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Original Contribution

A novel biochemical marker for community-acquired pneumonia: Ischemia-modified albumin

Mustafa Bolatkale [a,*], Mustafa Duger [b], Gözde Ülfer [c], Çağdaş Can [d], Ahmet Cagdas Acara [e], Türkan Yiğitbaşı [c], Ekrem Cengiz Seyhan [b], Mehtap Bulut [a]

[a] Medipol University Hospital, Department of Emergency Medicine, Istanbul, Turkey
[b] Medipol University Hospital, Department of Pulmonology, Istanbul, Turkey
[c] Medipol University Hospital, Department of Biochemistry, Istanbul, Turkey
[d] Merkezefendi State Hospital, Department of Emergency Medicine Manisa, Turkey
[e] Gaziemir State Hospital, Department of Emergency Medicine, Izmir, Turkey

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ABSTRACT

Introduction: Community-acquired pneumonia (CAP) is a frequent cause of hospitalization and a leading cause of mortality worldwide. Early diagnosis and the initiation of appropriate antibiotic therapy are essential to reduce pneumonia-related morbidity and mortality. CRP is a well-established biomarker in many clinical settings, but has been traditionally considered not specific enough to be a useful guide in the diagnostic process of pneumonia. There is still a need for more specific and practical markers in CAP for diagnosis. The aim of this study was to investigate the diagnostic value of ischemia-modified albumin (IMA) levels in the diagnosis of CAP in the Emergency Department.

Methods: The study included 81 patients admitted with CAP and 81 control patients. Initial hour levels of IMA and CRP were measured. The IMA mean levels were compared between the study and control group. Correlation analyses were performed to investigate the association of serum IMA levels with CRP.

Results: Mean levels of IMA were 0.532 ± 0.117 IU/ml in the study group and 0.345 ± 0.082 IU/ml in the control group. IMA levels were significantly higher in the study group compared to the control group. The IMA level of 0.442 IU/ml had sensitivity of 75.3% and specificity of 91.3% and was positively correlated with CRP levels ($r = 0.506$; $p < 0.05$).

Conclusion: Blood IMA levels significantly increase in adult patients presenting with CAP. IMA may be considered as a novel biomarker in the diagnosis of CAP.

1. Introduction

Community-acquired pneumonia (CAP) is defined as an infection of the lung parenchyma that is not acquired in a hospital, long-term care facility, or other recent contact with the health care system. CAP is a significant cause of morbidity and mortality in adults [1]. Some studies have also reported epidemiological and clinical data demonstrating that the incidence, prevalence, and mortality rate of CAP increase with ageing [2]. In clinical care, the mortality rate remains at 5–15% [3]. In the USA, the annual estimated costs for treating CAP exceed US$12 billion [4].

Several risk scores are available for the evaluation of the prognosis of patients with CAP [5].The pneumonia severity index (PSI) described by Fine et al. [6] in 1997 is widely used in the United States [7]. In Europe, CURB-65, a score covering the variables of acute confusion, serum urea, respiratory rate, blood pressure and age, is used to predict prognosis [7, 8]. Biochemical markers of inflammation have also been discussed as potentially important prognostic variables. These include, the readily available C-reactive protein (CRP) level and white blood cell count (WBC). However, the value of these markers remains unclear.

CRP is a well-established biomarker in many clinical settings, but has been traditionally considered not to be specific enough to be a useful guide in the diagnostic process of pneumonia. In fact, virtually all infective, autoimmune, ischemic and neoplastic diseases can contribute to increased serum CRP values. Nevertheless, some studies have confirmed that it may have a good performance in defining pneumonia diagnosis and severity [9]. New, simple, sensitive and specific tests to diagnose CAP are therefore warranted to reduce the number of advanced imaging techniques needed. Despite the use of various biochemical markers and

* Corresponding author.
E-mail addresses: dr.mustafa46@hotmail.com (M. Bolatkale), Mustafa_duger@hotmail.com (M. Duger), gozde.ulfer@medipol.com.tr (G. Ülfer), drcagdascan@yahoo.com (Ç. Can), cagdasacara@gmail.com (A.C. Acara), tyigitbasi@medipol.edu.tr (T. Yiğitbaşı), drekremcs@yahoo.com (E.C. Seyhan), mbulut94@yahoo.com (M. Bulut).

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probability calculation algorithms based on clinical findings for that purpose, there is still a need for more specific and practical markers in CAP diagnosis [10].

Ischemia modified albumin (IMA) is an FDA-approved test and one of the newly investigated cardiac markers [11]. IMA results from the modification of N-terminus cobalt binding sites of albumin, which is caused by the release of free radicals from ischemic tissue. The formation of this new albumin molecule, which has lost its ability to bind cobalt, is one of the earliest predictors of ischemia [12]. However, new studies have shown that IMA, which is evaluated as a cardiac ischemia marker, may also increase in different pathologies and affect other organs [13]. Previous studies have revealed that IMA levels are significantly increased in adults with severe sepsis [14]. However, there are no studies in literature regarding IMA levels in adult patients with CAP. In this study, the diagnostic value of IMA was investigated in patients who presented at the Emergency Department (ED) with CAP. The aim of the present study was to compare CRP and IMA in the diagnosis of community-acquired pneumonia and therefore the relationship of IMA and CRP with PSI was examined.

2. Methods

Approval for this prospective case-control study was granted by Medipol University Clinical Research Ethics Committee. The study was conducted in Medipol University Hospital Adult ED within 6 months of approval. (28.10.2015/E3200-509)

2.1. Study and control groups

The study group was formed of patients with a diagnosis of CAP who presented in ED and adult patients who experienced CAP in ED. The control group comprised healthy adults with no chronic disease. A written informed consent form was provided by patients (from patient himself/herself if conscious and from his/her relatives if unconscious) who agreed to participate in the study. All patients in both groups were ≥18 years old.

Gender, age, hemograms, CRP and IMA levels were recorded for both groups and the following values were examined such as vital signs, GCS of the patient, blood gases, glucose, BUN, creatinine, Na, K and PSI Scores of the study group. Morbidity and mortality were also noted on the study form.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

Study group: The radiological verification of a newly manifest infiltrate was required. Patients were enrolled who presented with clinically typical pneumonia, if at least two clinical symptoms were present suggestive of respiratory tract infection (i.e. dyspnea, cough, new or purulent sputum, fever >38.0 °C, pleuritic chest pain). Atypical cases presenting for example with mobility impairment, falls, confusion, incontinence or other signs of clinical deterioration were included when a newly manifest infiltrate was verified and no other cause could be detected which sufficiently explained the clinical condition of the patient.

Control group: Patients without any exclusion criteria who presented at the ED due to complaints not including any disease.

2.2.2. Exclusion criteria

Cases were excluded if they had stenosis-induced or aspiration pneumonia, malignancy and were receiving chemotherapy or radiotherapy. Patients were also excluded if they had been hospitalized within the previous 4 weeks, lacked radiological confirmation of an infiltrate within the first 24 h after admission or were receiving palliative treatment modalities. Patients with neutropenia ($<1.0 \times 10^9$ cells/l), human immunodeficiency virus (HIV) infection, tuberculosis, fungal infection and those treated with steroids in a prednisone-equivalent dosage of >20 mg/day for ≥2 weeks were excluded [15,16]. Patients with acute or chronic conditions that may affect IMA levels such as trauma, acute ischemic heart disease/myocardial infarction, peripheral vascular disease, mesenteric ischemia, acute ischemic cerebrovascular disease, pulmonary embolism, muscle diseases, and liver disease and patients who did not agree to participate in the study were excluded. Nursing home residents were not excluded.

2.3. Biochemical analysis

Blood samples from brachial veins of the study and control groups were collected in empty vacuum tubes to measure IMA and CRP levels. Serum samples were obtained after suitable centrifugation and the samples were stored frozen at −80 °C until the day of serum IMA analysis. Blood gases were taken from the radial artery in the study group (ABL 800 FLEX, Radiometer, Bronshoj, Denmark). Glucose, BUN, creatinine, Na and K were measured immediately in the study group (Cobas 6000 auto analyzer, Roche, Tokyo, Japan). Blood samples were collected in 2 ml EDTA tubes and analyzed on an automated hematology analyzer (XT-2000İ; Symex, Osaka, Japan) in the study and control groups on the first day of presentation.

CRP levels were measured with the immunoturbidimetric method immediately. Blood samples from the brachial veins of the study and control groups were collected in empty vacuum tubes which were initially covered with gel to measure CRP (Cobas 6000 auto analyzer, Roche, Tokyo, Japan).

2.4. Measurement of serum IMA levels

Blood samples from the brachial veins of the study and control groups were collected in empty vacuum tubes which were initially covered with gel to measure IMA levels. After the blood coagulated in the tubes, they were centrifuged at 1200*g* and 3000 rpm for 10 min, and then the upper remaining serum parts were collected into Eppendorf micro centrifuge tubes (Eppendorf AG, Hamburg, Germany) and stored at −80 °C. All blood samples were analyzed in Medipol University Research Laboratory after the end of patient enrollment.

IMA levels were measured with the method described by Bar-Or et al. The albumin Cobalt binding test was analyzed according to the method defined by Bar-Or et al. [12]. In this method 200 ml serum was added to the water solution of 50 ml 0.1% (w/v) cobalt chloridine (Sigma; $CoCl_2.6H_2O$). It was mixed gently and left for 10 min for sufficient cobalt-albumin binding. Then 50 ml dithiothreitol (DTT) (Sigma; 1.5 mg/ml H_2O) was added as a colorizing agent. After waiting for 2 min 1.0 ml 0.9% NaCl was added to stop the cobalt binding process of the albumin. Absorbance was then measured with a spectrophotometer at 470 nm (Shimadzu, model UV160U). Sample blanks without DTT were used as blinds. The results were reported as absorbance units (ABSU).

2.5. Statistical analysis

Statistical analyses of the data obtained in the study were made using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA). Variables were stated as means with standard deviation or median with interquartile range. The Student's *t*-test was used to compare mean values and the Mann-Whitney *U* test was used to compare median values. Frequencies were compared with the Chi-square and Fisher's exact tests. Spearman's and Pearson's correlation tests were applied for correlation analyses. Simple correlation analyses were performed to investigate the association of serum IMA levels with CRP. The median IMA value was calculated, and patients with pneumonia were classified into 2 groups, i.e., those above and equal to or below the median of IMA. To determine a cut-off value of IMA level for pneumonia, receiver operating characteristic (ROC) analysis was performed in sensitivity and specificity calculations. A value of $p < 0.05$ was considered statistically significant.