Prognostic Significance of Ischemia-Modified Albumin Levels in Community-Acquired Pneumonia Cases

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Abstract

Background: Community-acquired pneumonia (CAP) is an important public health problem because of its high morbidity, mortality, and health care costs. Many biomarkers have been used to determine the severity and prognosis of pneumonia. Ischemia-modified albumin (IMA) is a marker of the recently used oxidant-antioxidant mechanism and has been found to increase in many inflammatory conditions. Objectives: To investigate the role of the levels of IMA in CAP and to evaluate its relationship with pneumonia severity. Methods: A total of 150 patients with a diagnosis of CAP and 150 healthy individuals were included in the study. IMA levels were evaluated in both groups. The patients with CAP were divided into ambulatory, ward and intensive care groups, and their IMA levels were compared. Results: There was no significant difference between the two groups in terms of age or gender ($p > 0.05$ for both). No significant difference was observed in the IMA levels of the patient and control groups ($p > 0.05$). The lowest IMA level was observed in the ambulatory group ($p = 0.001$). When the patients in the ambulatory and hospitalized (ward and intensive care together) groups were evaluated, the cut-off value of IMA was 77.60 ABSU, sensitivity was 64.9%, specificity was 75.0%, positive predictive value was 89.2%, and negative predictive value was 40.3%. Conclusion: In the management of patients with CAP, IMA seems to be a useful marker for CAP severity and hospitalization decision. Keywords: Community-acquired pneumonia, ischemia-modified albumin, biomarker

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What is already known about this topic?

IMA is generated due to high oxidative stress not only in myocardial ischemia but also in different ischemia models affecting other organs. We noticed a decrease in IMA levels in our (CAP) patients whom are we diagnosed and treated.

What does this article add?

IMA in patients with CAP is particularly useful in distinguishing outpatients from those requiring hospitalization. We believe that IMA levels can also be a useful indicator for monitoring response to treatment, such as CRP and PCT. IMA is associated with the severity of the disease in CAP.

Introduction

Pneumonia is responsible for a significant portion of doctor consultations, treatment costs, missed work and school days, and deaths worldwide (1). It is the most common cause of infection-related deaths. The reported annual incidence of pneumonia in Europe is 0.5-1.1%, which increases with age (2, 3). While deaths due to infectious diseases have decreased with the widespread use of antibiotics and active immunization as a result of the great advances in medicine, community acquired pneumonia (CAP) still leads to high rates of morbidity and mortality. In Turkey, lower respiratory tract infections constitute the fifth cause of death at a rate of 4.2% (4).

Due to their localization, the lungs are exposed to many toxic, irritant and infectious agents. In case of infection caused by the entry of microorganisms into the body, there is a significant increase in the production of free radicals (5). A change in the balance between oxidants and antioxidants is defined as oxidative stress, which has been associated with various respiratory tract diseases. Asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis have been shown to be associated with oxidative stress (6,7). In cases of pneumonia, there are several inflammatory biological markers used for the prediction of disease severity and treatment follow-up (8). Moreover, various objective criteria have been defined to help the physician make treatment decisions in hospitalized patients. In such cases, the pneumonia severity index (PSI) is the most commonly used tool to Select an appropriate empirical antibiotic and determine disease severity in patients with pneumonia.

Among all the recently studied cardiac markers, ischemia-modified albumin (IMA) is the test approved by the U.S. Food and Drug Administration (9). The principle of this test is the reduction of cobalt-binding capacity of albumin by oxidative free radicals generated during hypoxic acidosis through chemical changes in albumin. This new albumin molecule is called IMA and measured spectrophotometrically using the albumin cobalt binding (ACB) test (10,11). The formation of this new albumin molecule that has lost its ability to bind cobalt is one of the earliest markers of ischemia (12). Recent studies have shown that IMA, which attract researchers' interest as a cardiac ischemia marker, can also increase in different pathologies (13-15). IMA is generated due to high oxidative stress not only in myocardial ischemia but also in different ischemia models affecting other organs (16). Serum IMA levels increase in non-cardiac ischemic diseases, pulmonary embolism, cardiopulmonary resuscitation, end-stage renal diseases, cerebrovascular ischemia, acute mesenteric ischemia, systemic sclerosis, arthroscopic knee surgery, postexercise skeletal muscle ischemia, diabetes mellitus, liver diseases, various cancers, infection, and peripheral arterial diseases (10,16).

In today's conditions where we are confronted with oxidative stress at any moment, there are not sufficient studies evaluating the relationship between pneumonia and oxidative stress. There is a study in the literature that was conducted in the emergency department, which reported that IMA was associated with pneumonia, but no comprehensive study has been undertaken to further investigate the relationship of this oxidative stress marker with pneumonia severity and etiopathogenesis.

The aim of this study was to investigate the role of the IMA level in CAP and to evaluate its relationship with pneumonia severity.

Materials and Methods

This single-center, prospective, case-control study was conducted in the Department of Chest Diseases between April 2018-March 2019. The study was approved by the Ethics Committee (date: 02.04.2018, issue no: 73). Inform consent was obtained from the control group and all the patients included in the study.

A total of 150 adult patients newly diagnosed with CAP and 150 healthy controls were included in the study. The controls were randomly selected from healthy individuals who attended routine controls in the outpatient clinic. In the subgroup analysis, the patients with CAP were divided into three groups according to PSI: those that received outpatient treatment (ambulatory group), those admitted to wards (ward group), and those to the intensive care unit (intensive care group). The demographic data, clinical and laboratory parameters of all the CAP groups and the healthy controls were recorded. The IMA and C-reactive protein (CRP) levels were also evaluated in the CAP and control groups and compared between the three CAP subgroups. In addition, the correlations between the IMA and (CRP) levels were assessed among the patients with CAP. Patients or control aged below 18 years, those with mental disorders, and pregnant women were excluded from the study.

Laboratory tests

IMA measurement was performed using the reduced ACB capacity test with the rapid and colorimetric method developed by Bar-Or et al. To summarize, 200 uL patient serum was transferred to glass tubes, to which 50 uL 0.1% CoCl2 x 6H20 (Sigma Aldrich Lot: S38901-248; Sigma Aldrich, St. Louis, MO, USA) was added. After shaking gently, the mixture was incubated for 10 minutes to ensure sufficient cobalt-albumin binding. Then, 50 uL 1.5 mg/mL dithiothreitol (DTT) (Sigma-Aldrich Lot: D5545-1G; Sigma-Aldrich) was added as the coloring agent. After 2 minutes, to stop the binding between cobalt and albumin, 1 mL 0.9% NaCl was added. A blank was prepared for each sample. At the DTT addition step, to obtain a blank, 50 µL distilled water was used instead of 50 µL 1.5 mg/mL DTT. Absorbance values at 470 nm were measured using a spectrophotometer and recorded. Color development in the samples with DTT was compared with the tubes containing the blank solution, and the results were presented as absorbance units (ABSU) (17).

CRP levels were measured turbidimetrically using a BNII Nephelometer Analyzer (Siemens, Munich, Germany) with the CardioPhase hsCRP kit (Siemens Healthcare Diagnostics Products, Marburg, Germany).

Statistical analysis

The statistical analysis of data was performed using IBM® SPSS® (ver. 20.0; SPSS Inc., Chicago, IL, USA) software package. The normality distribution of data was evaluated using the Kolmogorov-Smirnov test. Mean ± standard deviation were used in the descriptive statistics of continuous variables. Pearson's test was used for correlation analysis. In the intergroup comparisons of categorical variables, the chi-square and Fisher's exact tests were used. When comparing two groups in relation to continuous variables, Student's t-test was conducted. Analysis of variance was used. Tukey's test was employed as a post hoc method. The results were considered significant at a 95% confidence level and a p value of <0.05. The receiver operating characteristic analysis was performed to determine the cut-off value of IMA.

Results

The study included a total of 300 cases, of which 150 were in the CAP group and 150 were in the control group. In the CAP group, 38% (n = 57) of the patients were female and 62% (n = 93) were male, while 47.3% (n = 71) of the controls were female and 52.7% (n = 79) were male. The mean age of the 150 patients diagnosed with CAP was 61.03 ± 1.7 years, and that of the control group was 58.0 ± 10.6 years (p = 0.082). There was no significant difference in age and gender between the two groups (p = 0.102 and p = 0.082, respectively). The mean IMA levels were 77.97 ± 6.17 in the CAP group and 77.01 ± 7.51 in the control group. There were not significant differences between the two groups in terms of the IMA levels (p = 0.742).

The demographic data and laboratory findings of the patients with CAP are shown in Table 1 and their comorbidities in Figure 1 according to the ambulatory, ward and intensive care groups. The mean age of the ambulatory group was statistically significantly lower than the other two groups ($p = 0.035$). There were no significant differences in gender between the three groups ($p = 0.794$). IMA was 74.77 ± 5.57 ABSU in the ambulatory patients, 78.58 ± 6.01 ABSU in the ward patients and 80.60 ± 5.97 ABSU in the intensive care patients. Accordingly, IMA was statistically significantly lower in the ambulatory patients compared to the ward patients and those receiving intensive care ($p = 0.004$ and $p = 0.001$, respectively). The distribution of the mean IMA values between the groups is shown in Figures 2 and 3. The CRP value of the ambulatory patients was statistically significantly lower than those of the ward and intensive care patients ($p = 0.001$ and $p = 0.003$, respectively).

When the relationship between IMA and CRP was analyzed within the CAP group, a statistically significant positive correlation was detected ($r = 0.343$; $p = 0.001$). The results of this analysis are shown in Figure 4.

To determine whether an IMA cut-off value could be determined for patients hospitalized due to CAP, the patients were evaluated in two groups as ambulatory patients and hospitalized patients (both ward and intensive care unit). The area under the curve for the serum IMA levels was 0.708 ± 0.049 (95% confidence interval = 0.612-0.804) p [?] 0.001, cut-off value was 77.60 ABSU, sensitivity was 64.9%, specificity was 75.0%, positive predictive value was 89.2%, and negative predictive value was 40.3% (Figure 5).

Discussion

In this study, although the serum IMA levels were found to be statistically similar between the CAP and control groups, they were significantly lower among the ambulatory patients compared to the ward and intensive care groups. In addition, the IMA levels were positively correlated with the CRP levels in the CAP group. These results suggest that IMA levels may be useful in the evaluation of the severity of CAP cases. In addition, they may assist the physician in determining critically ill patients and making a decision for hospitalization.

While death due to infectious diseases continues to decrease with the widespread use of antibiotics and active immunization policies, CAP remains an important lower respiratory tract infection with a high risk of mortality and morbidity. In CAP, disease severity and prediction of clinical outcomes are prerequisites to manage health resources and provide sufficient treatment options. This involves decisions regarding hospitalization in the ward or intensive care unit, early discharge and antimicrobial therapy evaluation. To reduce the rate of unnecessary hospitalization, professional organizations have developed prediction rules (CURB-65, PSI) for classification based on the mortality risk of patients with CAP. Since the CURB-65 and PSI scoring systems are only moderately sensitive and specific in determining the risk in patients with CAP, there is still an emphasis on the need for additional risk factors and prognostic markers to improve the prognostic performance of risk scores (18).

IMA is a new acute coronary syndrome marker found to be associated with oxidative stress. Recent studies have revealed that in addition to its role in acute coronary syndrome, IMA can also play a role in many pathological processes, including pneumonia that alter the balance between oxidant-antioxidant systems. The lung is one of the organs that is most affected by oxidants, and therefore pneumonia is expected to affect the level of IMA.

In the current study, when the CAP cases were compared with the control group, there was no statistically significant difference in terms of the serum IMA levels ($p > 0.05$). In a prospective case-control study by Bolatkale et al., it was shown that the serum IMA levels significantly increased compared with the healthy controls. To our knowledge, that study was the first to analyze the serum IMA levels in adult patients admitted to the emergency department with CAP. The authors showed, for the first time, that IMA could be a new biomarker that was sensitive for and specific to CAP diagnosis in patients diagnosed in the emergency department (19). In our study, there was no statistically significant difference between the CAP cases and the control group in terms of the IMA levels. There were 150 subjects in our patient group and 150 subjects in our control group. Of the patients in the CAP group, 22 were admitted to the intensive care unit, 92 were

hospitalized in the ward, and 36 received ambulatory care. In a study by Bolatkale et al., the case group comprised 81 subjects and the control group comprised 81 subjects. In the case group, six patients required intensive care, 24 were hospitalized in ward, and 51 received ambulatory treatment. The incompatibility between the results of our study and the findings of Bolatkale et al. can be attributed to the differences in the number of individuals in the patient and control groups. Moreover, in the current study, the IMA value of the ambulatory patients was found to be statistically significantly lower than the ward and intensive care patients. To our knowledge, there are no studies in the literature that evaluate pneumonia severity and IMA levels according to disease prognosis. In light of our findings, we concluded that serum IMA levels could be a useful biomarker in the evaluation of severity of CAP cases, making a decision to admit the patient to the ward or intensive care unit, and patient follow-up.

We observed a statistically significant correlation between IMA and CRP in the pneumonia group. Similarly, in a study by Bolatkale et al., a positive correlation was detected between CRP and IMA. Acute inflammatory conditions such as CAP are characterized by the inflammation of pulmonary parenchyma as a response to an infectious event involving systemic and local cytokine secretion and neutrophil uptake. Excessive cytokine production triggers an inflammatory response that can cause organ failure and death. Severity of the infection is correlated with the degree of the inflammatory response of the immune system (20). Specifically, CRP has superior diagnostic value in bacterial infections with a high plasma concentration. However, in majority of viral infections, CRP levels remain normal or increase only slightly (21). A recent study reported a significant correlation between CRP and mortality and defined CRP as an independent risk factor for 30-day mortality (22). Regarding inflammatory markers, recent studies have found that CRP has limited diagnostic value for pneumonia at the first step in cases where the probability of pneumonia is below 10% (23). According to our study, the serum IMA levels, which were correlated with CRP, could be used as a biomarker like CRP in the diagnosis and follow-up of infectious processes such as pneumonia.

PSI is an important index to determine the prognosis and mortality of patients (24). In our study where we classified the patients with CAP according to PSI, we determined that the IMA level could be an important parameter in deciding whether a patient should be hospitalized and predicting the prognosis of CAP. In addition, IMA is similar to other biomarkers in terms of cost, which can be considered as another advantage of this parameter.

The limitations of our study include the IMA reference interval and the expected increase in IMA levels not being fully known in lung infections. In addition, the smoking status of the subjects in the patient and control groups was not recorded, and therefore we did not exclude smokers from either group. There are also no studies in the literature on the relationship between smoking status and IMA levels, and we consider that smoking may have been a factor affecting our results.

In conclusion, IMA levels can be useful in the evaluation of CAP severity. They can also be useful in making a hospitalization decision.

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Table 1. Comparison of the demographic data and laboratory findings between the three CAP groups

	Ambulatory treatment n= 36 PSI I-III Mean ± SD	Hospitalized in ward n= 92 PSI IV-V Mean ± SD	Admitted to intensive care unit n= 22 Mean ± SD	P value
Sex, n (%) Female Male	12 (33.3) 24 (66.7)	36 (39.1) 56 (60.9)	9 (40.9) 13(59.1)	0.794
Age (year)	55.47 ± 15.43	61.64 ± 19.08	67.59 ± 12.90	0.035
IMA (ABSU)	74.77 ± 5.57	78.58 ± 6.01	80.60 ± 5.97	0.001
CRP (mg/L)	63.64 ± 69.05	156.42 ± 105.49	153.26 ± 107.92	0.001
Saturation (%)	96.23 ± -1.79	88.08 ± 9.08	84.68 ± 9.68	0.001

*p¡0.05

CAP: Community Acquired Pneumonia

PSI: Pneumonia Severity Index

IMA: Ischemia-modified Albumin

CRP: C Reaktive Protein

SD: Standard Deviaton

Figure 1. Distribution of comorbidities in the patient group with community-acquired pneumonia (%)

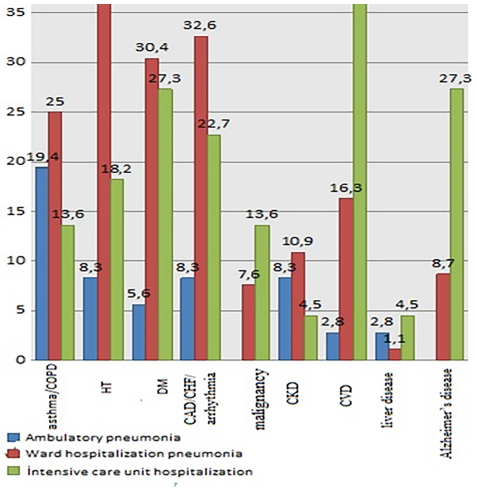
COPD; Chronic Obstructive Pulmonary Disease, CAD; Coronary Arterial Disease, CKD; Chronic Kidney Disease, DM; Diabetes Mellitus, CHF; Congestive Heart Failure, CVD; Cerebrovascular Disease

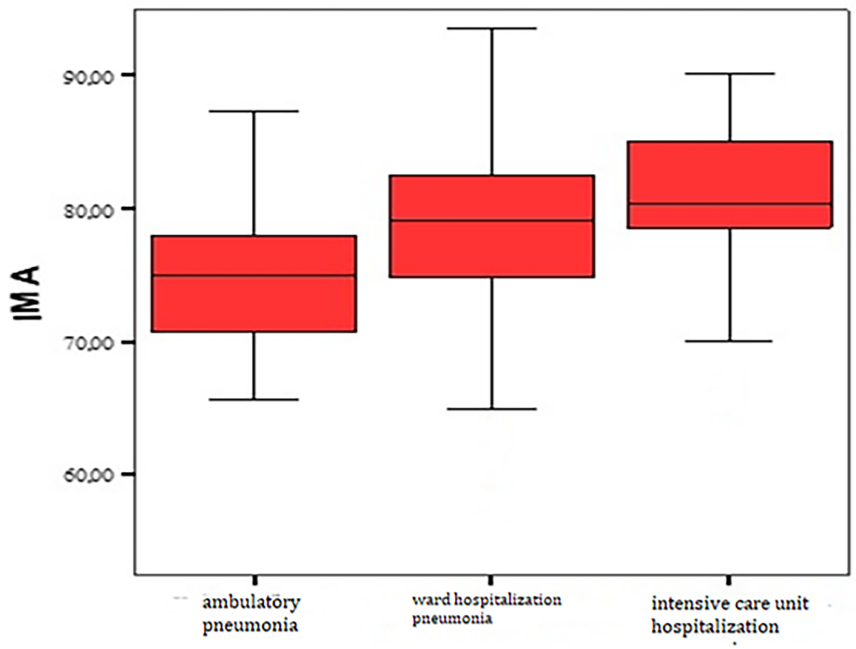
Figure 2. Distribution of IMA values among the community-acquired pneumonia cases

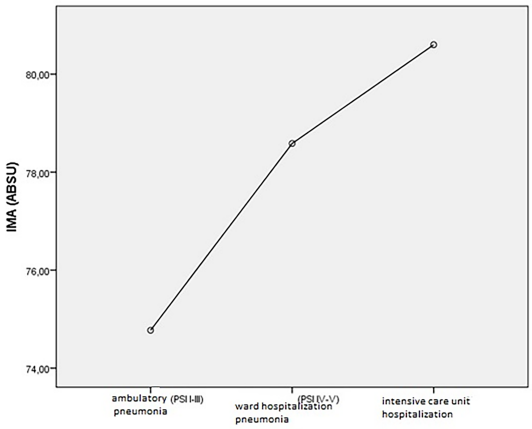
Figure 3. Distribution of IMA levels between the study groups

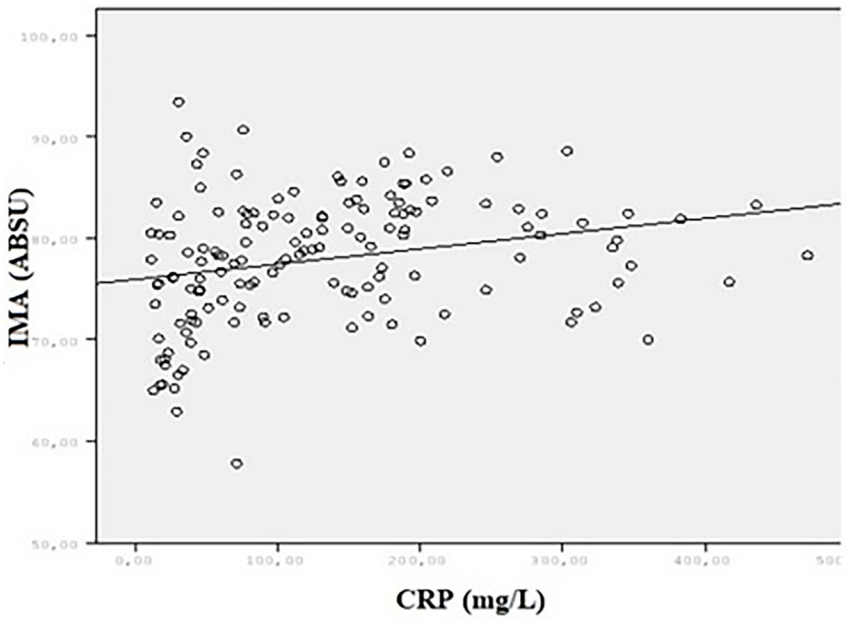
Figure 4. IMA-CRP correlation in the community-acquired pneumonia group

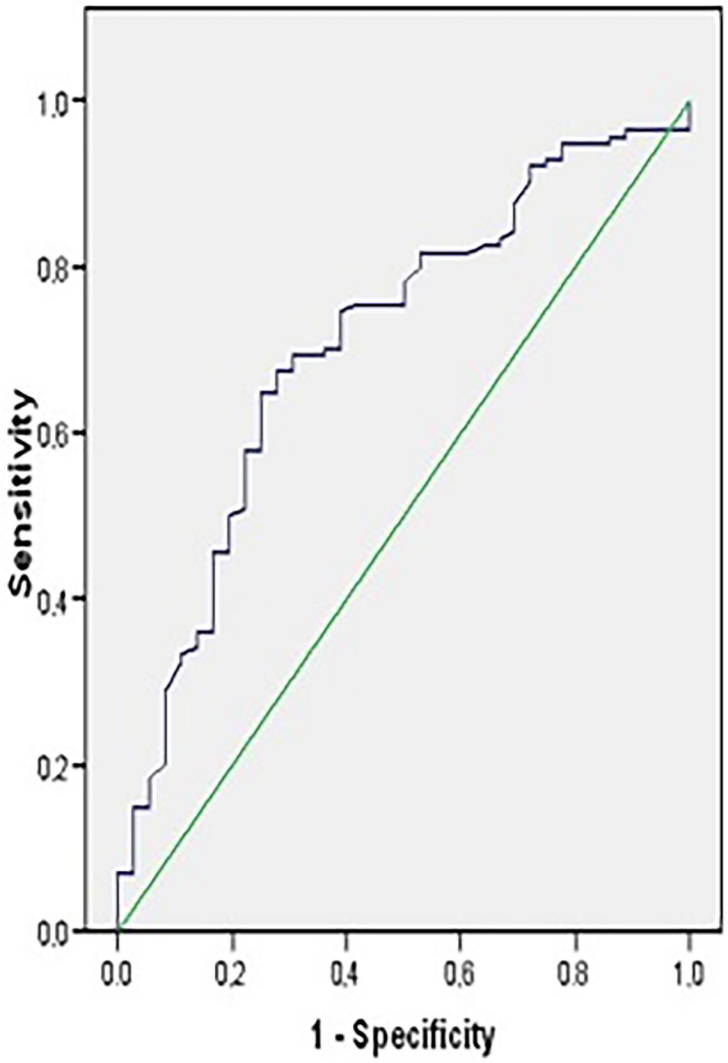
Figure 5. ROC curve demonstrating the correlation between community-acquired pneumonia and IMA











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