

## Original Article

# Serum alkaline phosphatase may play a role in the differential diagnosis of sarcoidosis and tuberculosis

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**Abstract:** Background: Reaching the differential diagnosis of tuberculosis and sarcoidosis can be difficult due to granulomatous inflammation. The aim of this study was to determine alkaline phosphatase (ALP) activity in serum for the differential diagnosis of tuberculosis and sarcoidosis. Methods: This study comprised 242 subjects: 105 acid-fast bacilli (AFB) positive and/or culture-positive patients with pulmonary tuberculosis, 90 patients with biopsy-proven sarcoidosis and a control group consisting of 47 healthy controls were included. ALP activity was measured in serum at the first admission of the patients. Results: The mean serum ALP was 112.74±55.14 IU/L in pulmonary tuberculosis, 76.14±34.23 IU/L in sarcoidosis, and 66.87±18.49 IU/L in the control group, respectively. There was a statistically significant difference between the patient population and the control group (P = 0.03). Also, there was a statistically significant difference between the tuberculosis and sarcoidosis groups (P = 0.034). According to the comparison of tuberculosis and sarcoidosis, the cut-off value was determined as 71.50 IU/L, which had sensitivity of 80%, specificity of 51%, PPV of 66%, NPV of 69%, accuracy of 67%, and the AUC was 0.728. Conclusion: ALP, as a little-known marker for tuberculosis and sarcoidosis, was significantly increased in the pulmonary tuberculosis group compared with the sarcoidosis group. As such, it may be a useful tool for the differentiation of tuberculosis and sarcoidosis.

**Keywords:** Alkaline phosphatase, diagnostic challenges, tuberculosis

## Introduction

Tuberculosis is an infectious disease that caused death of 1.5 million people in 2014 [1]. It has an important role among pulmonary and extrapulmonary granulomatous diseases. Its incidence is steadily increasing because of the association of tuberculosis with AIDS. So, physicians experience difficulties in the differential diagnosis and treatment of tuberculosis. To achieve a definite diagnosis of tuberculosis, *Mycobacterium tuberculosis* bacilli must be detected in sputum [1]. However, this is not always possible. The differential diagnosis of sarcoidosis leads to some difficulties because lung and lymph node involvement mimics tuberculosis. Also, both cause granulomatous inflammation. Therefore, in order to achieve the differential diagnosis between tuberculosis and sarcoidosis more easily, new methods are being developed [2-4].

Alkaline phosphatase (ALP) hydrolyzes phosphate esters at pH 9. The role of ALP has been investigated in other organ systems and their diseases [5, 6]. The importance of alkaline phosphatase in respiratory medicine was studied previously in a limited number of studies involving tuberculous pleurisy [7, 8].

For the differential diagnosis of sarcoidosis and tuberculosis, minimally invasive methods are being researched. We planned this study to evaluate the use of serum ALP in the differential diagnosis of tuberculosis and sarcoidosis, compared with healthy controls.

## Materials and methods

In our study, 105 patients with bacteriologically-proven pulmonary tuberculosis, 90 patients with biopsy-proven sarcoidosis, and a control group consisting of 47 healthy patients were

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**Table 1.** Characteristics of the groups

Parameters Mean $\pm$ SD or n/%	Sarcoidosis N = 90	Tuberculosis N = 105	Control N = 47	P value
Sex (male)	21/23.3%	51/48.6%	18/38.3%	0.001
Age (years)	44.3 $\pm$ 11.2	42.3 $\pm$ 19.4	43.7 $\pm$ 13.4	0.67
ALP (IU/L)	76.1 $\pm$ 34.2	112.7 $\pm$ 55.1	66.8 $\pm$ 18.4	<0.001
CRP (mg/L)	6.8 $\pm$ 7.1	98.2 $\pm$ 72.1	2.4 $\pm$ 2.5	<0.001
ESR (mm/st)	19.2 $\pm$ 18.5	63.5 $\pm$ 28.9	13.1 $\pm$ 9.1	<0.001
WBC (K/uL)	6.9 $\pm$ 1.7	10.2 $\pm$ 3.4	7 $\pm$ 1.4	<0.001

ALP: alkaline phosphatase, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell, P<0.05 is accepted significant.

included. Sputum analyses of all patients with tuberculosis were acid-fast bacilli (AFB)-positive and/or culture-positive. We included asymptomatic patients who were admitted to the internal medicine out-patient clinic for routine health checks for the control group. We excluded patients with known osteoporosis, cholestatic liver disease, and any malignancy.

The study design was retrospective data analysis. Between June 2011 and June 2014, a total of 368 patients' data were analyzed retrospectively. Inclusion criteria were definite diagnosis of tuberculosis or sarcoidosis, available archive data (biochemical values), absence of any other organ malignancies, absence of any disease causing increase in ALP (e.g., chronic liver disease, osteoporosis, osteomalacia), not receiving immune suppressive treatment.

Medical history and findings in physical examination were recorded. The complete blood count (CBC) taken at time of the first admission was used and analyzed using an Abbott Cell-Dyne 3700 System (Abbott Diagnostics, Santa Clara, CA, USA). Also, serum biochemical parameters taken at time of the first admission was used. Serum biochemical parameters were measured using a Beckman Coulter AU 2700 plus (Olympus, Tokyo, Japan).

The study was approved by the Institutional Ethics Committee (number: 3974; date: 22.06.2015). The study conformed to the ethical guidelines of the 2000 Helsinki declaration.

### Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22 (Armonk, NY: IBM Corp) software.

Descriptive values were given as mean and standard deviation. Categorical variables were expressed as the number of cases and the percentage value. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether continuous variables were normally distributed. In the comparison of groups, Student's t-test and Mann-Whitney U test were used according to the normality of distribution of the variables. The comparison of categorical variables was performed using Chi-square and Fisher's exact tests. P value less than 0.05 were considered statistically

significant. Receiver operating characteristics (ROC) curves and areas under the ROC curves (AUC) with 95% confidence intervals (CI) were calculated for the criteria to evaluate optimum cut-off points. In addition to using cut-off points derived from ROC curves, the utility of each criterion for identifying pulmonary tuberculosis was evaluated by calculating the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

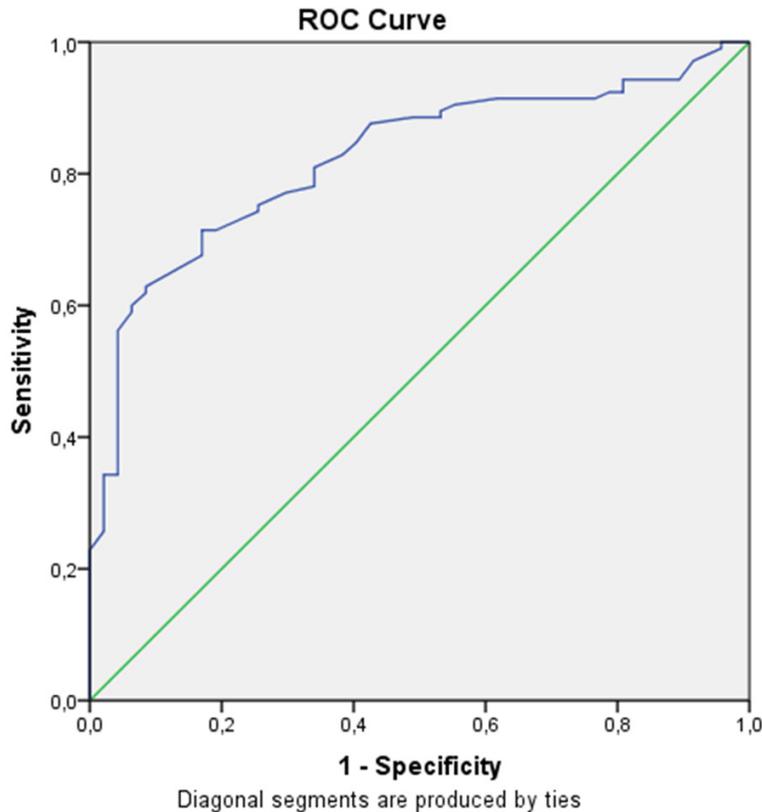
### Results

In the tuberculosis group, 54 patients were women (51.4%) and 51 men (48.6%) with a mean age of 42.3 $\pm$ 19.4 years. In the sarcoidosis group, 69 patients were women (76.7%) and 21 men (23.3%), with a mean age of 44.3 $\pm$ 11.2 years. In the control group, 29 individuals were women (61.7%) and 18 men (38.3%); the mean age was 43.7 $\pm$ 13.4 years. The study population was similar in terms of age in all groups (P = 0.67). Characteristics of the groups were given in **Table 1**.

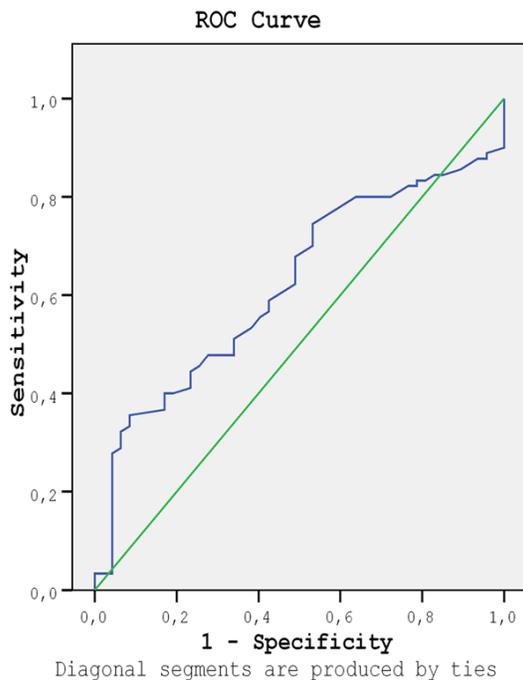
In the group of subjects with pulmonary tuberculosis, the mean serum ALP was significantly higher compared with the healthy control subjects (P = 0.034). In the comparison of tuberculosis with controls, a cut-off value of 64.50 IU/L was determined in the ROC analysis. This cut-off value of ALP had sensitivity of 89%, specificity of 51%, positive predictive value (PPV) of 80%, negative predictive value (NPV) of 67%, accuracy 77% to diagnose tuberculosis. The area under the curve (AUC) was 0.823. The ROC curve is shown in **Figure 1**.

When the sarcoidosis and control groups were compared, serum ALP was significantly higher

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**Figure 1.** ROC curves comparing pulmonary tuberculosis and the control group. For serum ALP, the cut-off value of 64.50 IU/L had sensitivity of 89%, specificity of 51%, positive predictive value (PPV) of 80%, negative predictive value (NPV) of 67%, accuracy of 77%, and area under the curve (AUC) was 0.823 to diagnose tuberculosis.



**Figure 2.** ROC curves comparing the sarcoidosis and control group. Serum ALP cut-off value of 63.5 IU/L had sensitivity of 68%, specificity of 52%, PPV of 73%, NPV of 45%, accuracy of 62%, and AUC was 0.371.

in the sarcoidosis group ( $P = 0.049$ ). Among these groups, the cut-off value of 63.5 IU/L was determined to diagnose sarcoidosis. For this cut-off value of ALP, we found sensitivity of 68%, specificity of 52%, PPV of 73%, NPV of 45%, accuracy of 62%, and AUC was 0.371. The ROC curve is presented in **Figure 2**.

Serum ALP was significantly higher in the tuberculosis group compared with the sarcoidosis group ( $P = 0.034$ ). According to the comparison of tuberculosis and sarcoidosis, the cut-off value of 71.50 IU/L was determined. For this cut-off value of ALP, there was sensitivity of 80%, specificity of 51%, PPV of 66%, NPV of 69%, accuracy of

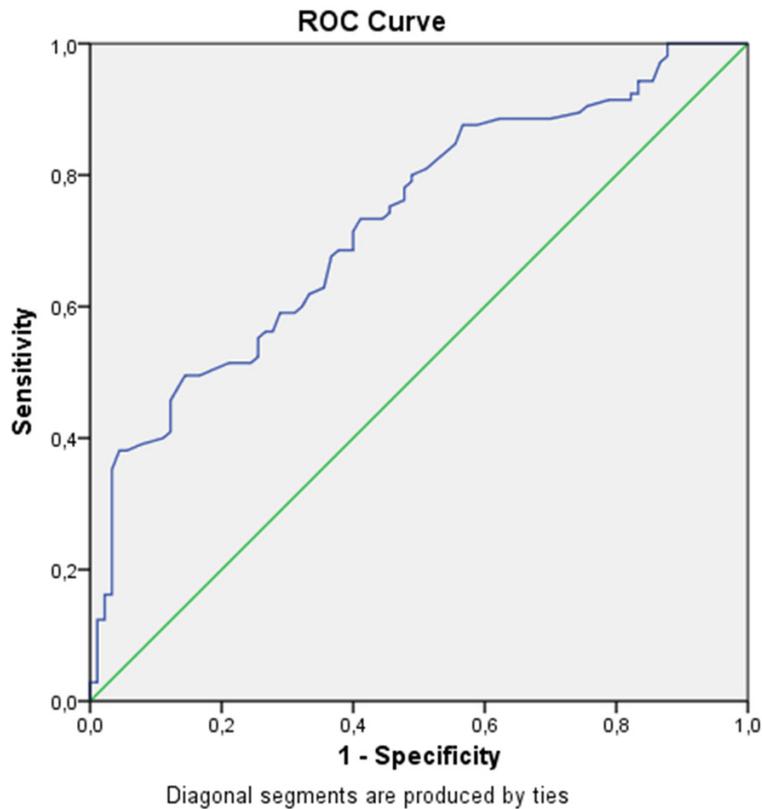
67%. AUC was 0.728. The ROC curve is shown in **Figure 3**. We also gave the ROC analysis results for CRP, ESR, and white blood cell count (WBC) to discriminate tuberculosis from sarcoidosis in **Table 2**.

In the correlation analysis, CRP had significant positive correlation with ALP in sarcoidosis group ( $P = 0.008$ ,  $r = 0.289$ ). In tuberculosis group, ALP had significant positive correlation with CRP and WBC ( $P < 0.001$ ,  $r = 0.378$  and  $P = 0.002$ ,  $r = 0.301$ , respectively). There were no such correlation for these parameters in the control group.

### Discussion

The differentiation of sarcoidosis and tuberculosis is sometimes challenging because they share similar clinical presentations and insufficient clinical evidence. The results of our study showed that serum ALP was a significantly dis-

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**Figure 3.** ROC curves comparing pulmonary tuberculosis and sarcoidosis. For the serum ALP cut-off value of 71.50 IU/L, there was sensitivity of 80%, specificity of 51%, PPV of 66%, NPV of 69%, accuracy of 67% and AUC was 0.728.

**Table 2.** ROC analysis results for biomarkers to discriminate tuberculosis from sarcoidosis

Biomarkers	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
ALP (IU/L)	71.5	80%	51%	66%	69%	67%	0.728
CRP (mg/L)	19	91%	91%	92%	86%	89%	0.965
ESR (mm/st)	34.5	86%	85%	84%	88%	86%	0.870
WBC (K/uL)	7.77	81%	78%	79%	76%	77%	0.832

ALP: alkaline phosphatase, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell, PPD: positive predictive value, NPV: negative predictive value, AUC: area under the curve.

tinctive feature in the differential diagnosis of tuberculosis with parenchymal involvement and sarcoidosis. Researchers are still investigating many invasive or non-invasive methods to support the distinction between these two granulomatous diseases. Recently, Du and colleagues proved that intercellular adhesion molecule-1 (ICAM-1) and leptin were potential markers for the differential diagnosis of sarcoidosis and sputum-negative tuberculosis [9]. Dhooria et al. demonstrated sonographic features of lymph nodes involved with tuberculosis or sarcoidosis on endobronchial ultrasonogra-

phy (EBUS). The authors reported that heterogeneous echotexture or coagulation necrosis in the lymph nodes evaluated using EBUS were specific for tuberculosis involvement and could differentiate tuberculosis from sarcoidosis [10].

Previously, a few researchers tried to contribute to the differential diagnosis of tuberculosis with ALP. Jadhav et al. investigated the activity of ALP and adenosine deaminase (ADA) in sputum as a noninvasive method and both parameters were proved to contribute to the differential diagnosis [11]. Our study demonstrated the value of ALP in tuberculosis with a larger number of cases.

ALP is produced by type II pneumocytes in the lungs. Capelli et al. studied ALP in interstitial lung diseases. They showed that, especially in patients with sarcoidosis with Stage 2 and ¾ disease, ALP increased significantly in bronchoalveolar lavage (BAL), but could not get enough availability in clinical practise [12]. Unlike the studies with respiratory samples, our study showed that serum ALP contributed to the differential diagnosis of tuberculosis and it was a minimally invasive method.

The mechanism of ALP increase has yet to be clearly defined in a variety of forms of tuberculosis. Metintas and colleagues investigated the differentiation of exudative pleural effusion with transudative effusion in a multiparametric study. Pleural ALP determined exudative effusion with a sensitivity of 82% and specificity of 76%, despite its lower contribution to diagnosis [8]. Similarly, Jadhav et al. proved that pleural ALP made the differential diagnosis of tuberculous and non-tuberculous pleural effusions with a sensitivity of 90% and specificity of 80% [13]. In contrast, Mushtaq showed that ALP had

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no significance in differentiating exudative pleurisy with transudative pleurisy [14]. Our study showed that serum ALP could be used to differentiate tuberculosis from healthy patients and patients with sarcoidosis with high sensitivity. The overlapping clinical manifestations of granulomatous diseases can make differentiation even harder, especially when seen associated diseases such as AIDS; it is not easy to reach a definitive diagnosis and physicians need additional supporting evidence.

The mechanism of ALP cannot be fully understood because there is a limited number of studies in the literature; however, it seems important for the differential diagnosis of sarcoidosis and tuberculosis. For complicated cases, taking blood at first admission for ALP analysis seems minimally invasive, fast, easily accessible, and inexpensive. We think it is a very valuable test. A prospective case series with a larger population could increase the significance of ALP.

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### Disclosure of conflict of interest

None.

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