Clinica Chimica Acta 462 (2016) 140–145

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Usefulness of plasma neutrophil gelatinase-associated lipocalin concentration for predicting the severity and mortality of patients with community-acquired pneumonia

Jong Won Kim, Dae Young Hong *, Kyeong Ryong Lee, Sin Young Kim, Kwang Je Baek, Sang O Park

Department of Emergency Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form 15 September 2016
Accepted 19 September 2016
Available online 20 September 2016

Keywords:
Biological markers
Neutrophil gelatinase-associated lipocalin
Pneumonia, procalcitonin, prognosis

ABSTRACT

Background: The usefulness of plasma neutrophil gelatinase-associated lipocalin (NGAL) concentration for predicting the outcome of community-acquired pneumonia (CAP) is unclear. We evaluated the prognostic value of plasma NGAL concentration for predicting disease severity in comparison with other widely used biological markers of inflammation in patients with CAP.

Methods: NGAL, procalcitonin, and C-reactive protein concentrations were measured in 362 patients with CAP, who were followed for up to 30 days. The Pneumonia Severity Index (PSI) and CURB-65 score were obtained for all patients.

Results: The median plasma NGAL concentration increased with CAP severity classified according to the PSI. Plasma NGAL concentration was higher in nonsurvivors than in survivors. The AUC for predicting mortality was highest for NGAL concentration (0.871), followed by that for PSI (0.865) and procalcitonin concentration (0.744). Multivariable logistic regression analysis showed that plasma NGAL concentration was an independent predictor of hospital mortality in CAP patients. Plasma NGAL concentration correlated positively with C-reactive protein and procalcitonin concentrations, CURB-65 score, and PSI.

Conclusions: Plasma NGAL concentration is a valuable biological marker in the assessment of the severity and prediction of the prognosis of patients with CAP in the emergency department.

1. Introduction

Community-acquired pneumonia (CAP) is a common infectious disease and an important health problem that frequently leads to hospital admission and death. It remains an important cause of morbidity and mortality despite improvements in diagnosis, critical care, supportive care, and antimicrobial therapy.

Assessment of disease severity and prediction of prognosis are recommended for ensuring adequate diagnosis and management of CAP. The Pneumonia Severity Index (PSI) is used widely for scoring the severity of CAP and was developed to identify patients at low risk of death. Although the PSI is useful for clinical decision-making, it is not effective for predicting a high risk of death in patients with CAP [1]. The CURB-65 (confusion, urea, respiration, blood pressure, age ≥ 65 years) is another system for scoring the patient's condition, but it does not include CAP as a comorbidity, and the results have limited applications in elderly patients [2]. Each scoring system has strength and weaknesses; the more complicated PSI was developed to identify low-risk patients, and the simpler CURB-65 was developed to identify patients with a serious condition.

In addition to the PSI and CURB-65, several biological markers are used in the assessment of the severity and prognosis of pneumonia during early infection. Among them, procalcitonin (PCT) has been reported to be a useful prognostic marker in high-risk patients with CAP [3,4]. However, inconsistent results have been reported for PCT concentration in patients with less-severe disease seen in the emergency department (ED) [5].

Neutrophil gelatinase-associated lipocalin (NGAL) is a large glycosylated protein that is released from activated human neutrophil granules in various clinical conditions. The exact function of this protein is unclear, although it is a considered to be a critical component of the innate immune system. A previous study reported that NGAL concentration was a good early biomarker of acute kidney injury in multiple clinical situations [6]. However, few studies have focused on NGAL concentration as a prognostic biological marker of hospital mortality.

* Corresponding author at: Department of Emergency Medicine, Konkuk University Medical Center, 120-1 Neungdong-ro (Hwayang-dong), Gwangjin-gu, Seoul 05030, Republic of Korea.
E-mail addresses: kuhemkjw@gmail.com (J.W. Kim), kuhemhdy@gmail.com (D.Y. Hong), kuhemlkr@gmail.com (K.R. Lee), 20110096@kuh.ac.kr (S.Y. Kim), kuhembkj@gmail.com (K.J. Baek), kuhempark@gmail.com (S.O. Park).

http://dx.doi.org/10.1016/j.cca.2016.09.011
0009-8981/

Therefore, the aim of this study was to evaluate the usefulness of NGAL concentration as a prognostic marker for assessing disease severity and mortality risk in CAP patients.

2. Materials and methods

2.1. Study design and population

This observational study of CAP patients presenting to the ED was conducted at the Konkuk University Medical Center, an 870-bed teaching hospital in Seoul, South Korea. This study was performed over a 35-month period, from May 2013 to March 2016, in the ED, which has an annual census of about 50,000 visits. The baseline characteristics and clinical and laboratory data of patients were collected prospectively and reviewed after the study period ended. The information and records of all enrolled patients were anonymized and deidentified before analysis.

All consecutive patients aged ≥ 19 years were included in the study. The exclusion criteria were a) age < 19 years; b) treatment in an outpatient setting; c) prior hospitalization within 14 days; d) chronic renal failure requiring hemodialysis or e) admission for palliative care. We analyzed the baseline characteristics, disease severity, inflammatory and biological markers, and outcomes of all patients.

The present study was approved by the Institutional Review Board (IRB) of Konkuk University Medical Center (IRB No: KUH1260025). Individual informed consent was not required by the IRB because the biological markers were measured routinely during the course of management.

CAP was defined as the presence of a new pulmonary infiltration on a chest radiograph together with at least one respiratory symptom including fever (>38.0 °C), cough, sputum production, hemoptysis, dyspnea, or pleuritic chest pain.

Using the patient demographics and baseline clinical data, the severity of CAP at ED admission was estimated using the PSI and CURB-65 score. The PSI was calculated using the following variables: age, sex, complications, abnormal vital signs, laboratory test results, blood gas analysis, and radiographic parameters [7]. The patients were classified into three groups as follows: low-risk (PSI ≤90), intermediate-risk (PSI 91–130), and high-risk (PSI ≥131) groups. The CURB-65 score was calculated using the following clinical criteria: new-onset confusion, blood urea concentration > 7 mmol/l or blood urea nitrogen > 19 mg/dl, respiratory rate ≥ 30/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years [8]. The primary outcome of this study was mortality within 30 days following ED admission. The secondary outcome of interest was intensive care unit (ICU) admission. Survival was obtained from medical record and patients or their relatives by phone call over 30 days after admission to the ED.

2.2. Sample size

A pilot study was performed during 3 months. The appropriate sample size was calculated based on means and SD. The mean NGAL concentrations were 284 ng/ml (SD 194) in survivors and 449 ng/ml (SD 161) in nonsurvivors. At 0.8 power and α error 0.05, the required sample size is 30 participants per group.

2.3. Measurement of NGAL and other markers

Plasma NGAL and serum PCT concentrations were measured within 1 h of arrival at the ED. Plasma NGAL concentration was measured using the Triage NGAL Test Kit (Alere Inc.), with a measurable range of 15–1300 ng/ml. Serum PCT concentration was measured using an electrochemiluminescence immunoassay (Brahms GmbH) on a Roche Cobas e-System (Roche Diagnostics). The measurable range of the assay was 0.02–100 ng/ml, and the functional assay sensitivity (interassay coefficient of variation, 20%) was 0.06 ng/ml. Total white blood cell (WBC) count and its differential were measured using a Sysmex XN Hematology analyzer. Serum separation tubes were used in the measurement of high-sensitivity C-reactive protein (hsCRP) concentration. The CRP-Latex ×2 latex immunoturbidimetric method (Denka Seiken Co) and a Toshiba 200FR analyzer were used.

2.4. Microbiologic studies

Two bottles of blood cultures was collected from all patients in the ED shortly after CAP diagnosis, and sputum was obtained when possible, before antibiotics were administered. Urinary antigen test for *Streptococcus pneumonia* and *Legionella pneumophila* was performed in most patients.

2.5. Statistics

All data were processed using Microsoft Office Excel 2010 (Microsoft Corp), and all statistical analyses were performed using IBM SPSS Statistics 21 (IBM Corp) and MedCalc 16. Continuous variables are presented as median (25th, 75th percentiles). The Mann–Whitney *U* test and the Kruskal–Wallis test were used to compare nonparametric data. Categorical variables are presented as numbers and percentages, and the χ^2 test was used for comparisons.

The prognostic values of biological markers and risk scores for predicting 30-day mortality were evaluated by constructing receiver-operating characteristic (ROC) curves, and the AUCs were determined to ascertain the efficacy of the biological markers. The methods of Hanley & McNeil were used for the calculation of the standard error of the AUC and of the difference between two AUCs. On the basis of the optimal cutoff values determined according to ROC curve analysis, the sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR–) were calculated. The patients were divided into two groups according to cutoff NAGL concentration, and Kaplan-Meier survival curves for subgroups were produced.

A multivariable Cox regression analysis was used to evaluate the independent predictors of 30-day mortality; the hazard ratios (HRs) and 95% confidence intervals (CIs) were also calculated. Spearman correlation tests were conducted to evaluate the relationships between NGAL concentration and WBC count, hsCRP concentration, PCT concentration, CURB-65 score, and PSI. All statistical tests were 2-sided, and $p < 0.05$ was considered significant.

3. Results

Between May 2013 and March 2016, 386 patients with a diagnosis of CAP were enrolled in this study. Of the patients, 22 patients were excluded because they had an alternative diagnosis, as were 2 more foreign patients, who were lost during follow-up. A final group of 362 patients with definite diagnostic of CAP at discharge was obtained. The baseline characteristics, comorbidities, clinical presentations, and outcomes of the participating patients are summarized in Table 1. The 30-day hospital mortality rate was 10.5% (38/362) for all patients.

The causative pathogen was identified in 64 (17.7%) patients; the specific pathogens were *Streptococcus pneumoniae* (n = 19), *Staphylococcus aureus* (n = 13), *Pseudomonas aeruginosa* (n = 9), *Klebsiella pneumoniae* (n = 6), *Haemophilus influenza* (n = 2), *Escherichia coli* (n = 2), and others (n = 13).

All participating patients were stratified into three risk groups based on the PSI (Table 2). The high-risk group comprised 13.3% of the CAP patients. The 30-day hospital mortality was significantly higher in patients in the high-risk group than in those in the other two risk groups.

The median WBC count and concentrations of hsCRP, PCT, and NGAL in each PSI risk group are presented in Table 2. The WBC count did not differ significantly between the three groups, but the concentrations of hsCRP, PCT, and NGAL did. The median NGAL concentration was 217 ng/ml (range 134–310) in the low-risk group, 308 ng/ml (range