

The evaluation of interleukin-4 and interleukin-13 in the serum of pulmonary sarcoidosis and tuberculosis patients

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Background: Sarcoidosis and tuberculosis (TB) are two granulomatous inflammatory diseases with several common symptoms. The aim of the present study was to compare the serum levels of biomarkers including interleukin-4 (IL-4) and IL-13, calcium (Ca), hemoglobin, sedimentation rate, and lymphocyte-to-neutrophil ratio between patients with pulmonary TB, patients with sarcoidosis, and control group. **Materials and Methods:** This case-control study was performed on patients referred to the Masih Daneshvari Hospital, Tehran, from April 2017 to 2018. In this study, 24 newly diagnosed patients with active pulmonary TB, 34 patients with pulmonary sarcoidosis, and 30 healthy individuals as the control group were enrolled. Demographic data, erythrocyte sedimentation rate (ESR), the ratio of neutrophil-to-lymphocyte (NLR), serum Ca level, hemoglobin (Hb), and IL-4 and IL-13 were compared between the study groups. Receiver operating characteristic (ROC) curve analysis, sensitivity, and specificity were also calculated using SPSS 16.0 software. **Results:** The mean age was 47.71 ± 10.88 and 55.25 ± 21.58 years in the sarcoidosis and TB. The mean ESR in sarcoidosis patients was 21.45 ± 13.37 mm/h and 41.4 ± 17 mm/h in the TB group. The percentage of peripheral blood lymphocytes in sarcoidosis and TB patients was 28.02 ± 12.20 and 21.41 ± 12.49 , respectively, which was significantly higher among patients with sarcoidosis. NLR was also 2.4 ± 1.6 and 4.4 ± 2.9 in sarcoidosis and TB patients, respectively, which showed a significant difference among the groups. Regarding the evaluation of the level of IL-4 and IL-13 in patients, it is worth noting that IL-4 in patients with sarcoidosis was 90 pg/ml compared to 20 pg/ml for TB patients ($P < 0.001$). There was no significant difference in the levels of IL-13 in the TB and control groups, which varied between 20 and 80 pg/ml ($P = 0.35$). However, its value was significantly higher in patients with sarcoidosis ($P = 0.01$) than in the healthy control group and TB ($P = 0.01$). The ROC curves showed that the diagnostic cutoff of ESR level, Ca, NLR, and Hb could be valuable due to the area under the curves. The cutpoint of 34 mm/h for ESR had a sensitivity of 86% as well as 80% specificity to distinguish TB from the sarcoidosis. **Conclusion:** Serum levels of the biomarkers indicated a stronger immunological background in sarcoidosis using NLR, Ca, ESR, and Hb.

Key words: Biomarkers, cytokines, interleukin-13, interleukin-4, sarcoidosis, serum, tuberculosis

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INTRODUCTION

Sarcoidosis is a chronic granulomatous disorder that involves multiorgans with unknown etiology.^[1] This

multisystemic disease almost affects the lungs and is worldwide with a high different prevalence. Clinical symptoms in pulmonary sarcoidosis vary from an asymptomatic patient (radiologic findings) to a case with chronic progressive dyspnea that is almost

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refractory to therapeutic approaches.^[2] Tuberculosis (TB) is another granulomatosis disorder with a different confusing appearance.^[3] The relationship between TB and sarcoidosis is still challenging to argue,^[4] and notable similar clinical manifestations make the differentiation difficult. While TB considers as one of the first ten causes of morbidity and has placed above HIV in the top list of infectious agents. Unfortunately, TB incidence and mortality raise each year, so that in 2017, TB was responsible for almost more than one million deaths among non-HIV people.^[5]

Sarcoidosis is a multifactorial disorder including infectious and noninfectious parameters. At present, the focus is on infectious agents, especially mycobacterium species and *Propionibacterium*, and research on other infectious agents such as *Borrelia burgdorferi*, *Chlamydia pneumonia*, viruses, and fungal infections is not a hot topic.^[6,7] In a meta-analysis conducted by Esteves *et al.* in 2016, on 6,000 patients, two pathogens i.e., *Propionibacterium acnes* and *Mycobacterium tuberculosis* were mostly associated with sarcoidosis.^[6] In this regard, in 1984, Abe *et al.*^[7] emphasized that *P. acnes* was the only pathogen found in the lymph nodes of patients at the time of biopsy. However, this is a normal flow microorganism of the lung and mediastinal lymph nodes but not in the skin. However, studies have often pointed to its key role in pathogenesis. In their study, most patients were Japanese, which may influence the interpretation of the findings. The involvement of sarcoidosis in Japanese patients is mostly cardiac, ocular, and skin, whereas in Europe and the United States, the disease mainly affects the lungs.^[8-10]

To diagnose TB, we aim clinical as well as pathological and radiological findings due to the slow growth of *M. tuberculosis*. Based on lymph nodes involvement, granuloma, fever, fatigue, cough, weight loss, to different sarcoidoses from TB, and new biomarkers including neutrophil-to-lymphocyte ratio (NLR), tumor necrosis factor- α (TNF- α), and interleukin (IL)-8 and IL-13 have been investigated.^[11-13] The serum level of IL-8 was higher in pulmonary sarcoidosis compared to extrapulmonary sarcoidosis. TNF- α was also higher among TB patients rather than those with pulmonary sarcoidosis and healthy control ones. However, in both the granulomatous disorders, IL-13 was higher than the control group.^[11]

It is noteworthy that some data corresponded to cytokines denoted that the source of these agents is not only immune cells but also airway epithelial cells are able to produce IL-18 in TB and sarcoidosis.^[14] Therefore, cytokines may play an important role in the differential diagnosis.

Serum level of cytokines creates rapid diagnostic tools rather than bronchoalveolar lavage; hence, in the current study, we

aimed to compare the serum level of IL-4 and IL-13 in TB and sarcoidosis patients. IL-4 and IL-13 are secreted by T-helper 2 cells (Th2). One of the most important effects of both IL-13 and IL-4 is the induction of human B-lymphocytes to produce IgE and IgG4 and the increase of cell surface molecules including major histocompatibility complex (MHC) on B-lymphocytes and macrophages, which results in increased antigen load capacity. These cytokines have the same secondary structure and elevate in atopy situations and share a common receptor component, IL4R α . IL-4 is also widely used as a growth factor for T-lymphocytes alone or with other cytokines such as IL-2 in the growth and maintenance of T-lymphocyte lines in cell culture.^[15,16] Hence, in the present study, we aimed to compare the serum levels of biomarkers including IL-4, IL-13, calcium (Ca), hemoglobin (Hb), sedimentation rate, and lymphocyte-to-neutrophil ratio between patients with pulmonary TB, patients with sarcoidosis, and the control group.

MATERIALS AND METHODS

Study design

The research was a case-control study that was approved by the Ethical Committee of the National Research Institute of Tuberculosis and Lung Diseases (IR.SBMU.MSP.REC.1395.550). The study was performed on the patients referred to the Masih Daneshvari Hospital, Tehran, from April 2017 to April 2018.

Participants

Participants in the sarcoidosis group were the known case of sarcoidosis based on the pathology findings and the observation of granuloma according to the diagnostic criteria of sarcoidosis established by the American Thoracic Society Consensus Panel^[17] ($n = 34$).

Pulmonary TB group was also the known case of patients based on the positive acid-fast bacilli (*M. tuberculosis*) in the smears or culture of sputum ($n = 24$).

A control group of 30 healthy volunteers was included.

Inclusion criteria included all patients who met the above-mentioned criteria from both genders.

Exclusion criteria were defined as an active malignancy or coronary syndrome, hematologic disease, recent (1 month) steroid use or immunosuppressive therapy, and any active infections.

Measurements and data gathering

Data including patients' age, sex, erythrocyte sedimentation rate (ESR), ratio of neutrophils to lymphocyte (dividing the absolute number of neutrophils by lymphocytes

incomplete blood count), hemoglobin, and serum Ca level were collected.

To measure IL-4 and IL-8 serum level, after centrifuging at 3000 rpm for 10 min, we stored serum at -70°C for further use on processing day, and concentrations were quantified by ELISA (BD Biosciences Pharmingen, Breda, The Netherlands) according to the manufacturer's instructions.

Statistical analysis

All statistical analyses were performed using SPSS statistics software version 16.0. Data were expressed as mean \pm standard deviation or percentage. The normal distribution of quantitative data was tested by Kolmogorov–Smirnov. Mann–Whitney U-test or Student's *t*-test was used to analyze according to the data distribution.

IL levels were compared among three groups including sarcoidosis patients, TB patients, and control group using ANOVA and proper *post hoc* test. According to the normal distribution of data, Student's *t*-test was employed for the comparison of TB and sarcoidosis. $P < 0.05$ was considered statistically significant and confidence interval (CI) was 95%.

Based on significant findings corresponded to different parameters, the receiver operating characteristic (ROC) curve was created for ESR, NLR, Ca, and Hb using GraphPad Prism 6. The area under the curves, sensitivity, specificity, and likelihood ratio on the best cutoff point were reported (CI: %95).

RESULTS

A total of 88 patients were included in the study. Twenty-four patients ($n = 11$, 45.8% female) entered in TB group with a mean age of 55.25 ± 21.58 years, 34 patients ($n = 19$, 55.9% female) entered in sarcoidosis group with a mean age of 47.71 ± 10.88 years, and 30 healthy individuals ($n = 15$, 50% female) were enrolled in the control group with a mean age of 52.2 ± 12.54 years.

Normal distribution was assessed using the Kolmogorov test and revealed that age, ESR, NLR, Ca, and Hb have a normal distribution. Demographic data and disease duration of patients with pulmonary sarcoidosis, patients with pulmonary TB, and healthy volunteers are summarized in Table 1.

A comparison of ESR in patients showed that the mean ESR value in sarcoidosis patients was 21.45 ± 13.37 and 71 ± 42.17 in TB patients, which was significantly higher in patients with TB than sarcoidosis ($P < 0.001$).

The percentage of peripheral blood lymphocytes in sarcoidosis and TB patients was 28.02 ± 12.20 and

21.41 ± 12.41 , which was significantly higher among patients with sarcoidosis than patients with TB, $P = 0.025$. Peripheral blood neutrophils were also $0.59.59 \pm 15.97$ and 68.10 ± 10.01 of patients with sarcoidosis and TB, but there was no significant difference between the groups, $P = 0.074$. The ratio of neutrophil to lymphocyte was 1.6 ± 2.48 and 2.9 ± 4.4 , respectively, which showed a significant difference among the groups and was lower in patients with sarcoidosis than TB, $P = 0.02$.

Serum Hb level ($P < 0.001$), as well as total Ca ($P < 0.001$), was also significantly lower in TB patients as compared to the sarcoidosis group. Data are summarized in Table 2 and Figure 1.

The relationship between ESR and NLR among TB, sarcoidosis and control subjects is illustrated in Figure 2. In TB patients, ($R^2: 0.2$, $p=0.8$) and sarcoidosis patients ($R^2: 0.4$, $p=0.2$) there was no correlation. Regarding the evaluation of the level of IL-4 and IL-13, IL-4 was significantly higher in patients with sarcoidosis (90 Pg/ml) than those with TB (20 Pg/ml), ($P < 0.001$) [Figure 3].

There was no significant difference in the levels of IL-13 in the TB and control groups, which varied between 20 and 80 pg/ml ($P = 0.35$). However, its value was significantly higher in patients with sarcoidosis ($P = 0.01$) than in the healthy control group and TB ($P = 0.01$). Considering to significant difference of ESR, Ca NLR and Hb we created a ROC curve for differentiation of TB and sarcoidosis [Figure 4]. The area under the curve and cut of points are summarized in Table 3.

DISCUSSION

In this study, we compare some laboratory parameters to differentiate TB and sarcoidosis. ESR as well as NLR was more elevated in TB, while Hb and Ca levels were lower among TB patients. Both serum levels of IL-4 and IL13 were higher in sarcoidosis patients, whereas, in the TB group, there was no difference in the level of IL-13 between the TB and the control group. The area under the curve was appreciated to distinguish TB and sarcoidosis employing ESR, NLR, Ca, or Hb.

Table 1: Demographic data and disease duration of patients with pulmonary sarcoidosis, patients with pulmonary tuberculosis, and healthy volunteers

Parameter	TB	Sarcoidosis	Control group	P
Age (years)	55.25 \pm 21.58	47.71 \pm 10.88	52.2 \pm 12.54	0.08
Gender: female, n (%)	11 (45.8)	19 (55.9)	15 (50)	0.68
Disease duration (weeks)	1-3	1-3	N/A	N/A

N/A=Not available; TB=Tuberculosis

Table 2: Comparison of serum concentration of biomarkers between tuberculosis and sarcoidosis and control group

Parameter	TB	Sarcoidosis	Control group	P	Post hoc TB/sarcoidosis	Post hoc TB/control	Post hoc Sarcoidosis/control
ESR mm/h	71±42.17	21.45±13.37	15.34±9.5	<0.001	<0.001	<0.001	<0.001
NLR	4.4±2.98	2.48±1.66	1.52±0.89	0.018	0.025	<0.001	0.33
Hb mg/dl	11.6±2.16	13.7±1.96	13.9±1.5	<0.001	<0.001	<0.001	0.99
Total calcium mg/dl	9.12±0.63	9.78±0.68	9.1±0.93	<0.001	<0.001	0.20	<0.001

Serum concentration of biomarkers among tuberculosis, sarcoidosis, and healthy individuals. ESR=Erythrocyte sedimentation rate; NLR=Neutrophil-to-lymphocyte ratio; Hb=Hemoglobin; TB=Tuberculosis

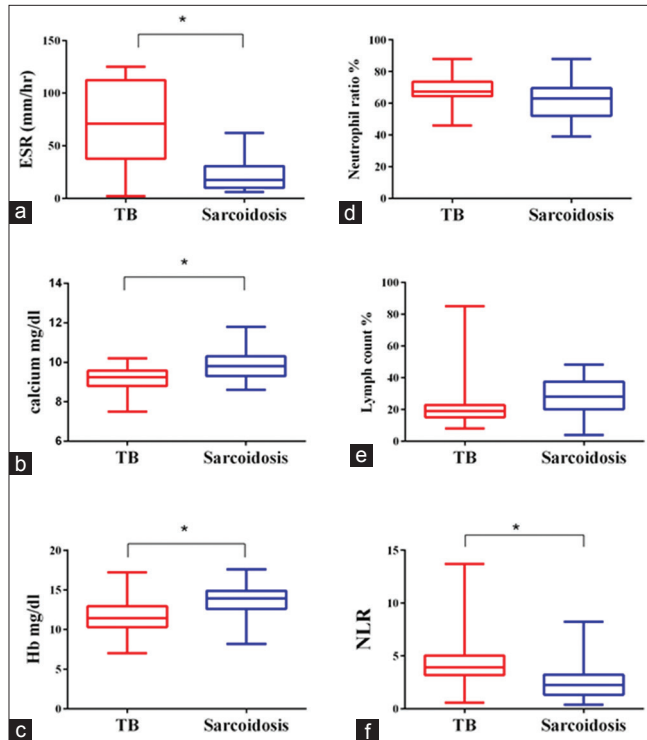


Figure 1: The relation between blood Hb and ESR in TB and sarcoidosis patients shows plotted data of (a) ESR, (b) Ca, (c) Hb, (d) neutrophils, (e) lymphocyte, (f) is indication for N/L ratio of TB and sarcoidosis patients. The result is a representative of 30 patients' serum (TB and sarcoidosis) and 40 control subjects. Data shown are mean ± SEM of three independent experiments. The asterisks represent significant differences compared sarcoidosis with TB group (**P* < 0.05). ESR = Erythrocyte sedimentation rate; Hb = Hemoglobin; Ca = Serum calcium; TB = Tuberculosis; SEM = Standard error of mean

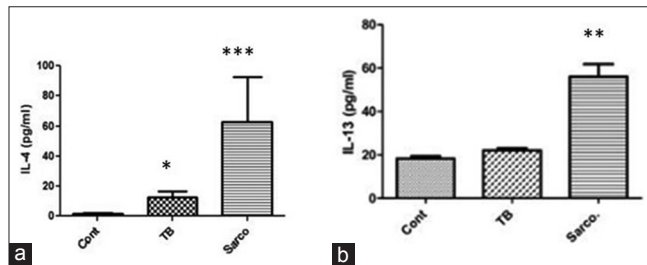


Figure 3: Serum level of IL-4 and IL-13 in the control group, TB and Sarcoidosis patients. (a) As the picture shows that IL-4 was significantly higher in sarcoidosis compared to TB and control group. (b) IL-13 was in the same range in control group and TB but was significantly higher in sarcoidosis. Data shown are mean ± SEM of three independent experiments. The asterisks represent significant differences compared with control (**P* < 0.05; ***P* < 0.01; ****P* < 0.001). IL = Interleukin; TB = Tuberculosis; SEM = Standard error of mean

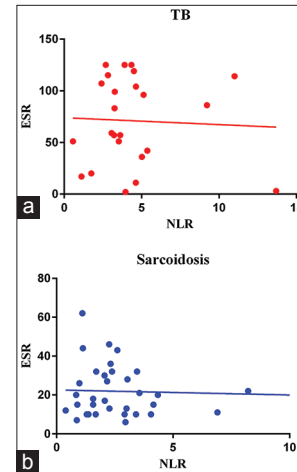


Figure 2: Relationship between ESR and NLR distribution in TB and sarcoidosis patients. (a) There was no correlation between ESR and NLR in TB. NLR is mostly localized in 3.4–4.5. (b) There was no relationship between ESR and NLR among sarcoidosis patients. NLR in this group has a wide distribution. ESR = Erythrocyte sedimentation rate; NLR = Neutrophil-to-lymphocyte ratio; TB = Tuberculosis

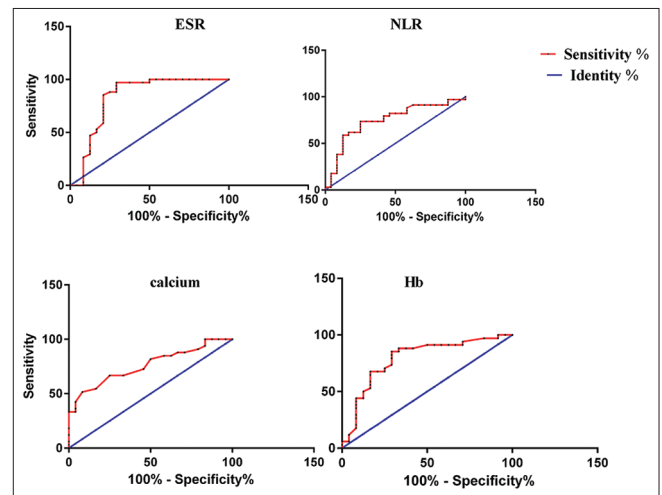


Figure 4: ROC plot of serum level of biomarkers to differentiate TB and sarcoidosis using ESR, NLR, calcium, and Hb. ROC = Receiver operating characteristic; ESR = Erythrocyte sedimentation rate; Hb = Hemoglobin; TB = Tuberculosis; NLR = Neutrophil-to-lymphocyte ratio

In the present study, in contrast to the study of Thillai *et al.*, we showed that IL-4 differs among TB and sarcoidosis. However, their study on 30 patients with TB or sarcoidosis indicated no difference in regard to IL-4 in either BAL or

Table 3: Diagnostic value of different parameters to identify tuberculosis from sarcoidosis

	ESR	NLR	Ca	Hb
Area under the curve	0.83	0.74	0.76	0.79
95% CI	0.71-0.96	0.61-0.88	0.64-0.88	0.67-0.92
Cut of point	34	2.39	9.9	14.4
Sensitivity (%)	86	60	45	45
Specificity (%)	80	68	69	92
Likelihood ratio	4.9	4.7	10.2	5
P	0.001	<0.001	0.009	0.002

CI=Confidence interval; ESR=Erythrocyte sedimentation rate; NLR=Neutrophil-to-lymphocyte ratio; Hb=Hemoglobin; Ca=Serum calcium

serum.^[18] IL-4 is produced by T-lymphocytes, macrophages, mast cells, and natural killer cells, and the main function of this lymphokine is the induction of rapid differentiation and production of IgG and IgE antibodies.

In a case series on five patients with granulomatous TB and hemoptysis, researchers concluded that high levels of IL-4 in the granuloma are related to disease severity and poor prognosis,^[19] which may be due to inappropriate immune response. Subsequently, disease severity and duration may affect the serum level of IL-4.

Recently, Sohal *et al.* demonstrated that the level of IL-13 was higher among patients with sarcoidosis as compared to healthy controls and TB. In their study, IL-13 levels were also high in TB patients compared to healthy controls. However, in the present study, the serum level of IL-13 in TB was similar to the control group.^[20]

In regard to differentiating TB and sarcoidosis, comorbidity of TB and sarcoidosis is another debate. A QuantiFERON-TB test was used to diagnose the concurrent occurrence of TB and sarcoidosis among 90 patients with sarcoidosis and a 3.3% association was reported. This is similar to those of nonsarcoidosis patients.^[21-23]

To distinguish TB and sarcoidosis, ESR is used widely with no standard cutoff point. In the study of Iliaz *et al.*, a cutoff point of 45 showed 84% sensitivity and 77% specificity for the differential diagnosis of TB and sarcoidosis. The sensitivity and specificity of this cutpoint were 71% and 95%, respectively, in the present study, and we suggested the cutoff point of 34 mm/h to separate TB patients with 86% sensitivity and 80% specificity [Table 3].

In our study, a cutoff value for NLR of 2.39 yielded a 60% sensitivity and 68% specificity, while there are some reports regard cutoff point of 2 to diagnose sarcoidosis patients (80% sensitivity and 59% specificity)^[24] and 2.55 to differ sarcoidosis from TB (80% sensitivity and 59% specificity).^[24] Our study did not confirm any relationship between NLR and ESR, while ESR levels were directly

correlated with NLR in sarcoidosis patients in another study.^[24]

The present study indicated that Ca and hemoglobin could be employed to diagnose TB from sarcoidosis. Hb in the cutoff point of 14.4 had 92% specificity, although sensitivity was low (45%). Overall, to differentiate TB from sarcoidosis, possible malnutrition in patients at the risk of TB (for example, iron deficiency) and risk factors contributed to TB infection, and rarer complications of TB like autoimmune hemolytic anemia should be considered.^[25] Consequently, low Ca and Hb in these patients are rational. However, our study lacks some data related to disease severity and duration which could affect cytokine profiles. Furthermore, the patient's outcome was not assessed. Another limitation of our study corresponds to mycobacterium subtypes which diver in different regions.^[26]

CONCLUSION

New inflammatory markers in serum could rapidly differentiate TB from sarcoidosis in the clinic to prevent invasive procedures.

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Conflicts of interest

There are no conflicts of interest.

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