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Original Contribution

Prognostic value of serum pregnancy-associated plasma protein A level at the initial ED presentation in elderly patients with CAP☆,☆☆

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ABSTRACT

Objective: This study aims to compare serum pregnancy-associated plasma protein A (PAPP-A) levels in surviving and nonsurviving elderly patients with community-acquired pneumonia (CAP), investigating whether PAPP-A is correlated with CAP prediction scores and whether PAPP-A can successfully predict 28-day mortality rates in elderly patients.

Methods: This prospective, observational, single-center, cross-sectional study was conducted at the emergency department (ED) of Celal Bayar University Hospital in Manisa, Turkey, between January and September 2014. All patients underwent follow-up evaluations 28 days after admission. The end point was defined as all-cause mortality.

Results: A total of 100 elderly patients (mean age, 77.3 ± 7.6 years [range, 65-94 years]); 60% men) with CAP were enrolled in this study. All-cause mortality at the 28-day follow-up evaluation was 22%. Admission PAPP-A levels were significantly higher in nonsurvivors compared with 28-day survivors (10.3 ± 4.5 vs 3.8 ± 2.6 ng/mL, $P < .001$). A significant and positive correlation between admission PAPP-A levels and pneumonia severity index; confusion, oxygen saturation, respiratory rate, blood pressure, and age 75 years or older; and confusion, urea, respiratory rate, blood pressure, and age older than 65 years scores was found ($r = .440$, $P < .001$; $r = .395$, $P < .001$; and $r = .359$, $P < .001$, respectively). Moreover, we determined that the optimal PAPP-A cutoff for predicting 28-day mortality at the time of ED admission was 5.1 ng/mL, with 77.3% sensitivity and 77.9% specificity.

Conclusions: Serum PAPP-A level is valuable for predicting mortality and the severity of the disease among elderly patients with CAP at ED admission. Thus, PAPP-A might play a further role in the clinical assessment of the severity of CAP.

1. Introduction

Community-acquired pneumonia (CAP) is one of the most common infectious diseases in emergency departments (EDs) and causes of hospitalization and mortality, even in patients receiving advanced medical care and especially the elderly [1]. Several guidelines, clinical scoring tools, and biomarkers have therefore been developed to predict mortality, safe management in the outpatient setting, and hospitalization or intensive care unit (ICU) admission of patients with CAP [2,3].

Pregnancy-associated plasma protein A (PAPP-A) is a zinc-binding matrix metalloproteinase that regulates extracellular matrix remodeling [4]. Pregnancy-associated plasma protein A degrades insulin-like growth factor binding protein 4, increasing levels of local insulin-like growth factor-1 in response to local and systemic injury [5,6]. Recently, several studies investigated the prognostic role of serum PAPP-A levels in different diseases such as acute coronary syndromes, end-stage renal disease, type 2 diabetes, and cancer [7,8]. In contrast, data on serum PAPP-A levels and their prognostic value in elderly patients with CAP have not yet been considered to our knowledge [9]. The main objective of this study was to compare serum PAPP-A levels in surviving and nonsurviving elderly patients with CAP, investigating whether PAPP-A is correlated with CAP

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☆☆ Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the manuscript.

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prediction scores and whether PAPP-A can successfully predict 28-day mortality rates in elderly patients at the time of admission to the ED [10].

2. Methods

2.1. Study design and setting

This prospective, observational, single-center, cross-sectional study was conducted at the ED of Celal Bayar University Hospital in Manisa, Turkey [11]. Data were collected from consecutive elderly patients who were admitted to the ED with a diagnosis of CAP between January and September 2014 [12]. The hospital has more than 500 beds, and the annual number of ED patient visits is approximately 40 000 per year. The study was approved by local ethical committee of the university (reference no. 20478486-241). Written informed consent was obtained from every patient or patient representative who participated in the study.

2.2. Definitions and clinical scoring tools

Community-acquired pneumonia was defined in our study as occurring when patients showed evidence of new pulmonary infiltrates on chest imaging and symptoms consistent with pneumonia, including cough with or without sputum production, dyspnea, fever (>38.0°C) or hypothermia (<36.0°C), and/or pleuritic chest pain, none of which was acquired in a hospital. Hospital-acquired pneumonia (HAP) was defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission. Health care–associated pneumonia (HCAP) was defined for patients who (1) had undergone hospitalization (for ≥2 days), home infusion therapy (including antibiotics), and/or home wound care in the preceding 90 days; (2) had undergone chronic dialysis within the last 30 days; (3) were residents of nursing homes or extended care facilities; and/or (4) had family members with multidrug-resistant pathogens.

The severity of CAP was evaluated using the confusion, urea, respiratory rate, blood pressure, and age older than 65 years (CURB-65) (confusion, urea >7 mmol/L [19 mg/dL], respiratory rate ≥30 breaths/min, systolic blood pressure <90 mm Hg and/or diastolic blood pressure ≤60 mm Hg, and age ≥65 years) [13]; confusion, oxygen saturation, respiratory rate, blood pressure, and age 75 years or older (CORB-75) (confusion, peripheral oxygen saturation ≥90%, respiratory rate ≥30 breaths/min, systolic blood pressure <90 mm Hg and/or diastolic blood pressure ≤60 mm Hg, and age ≥75 years) [14]; and pneumonia severity index (PSI) [15] scores.

2.3. Pregnancy-associated plasma protein A assay

At the time of enrollment, before the patients with CAP received treatment protocols, 2 mL of peripheral blood was collected for the measurement of serum PAPP-A in samples using direct venipuncture of the antecubital vein. Blood samples were centrifuged at 4000*g* for 10 minutes; serum was separated and immediately stored at −80°C in Eppendorf tubes until analysis. At the end of the study, samples were kept at room temperature and melted. The concentration of PAPP-A in plasma was analyzed using the chemiluminescent method (Unicel DxI 600; Beckman Coulter Inc, Fullerton, CA) using commercial kits (Access PAPP-A assay) in accordance with the manufacturers' instructions. The analysis was performed by laboratory specialists blinded to all patient details, treatments, and clinical outcomes. All serum samples were analyzed on the same day and in duplicate to avoid interassay variance. Other laboratory results were determined by standard methods.

2.4. Selection of participants

All consecutive ED patients older than 65 years old with a diagnosis of CAP were included. We excluded patients who met any of the following criteria: younger than 65 years; pregnant; premenopausal; readmission; diagnosed with HAP, HCAP, or aspiration pneumonia; active pulmonary tuberculosis; known human immunodeficiency virus positivity; and chronic immunosuppression (defined as immunosuppression for solid organ transplantation, postsplenectomy, receiving ≥10 mg/d prednisolone or equivalent for <30 days, treatment with other immunosuppressive agents, or neutropenia [$<1.0 \times 10^9$/L neutrophils]). Patients whose PAPP-A measurements were unavailable or who were lost to follow-up were also excluded.

2.5. Data collection

The following parameters were collected upon admission to the ED: age, sex, admission from home or a nursing home, comorbidities, and medication use. Hemodynamic parameters were also assessed upon admission as follows: blood pressure, pulse rate, respiratory rate, peripheral oxygen saturation in room air, body temperature, and mental confusion (defined in our study as new disorientation in time, place, or person). Additional data collected for all patients included laboratory tests at the ED, chest x-ray or chest computed tomography scan findings, and outcome variables (the requirement for ICU admission or mechanical ventilation, length of stay [LOS] in the hospital, and all-cause 28-day mortality). The severity of CAP was graded according to the CURB-65, CORB-75, and PSI scores on admission.

2.6. Study protocol and follow-up evaluation

All patients included in this study were treated according to the Infectious Diseases Society of America/American Thoracic Society consensus guidelines for the management of CAP in adults and were followed up with after a 28-day period. The primary end point was 28-day all-cause mortality. The secondary outcomes of interest were hospital admission, ICU admission, requirement for mechanical ventilation, and LOS in hospital. Survival status and dates of death were obtained from patients or their relatives by telephone interviews at 28 days; the data were further validated by reviewing the hospital's medical records. For deaths occurring outside the hospital, we reviewed the local civil demographics database, which reports all deaths that have occurred in the study area on a daily basis.

2.7. Statistical analysis

Patients were divided into 2 groups (survival and nonsurvival) based on their survival at the 28-day mark. The normality of data distribution was checked with the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± SD or median (interquartile range) according to normal or nonnormal distributions. Categorical variables were presented as absolute values and percentages. The demographic, clinical, and laboratory variables were compared between the 2 groups. Differences between survivors and nonsurvivors were investigated using the Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables. The correlations between PAPP-A and clinical scoring tools were analyzed using Spearman rank correlation. A receiver operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff value of PAPP-A for predicting 28-day mortality. The area under the ROC curve was calculated and used to evaluate diagnostic accuracy. The cumulative survival rate was calculated using the Kaplan-Meier method, and differences in survival between the groups were compared using the Mantel-Cox log-rank test. To identify variables associated with 28-day mortality, data were initially analyzed by univariate analysis. Significant variables were subsequently entered into a stepwise forward logistic regression analysis. For all tests, $P < .05$ was considered statistically significant. The analyses were performed using SPSS for Windows, release 21.0 (SPSS Inc, Chicago, IL).