteria. SCr and UOP were recorded also after the study time and one patient (5%) developed late AKI on the 14th day after burn. Two patients (11%) underwent RRT with subsequent recovery of renal function. Two patients (11%) succumbed during their intensive care unit (ICU) stay within 48 h after admission.

Patients with AKI had longer ICU stay time, higher BMI, greater number of co-morbidities, higher %TBSA, and higher ABSI and SOFA score during ICU stay but only BMI ($p = 0.011$), SOFA-score on admission ($p = 0.015$), and highest SOFA score ($p = 0.018$) were statistically significant in predicting AKI. Demographic data is presented in Table 2.

Patients who developed AKI had on days four and five significantly higher ($p < 0.05$) p-NGAL values than did the

Table 2 – Characteristics and baseline parameters of patients.

Variable	Non-AKI (n = 10)	AKI (n = 9)	p
Age	48.2 ± 18.8	59.7 ± 12.4	0.14
Male gender	5 (50%)	6 (67%)	0.46
BMI	24.3 ± 2.9	35.7 ± 10.4	0.011*
Number of co-morbidities	1.1 ± 0.88	1.9 ± 1.76	0.25
%TBSA	37.6 ± 21.4	45.6 ± 12.5	0.34
Burn mechanism (Flame:steam)	10:0	8:1	0.28
Inhalation injury	4 (40%)	2 (22%)	0.7
Intubated on arrival	4 (40%)	5 (56%)	0.5
Need for ventilation	5 (50%)	5 (56%)	0.81
ABSI scoring	8.5 ± 2.4	10.6 ± 2.0	0.059
SOFA scoring on arrival	4.2 ± 2.9	7.8 ± 2.3	0.015*
Highest SOFA score	7.1 ± 3.0	10.8 ± 2.6	0.018*
Escarotomies needed	6 (60%)	6 (67%)	0.76
Duration of ICU time	21.6 ± 10.4	34.9 ± 21	0.107
Need of RRT	0 (0%)	2 (22%)	0.12
Non-survivors	0 (0%)	2 (22%)	0.12
Grading of AKI			
AKIN 1		2 (22.2%)	
AKIN 2		3 (33.3%)	
AKIN 3		4 (44.4%)	
Type of AKI			
Early AKI		8 (88.9%)	
Late AKI		1 (11.1%)	

AKI, acute kidney injury; BMI, body mass index; TBSA, total body surface area; ABSI, abbreviated burn severity index; SOFA, sequential organ failure assessment; ICU, intensive care unit; RRT, renal replacement therapy; AKIN acute kidney injury network. Data are reported as mean ± SD or percentage, when appropriate.

* Statistically significant ($p < 0.05$).

non-AKI group. Higher grading of AKI correlated with higher p-NGAL values, but p-NGAL rose remarkably after impairment of renal function. Serum creatinine values were significantly higher in the AKI group ($p < 0.05$) at every measure point, except on arrival ($t = 0$) and at 48 h. CysC values were significantly higher ($p < 0.05$) in the AKI group at all times, except on arrival ($t = 0$) and at 12 h. Laboratory values of both groups are presented in Fig. 1a–c. The amount of fluid resuscitation during first 24 h was $6.6 \text{ ml} \times \text{kg} \times \% \text{TBSA}$ in non-AKI group, and 7.4 in AKI group respectively.

Only in the one late-AKI case, developed 14 days after admission, did p-NGAL rise to over 400 ng/ml a week earlier than the SCr value reached its cut-off point of $100 \mu\text{mol/l}$ (1.14 mg/dl). In all the rest of the cases, SCr rose earlier. On average p-NGAL values rose above their cut-off point (400 ng/ml) $72 \text{ h} \pm 29 \text{ h}$ (95% CI) later than did SCr and $36 \text{ h} \pm 43 \text{ h}$ (95% CI) later than did CysC in patients with early AKI. Differences between time delays were not significant by sign test analysis ($p = 0.625$).

AUC values were 0.92 for SCr, 0.87 for CysC, and 0.62 for p-NGAL by the ROC method. The differences of AUC between NGAL and two other biomarkers were significant ($p < 0.05$). However, the difference between SCr and CysC was not significant ($p = 0.0525$).

All laboratory results available of for each biomarker during the first seven days from admission were included to ROC-analysis. Optimal cut-off points estimated for creatinine were $75 \mu\text{mol/l}$ (0.85 mg/dl) (sensitivity 80% specificity 84%), for

CysC 0.95 mg/l (sensitivity 85% specificity 80%) and for p-NGAL 152 ng/ml (sensitivity 60% specificity 53%) ROC-curves for each biomarker are presented in Fig. 2a–c.

4. Discussion

In this study we investigated the role of p-NGAL as an early biomarker of AKI in adult burn patients. Our study demonstrated that in every early AKI case, serum creatinine, and cystatin C revealed AKI before p-NGAL rose over the cut-off point (400 ng/ml), and only in one patient with late AKI (11% of the AKI patients) p-NGAL rose earlier than SCr. This happened almost one week earlier, but due to the wide variation of the values even in the non-AKI group this may as well be interpreted as a non significant rise caused by some other factor not known by us. P-NGAL levels were in AKI group higher than in non-AKI group, but not at an earlier stage than those of SCr and CysC. Levels correlated at least partly with %TBSA and with AKI severity. When lowering the cut-off point of p-NGAL to 150 ng/ml (as recommended by the Triage[®] manufacturer), 2/9 AKI patients showed elevated p-NGAL values before SCr reached its cut-off point. On the other hand, 9/10 non-AKI patients had p-NGAL over 150 ng/ml without any impairment of renal function. On average, p-NGAL rose $6 \text{ h} \pm 20 \text{ h}$ (95% CI) later than SCr when the lowered cut-off point was applied.

The specificity of NGAL to AKI increases justifying the use of higher cut-off point than 150 ng/ml [13].

We defined AKI according to the AKIN classification that is based on either the lowest urine output value or highest creatinine criterion, a classification estimated as more accurate than the generally used RIFLE criteria (Risk-Injury-Failure-Loss-End stage kidney disease) in patients with burn injury [14].

The manufacturer of the Triage[®] meter recommends a cut-off point of 150 ng/ml for p-NGAL. Cut-off values between 150 and 400 ng/ml with Triage[®] meter have been applied with AKI diagnosis with various critical-care study populations [15]. In our study, p-NGAL values over 200 ng/ml were observable in 17 of 19 patients (89%), whether having AKI or not. Two non-AKI patients had high p-NGAL values (over 600 ng/ml) without any evidence of impaired renal function. In addition, in the non-AKI group, p-NGAL rose constantly, on average to over 200 ng/ml (Fig. 1c) after day four, without impairment of renal function.

Moreover, in the two non-survivors, p-NGAL remained clearly below the cut-off point of 400 ng/ml. They rapidly developed early AKI and progressive multiple organ failure (MOF) with anuria, sepsis, and severe coagulopathy. A clear rise in SCr and CysC was recorded, whereas p-NGAL levels did not rise considerably before death. We observed however remarkably high NGAL values ($>980 \text{ ng/ml}$) in two AKI patients who needed RRT. ROC analysis showed a high diagnostic value for creatinine to predict AKI and a notably low value for p-NGAL, which differs greatly from earlier findings.

Interestingly, patients in AKI group had significantly higher BMI and also more co-morbidities than non-AKI patients. This may be a confounding factor since elevated NGAL levels have been discovered in obese human. Elevated NGAL levels have

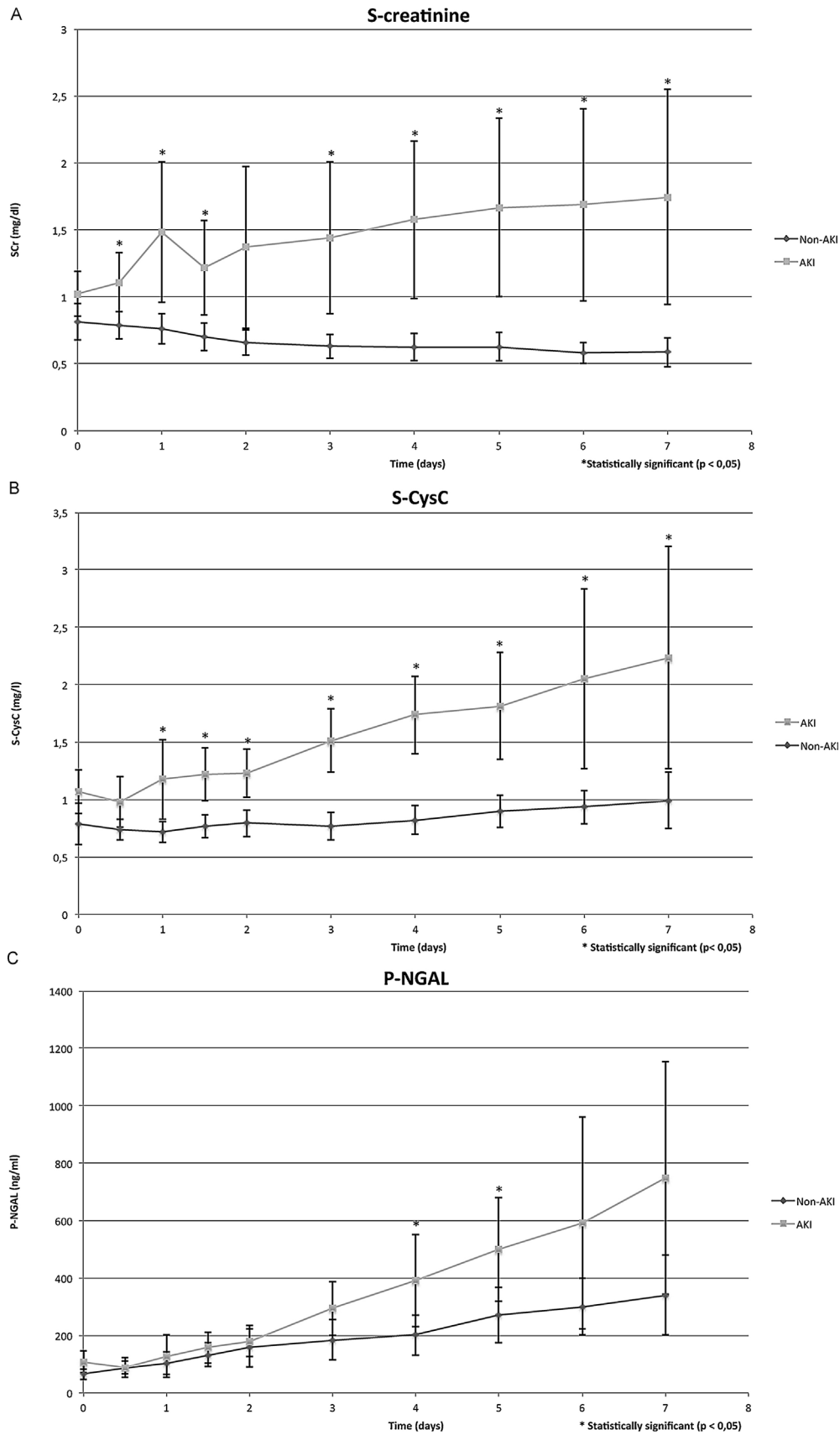


Fig. 1 – (a–c) Changes of biomarkers in non-AKI and AKI-patients during the first seven days after admission. Values are presented as means and 95% confidence intervals (CI). Values marked with star includes a statistically significant difference between groups.

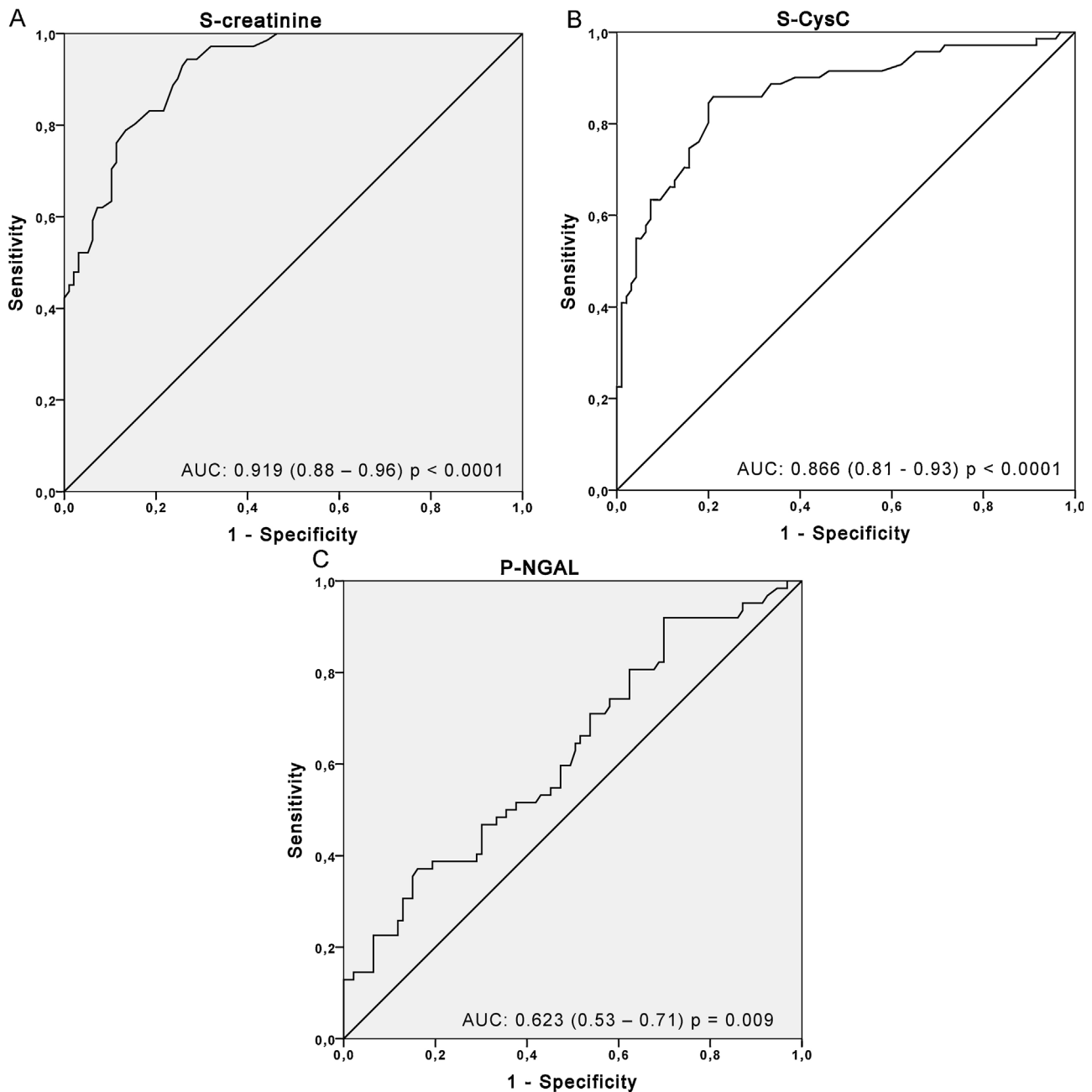


Fig. 2 – (a–c) ROC (Receiver operating characteristic)—curves, presenting AUC (area under curve) and 95% confidence intervals (CI) for each biomarker predicting AKI using every value available during the first seven days after admission.

also been found to correlate with an indicator of inflammation, the high sensitivity C-reactive protein [16]. In addition, NGAL has been described to be associated with elevated aldosterone levels and fibrosis, often present in congestive heart disease [17].

The role of NGAL in AKI diagnostics related to burns is not well established, and few studies have been appeared. In a Turkish study of 22 burned children younger than seven years, six developed AKI within 48 h after burn. Plasma and urine NGAL evaluation was superior to SCr to predict AKI development. Kidney function measured by RIFLE criteria returned within two to four days of the injury, reflecting its moderate

nature. Their ages may have some influence, but the authors also postulated that elevated NGAL values may reflect the severity of the burn insult and also serve as an indicator of inflammation in burned children [18].

In a large South-Korean study of 90 patients (aged under 17), Yang et al. estimated the value of SCr, CysC, and plasma and urine NGAL in predicting AKI during the 48 h after trauma. Elevated NGAL was an independent risk factor at 48 h for early AKI [19]. Plasma NGAL was determined by Triage[®] meter and NGAL was better at predicting early AKI until 12 h from arrival, whereas SCr was better from 12 h until 48 h [19]. However, our results do not support the supremacy of NGAL even at the

hyperacute stage due to many false-positive results. Using 150 ng/ml cut-off point for p-NGAL, 9/10 non-AKI patients would have been considered as AKI patients. Furthermore, in the two early deaths (within 48 h from admission) there was no detectable NGAL rise (at least 150 ng/ml), although grade II AKIN was observed in both cases.

The average %TBSA (\pm SD) for Yang et al. was 70.7 ± 22.0 in patients with early AKI, whereas ours was 45.6 ± 12.5 , a significant difference between our study populations.

Hong et al. investigated NGAL in 45 severely burned patients, finding levels significantly higher at admission, at day three and at day seven for patients who developed late AKI [20]. Our proportion of early AKI patients was nearly 90%, whereas for Hong et al., all patients had late AKI, in which NGAL is not preferable to SCr in predicting late AKI or mortality, as seen by our study or in the study by Yang et al. [19].

Howell et al. made a pilot study on 15 adult patients. P-NGAL reacted to early AKI within 48 h from admission, on average 12 h before SCr rise, and levels were significantly higher in the AKI group. The time gap between plasma NGAL and SCr rise was determined in our study individually for every patient in contrast to Howell et al. who calculated the difference from mean values in their pilot study with 15 burned adults, which may explain the variance in results [21].

Recent study with various ICU populations of 728 patients demonstrated urine NGAL superior to plasma NGAL in predicting AKI [22]. Studies made with burn patients have similar results [18,19].

NGAL has been shown to be a very sensitive and specific biomarker for detecting AKI after cardiopulmonary bypass within infants and adults [23,24], although Demirtas et al. found no significant difference with 72 adult patients after coronary artery bypass by graft [25].

The role of NGAL has also been studied in detecting contrast-medium-induced AKI. Valette et al. found p-NGAL as no better biomarker than SCr, although NGAL was specific in predicting the need for RRT [26].

Recently the diagnostic value of NGAL as a biomarker for AKI has been questioned due to different isoforms that may confound p-NGAL measurement with current point-of-care devices [27].

According to our results the cost-benefit analysis is not favorable for pNGAL. Measurement of SCr at our institution costs 0.95 EUR vs. that of p-NGAL, 30 EUR (point-of-care device).

Our study has some strengths. It is a prospective study made with severely burned patients, where p-NGAL is daily compared with SCr and CysC, during one week's time after injury. Possible later impairment of renal function was also followed after the study period of seven days by continuous urine output and SCr measurements.

However, we want to emphasize that this is a single center study with only 19 patients. AKIN classification, that includes creatinine criterion, sets a major risk for circular reasoning although it is broadly accepted as an accurate and sensitive tool for AKI determination. Nevertheless, the large variation of p-NGAL, whether in AKI or non-AKI group does not support its use in AKI diagnostics of severe burns.

5. Conclusions

Serum CysC and SCr react more rapidly to changes in kidney function and do have better accuracy. This study could not support NGAL as a better biomarker in detecting early AKI with severely burned patients.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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