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Value of plasma neutrophil gelatinase-associated lipocalin in predicting the mortality of patients with sepsis at the emergency department

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ABSTRACT

Background: Sepsis is a major cause of morbidity and mortality in the emergency department. This study aimed to evaluate the assessment of severity of sepsis by and prognostic value of plasma neutrophil gelatinase-associated lipocalin (NGAL) compared with other widely used biological markers of inflammation in patients with sepsis.
Methods: NGAL, procalcitonin, and C-reactive protein values were measured in 470 patients with suspected sepsis, and the Mortality in Emergency Department Sepsis (MEDS) score was obtained for all enrolled subjects, who were followed for up to 28 days.
Results: The median plasma NGAL value was increased with sepsis severity according to the MEDS score. The plasma NGAL value was higher in nonsurvivors than in survivors. The area under the receiver operating characteristic curve of NGAL (0.797) was greater than that of procalcitonin (0.599) and MEDS score (0.774) in predicting 28-day hospital mortality. Multivariable logistic regression found that the plasma NGAL value was an independent predictor for hospital mortality in patients with sepsis. The plasma NGAL values were positively correlated with C-reactive protein and procalcitonin levels, and MEDS scores.
Conclusions: Plasma NGAL is a valuable biological marker in the assessment of severity and prediction of prognosis of patients with sepsis in the emergency department.

1. Introduction

Sepsis is a manifestation of the host's inflammatory response to microbial infection and can lead to life-threatening medical conditions. Despite advances in medical science and the use of modern antibiotics, the associated morbidity and mortality of patients with sepsis have decreased only slightly [1]. Early recognition, appropriate classification, and proper and specific treatment in the initial phases of sepsis have resulted in improved outcomes in emergency departments (EDs) and intensive care units (ICUs) [2,3].

Scoring systems for acute critical disease such as the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Evaluation (APACHE) have been commonly used to evaluate organ function or for prognosis of outcomes in ICU patients [4,5]. Most patients with sepsis are initially evaluated and treated in an ED during the early phase of sepsis. The application of these scoring systems has not provided sufficient information to evaluate their prognostic accuracy for predicting the severity of sepsis and hospital mortality in patients with sepsis admitted to an ED [6]. However, a recent study reported that the performance of the Mortality in Emergency Department Sepsis (MEDS) score is better than that of other clinical scoring systems and, therefore, could be reliably used for predicting hospital mortality in patients diagnosed with sepsis who were admitted to an ED [7].

Procalcitonin (PCT) is regarded as a potential marker for the inflammatory response to infectious conditions. PCT has been evaluated as a marker for predicting outcome in various clinical settings, but in patients with sepsis, the prognostic value of PCT has been variable [8,9].

Neutrophil gelatinase-associated lipocalin (NGAL) is a large glycosylated protein monomer synthesized in renal tubular epithelial cells. Following acute tubular damage of various causes, NGAL is greatly increased in the blood and urine. Therefore, NGAL appears to be a good diagnostic and prognostic marker for acute kidney injury (AKI) [10,11]. Moreover, NGAL is an independent predictor of outcome for patients admitted to hospital for heart failure and preeclampsia [12,13]. However, few studies have focused on NGAL as a prognostic biomarker for hospital mortality in patients with sepsis in EDs [14,15].

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2. Methods

2.1. Study population

An overall study protocol was reviewed and approved by the Institutional Review Board of the Konkuk University Medical Center (KUH1260024). Individual informed consent was not required by the review board because the biological makers were routinely examined during the course of treatment in patients with sepsis. The information and records of all enrolled patients were anonymized and de-identified prior to analysis.

This observational study was performed from November 2012 to September 2014 in the ED of Konkuk University Medical Center, a tertiary teaching hospital with approximately 53,000 annual ED visits. We enrolled 470 patients with sepsis from the ED. The baseline characteristics, clinical presentations, and laboratory results were prospectively collected, and reviewed after the study period.

All patients over 18 years old who fulfilled diagnostic criteria of the 2001 International Sepsis Definitions Conference were enrolled [16]. The exclusion criteria were age <18 years, patients admitted for hemodialysis or peritoneal dialysis, transferred from other hospitals, or admission for palliative care. The primary end point was 28-day hospital mortality. We used the Acute Kidney Injury Network group criteria to define AKI [17].

2.2. Data collection

To measure biological markers, blood specimens were obtained from a peripheral vein within 1 h of arrival at the ED. Specimens for NGAL and PCT were obtained at the same time. Plasma NGAL was measured using a Triage NGAL Test (Alere Inc.). This point-of-care fluorescence immunoassay has a measurable range from 15 to 1300 ng/ml, and the upper normal limit of NGAL was 150 ng/ml. Serum PCT was measured using an Elecsys Brahms PCT assay (Thermo-Fisher). This electrochemiluminescence immunoassay has a measurable range from 0.02 to 100 ng/ml.

The MEDS score was calculated using nine variables (terminal illness, age, respiratory difficulty, septic shock, platelets, band count, nursing home resident, lower respiratory tract infection, and altered mental status) assessed in the ED [18]. All enrolled patients were categorized into 5 risk groups according to their MEDS score. The APACHE II score was calculated for each patient using previously defined criteria by Knaus et al. [19].

2.3. Statistics

Collected data were recorded using Microsoft Office Excel 2010 (Microsoft Corp), and all statistical analyses were performed using IBM SPSS ver 22. Nonnormally distributed variables including age, creatinine, C-reactive protein (CRP), PCT, plasma NGAL, and MEDS score are expressed as median (25%–75% interquartile range). Multigroup comparisons were conducted using a Kruskal–Wallis test, and a Mann–Whitney *U* test was used for two-group comparisons. Categorical variables are presented as numbers and percentages, and a χ^2 test was used for comparison.

To compare the prognostic value of biological markers for hospital mortality, receiver operating characteristic (ROC) curves were generated, and the areas under the curve (AUC) were determined. A multivariable Cox regression analysis was used to evaluate the independent predictors of hospital mortality, and hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. Spearman correlation tests were conducted to evaluate the relationships between NGAL, PCT, CRP levels, MEDS and APACHE II scores. All statistical tests were 2-sided, and $p < 0.05$ was considered significant.

3. Results

Between November 2012 and September 2014, 470 patients were enrolled and observed for 28 days. The characteristics, comorbidities, biological marker levels, and outcomes of enrolled patients are summarized in Table 1. Primary infection sites were respiratory infection (n = 196), intra-abdominal infection (n = 143), urinary tract infection (n = 84), and soft tissue infection (n = 18). AKI occurred in 76 patients (16.2%), and the 28-day hospital mortality was 8.9% (42/470) in all subjects.

Enrolled subjects were stratified into five risk categories based on their MEDS score: very low-, low-, moderate-, high-, and very high-risk. The 28-day hospital mortality increased with MEDS score, especially in the very high-risk category (Table 2).

The median CRP, PCT, and NGAL levels in each MEDS risk category are presented in Table 2. The median NGAL levels in each risk category were 216 (137–354), 281 (146–472), 290 (155–610), 273 (152–565), and 896 (415–1200) ng/ml, respectively. The median NGAL levels were significantly higher in the very high-risk patients than in patients with another MEDS risk score (all $p < 0.001$) (Fig. 1). There were no significant differences between the low-, moderate-, and high-risk groups (all $p > 0.05$).

The initial median creatinine, CRP, PCT, and NGAL levels in survivors and nonsurvivors at ED admission are presented in Table 3. The median NGAL level was significantly higher in the nonsurvivors than in the survivors (658 (410–1300) vs. 260 (147–475) ng/ml; $p < 0.001$). The creatinine, CRP, and PCT levels on admission to the ED were not significantly different between the survivor group and nonsurvivor group ($p =$ 0.054, 0.373, and 0.088, respectively).

The NGAL and PCT levels were higher in patients with AKI than in patients who did not develop AKI (514 (235–1177) vs. 260 (142–454) and 5.40 (0.47–15.37) vs. 0.69 (0.26–5.31) ng/ml, respectively; all $p <$ 0.001). The AUC for predicting AKI was 0.721 for NGAL level, significantly higher than that for PCT (0.642) and MEDS score (0.633).

The ROC curves for CRP, PCT, NGAL levels, MEDS score, and APACHE II score for predicting 28-day hospital mortality in patients with sepsis are shown in Fig. 2. The AUC of NGAL was 0.797 (95% confidence interval (CI) 0.757–0.832; $p < 0.001$), which was higher than PCT (0.599 (95% CI 0.549–0.647; $p = 0.054$)), CRP (0.542 (95% CI 0.495–0.587; $p = 0.382$)), and MEDS score (0.774 (95% CI 0.734–0.811; $p < 0.001$)).

Table 1
Baseline characteristics of enrolled subjects.

Characteristics	Total subjects (n = 470)
Age (y)	74 (61–81)
Male sex (no.)	224 (47.7%)
Comorbidity (no.)	
Hypertension	189 (40.2%)
Diabetes mellitus	123 (26.2%)
Cerebrovascular disease	83 (17.7%)
Chronic liver disease	52 (11.1%)
Chronic heart disease	38 (8.1%)
COPD	23 (4.9%)
Clinical presentation	
Systolic BP (mmHg)	130 (114–146)
Diastolic BP (mmHg)	72 (62–84)
Pulse rate (beats/min)	101 (88–115)
Respiratory rate (breaths/min)	22 (20–23)
Body temperature (°C)	37.3 (36.7–38.3)
Biological marker	
WBC ($\times 10^3/\mu l$)	11.5 (7.4–16.4)
CRP (mg/dl)	10. 7 (3.8–19.6)
PCT (ng/ml)	0.94 (0.28–6.73)
NGAL (ng/ml)	310 (172–548)
Bacteremia	147 (31.3%)
ICU admission	124 (26.4%)

Abbreviations: COPD, chronic obstructive pulmonary disease; BP, blood pressure; PCT, procalcitonin; NGAL, neutrophil gelatinase-associated lipocalin.