Am J Transl Res 2021;13(6):6166-6174
www.ajtr.org /ISSN:1943-8141/AJTR0133431

Original Article

Development of a random forest model to classify sarcoidosis and tuberculosis

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Received March 23, 2021; Accepted April 23, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Objective: To identify significant diagnostic factors and establish a predictive model for diagnosis of sarcoidosis and tuberculosis. Methods: This study included 252 patients (123 cases of lung sarcoidosis and 129 cases of lung tuberculosis) who underwent laboratory evaluation, including routine hematologic testing, serum immunology, blood coagulation, angiotensin-converting enzyme, and T lymphocyte subset. The factors that statistically different between the two groups were identified by an independent sample t test first, and then processed by the random forest model to distinguish two diseases with the classification function. Moreover, the diagnostic performance of the predictive random forest model was evaluated through the identification of individual contribution of various diagnostic factors conducted by the model. Results: The random forest model revealed a classification error rate of 24.9%. Among all of the statistically significant diagnostic factors, the individual factors with the greatest and second contribution were angiotensin-converting enzyme and prothrombin time, respectively. The area under the receiver operating characteristic (ROC) curve of the random forest prediction model was 0.915. Conclusion: The random forest model can be used to distinguish between sarcoidosis and tuberculosis by incorporating statistically significant diagnostic factors, which is of potential clinical application value.

Keywords: Random forest model, sarcoidosis, tuberculosis, differential diagnosis, ACE

Introduction

Sarcoidosis is an idiopathic systemic disease with unknown etiology [1, 2] that sweeps across the world. Data on incidence and prevalence vary in light of different research methods and epidemiologic factors. However, prior studies have confirmed a slightly higher worldwide prevalence in women than men [2], and an overwhelmingly high incidence among young adults (20-29 years old) and middle-age population (over 50 years old) [3, 4]. In China, patients diagnosed as sarcoidosis are mainly over 40 years old.

Tuberculosis (TB), a common disease in China, is triggered by the infection of Mycobacterium tuberculosis through the respiratory tract [5], to which individuals with lower immunity are more susceptible. It is reported that one third of the world's population has been infected with M. tuberculosis, and more than 9 million new cases of TB occur each year [6]. A major disease with high morbidity and mortality, TB has now been substantially controlled due to the continuous advancement in anti-TB drugs and the vigorous development of anti-TB programs [7].

The challenges for the diagnosis of sarcoidosis reside in the following three dimensions. First, in terms of etiology, TB is caused by Mycobacterium tuberculosis infection [5], whereas it is generally believed that sarcoidosis is caused by the exposure of individuals with genetic susceptibility to a pathogenic factor in the environment [8]. If the detection rate of Mycobacterium tuberculosis can be improved, it will be helpful for the differential diagnosis of the two. However, the difficulty of traditional etiological detection methods to distinguish the two is attributed to various human factors. Secondly, from

the perspective of clinical manifestations, two kinds of diseases are both characterized by night sweats, afternoon fever, fatigue and similar respiratory symptoms including cough, hemoptysis, chest pain, shortness of breath and so on [4-10]. Therefore, clinical manifestations fail to differentiate the two. In terms of imaging, different features of chest sarcoidosis and tuberculosis in X-ray chest radiography, chest CT or high-resolution CT manifestations, are conducive to the differentiation of the diagnosis of the two diseases [11, 12], yet only by the combination of these features, the two diseases cannot be clearly distinguished.

Pathologically, both diseases present as epithelioid granulomas. Sarcoidosis is characterized by the formation of non-caseating granulomas, whereas TB is characterized by caseous granulomas [13]. In general, caseous necrosis or acid-fast staining can be seen in tuberculous granulomas, which are easy to distinguish. However, the atypical manifestation of tuberculous granuloma, also known as proliferative tuberculosis, invariably results in no caseous necrosis and a negative result in acid-fast staining, which is similar to nodular granuloma, thus presenting a low certainty in the differentiation [14-16].

The traditional identification method integrates clinical symptoms, imaging, etiology, and pathology [17]. At present, the combination of the above methods is considered mediocre in the diagnosis of the diseases. The difference in medication, specifically, anti-TB drugs for TB and corticosteroids for sarcoidosis [18] results in serious consequences once the patient is misdiagnosed. Of all, in recent years, the research on the differential diagnosis of tuberculosis and sarcoidosis is still a hot topic in the world. Thus, the research on differential diagnosis of the two diseases has captured great attention all over the world. However, few studies have been performed on the identification of sarcoidosis and TB through blood testing to detect relevant indicators.

The goal of our study was to detect the level of relevant indicators by evaluating blood samples from 252 patients (123 cases of sarcoidosis and 129 cases of TB). Laboratory tests include hematologic examination, serum immunology, blood coagulation, angiotensin-converting enzyme (ACE), and T lymphocyte subset. By identifying the diagnostic factors that are significantly different between the two groups, the random forest model was employed to distinguish sarcoidosis and TB in diagnosis. The individual contribution value of the various diagnostic factors was calculated. Using the area under the receiver operating characteristic (ROC) curve, the diagnostic efficacy of the random forest model was detected with the blood test results of the remaining 51 patients (25 cases of sarcoidosis and 26 cases of TB).

Materials and methods

Sample selection

A retrospective study was conducted to compare 123 cases of pulmonary sarcoidosis and 129 cases of TB that were diagnosed at a pulmonary hospital in Shanghai between January 2012 and January 2017. The study was approved by Ethics Committee of Shanghai Pulmonary Hospital (K18-145).

Inclusion criteria

The diagnostic criteria for sarcoidosis followed the definitions of sarcoidosis by the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) [19], which are summarized as follows: A. Unknown cause. B. Multiple system involvement, especially the lung, eye and skin. C. Onset in young adults and middle age. D. Confirmation by biopsy findings, including subcutaneous nodules, mediastinum, pulmonary lymph nodes, and lung tissues, presenting as non-caseating granuloma. E. No evidence of M. tuberculosis infection on pathologic, morphologic and antacid staining and exclusion of other known causes.

Based on the consensus of the Official American Thoracic Society/Infectious Diseases Society of America for the diagnosis and treatment of TB [20], the diagnostic criteria for TB are listed. For the inclusion to the study, each case of TB had superficial lymph node, mediastinal lymph node, or pulmonary tissue biopsy smear or biopsy. Other specific criteria include: A. Pathologic manifestation of a caseous necrotic

granuloma. B. Positive findings on acid-fast bacilli smear with puncture solution. C. Positive culture findings of mycobacteria with puncture solution.

Exclusion criteria

A. Positive findings of TB on sputum or lavage smear. B. Malignant tumor. C. Serious disease or dysfunction of another organ system. D. Autoimmune disease. E. Use of immunosuppressant or immuno-enhancer 2 weeks before admission.

Sample collection and processing

In the morning after admission, 6 ml fasting elbow venous blood was obtained. 4 ml was collected with an EDTA anticoagulation tube for routine hematologic examination, serum immunology, and T lymphocyte subset; the other 2 ml was stored in a sodium citrate anticoagulant tube to detect blood coagulation. The test procedures were followed strictly to ensure the accuracy of the results.

Instruments and reagents

Routine hematologic examination (hemoglobin [Hb], red blood cell [RBC] count, white blood cell [WBC] count, neutrophil count, lymphocyte count, NLS, monocytes, MLS) was performed with the Ac·T 5diff blood analyzer (Beckman Coulter, California, America).

Immune scattering was used to perform serum immunology, including IgG, IgA, IgM, C-reactive protein (CRP), complement C3, and complement C4 with the IMMAGE 800 specific protein analysis system (Beckman Coulter).

To determine blood coagulation (prothrombin time [PT], international normalized ratio [INR], fibrinogen [FIB], activated partial thromboplastin time [APTT], antithrombase III [AT3], d-dimer, fibrinogen degradation products [FDP]), a Coatron1800 Automated coagulometer and its supporting reagent were used (TECO, Munich, Germany). Angiotensin-converting enzyme was tested with a 7170A Automatic biochemical analyzer (HITACHI, Tokyo, Japan).

An EPICS-XL Flow Cytometer (Beckman Coulter, California, America) and its accompanying antibody reagents (BioLegend, San Diego, California, America) were used to detect T lymphocyte subsets.

100 ul fully mixed anticoagulated whole blood was added to the bottom of the sample tube by using a micropipette to avoid the blood sample from sticking to the test tube wall to ensure the accuracy of the blood sample volume. 20 ul monoclonal antibody was added and shaken at low speed, mixed for 3 s, and placed at room temperature for 30 min; 2 mL of lysate was added, vortexed and mixed at low speed immediately, and placed still in the dark at room temperature for 10-12 min. The hemolysis time should be under control to avoid damage to the T lymphocyte cells. Immediately after centrifugation (300×g, 5 min, room temperature), the supernatant was aspirated, then 2 mL of PBS was added and shaken at low speed for a mixture, and the above washing and centrifugation process were repeated twice. 1% paraformaldehyde was added to fix, mix, and protect from light and stored at 2-8°C for testing on the machine.

Statistical analysis

Statistical analysis was performed with SPSS 19.0 software (SPSS IBM Inc., Chicago, IL). The differences between the sarcoidosis and TB groups were compared with an independent samples t test. Data were expressed as mean ± standard deviation (SD). Statistically significant diagnostic factors were processed by the random forest model. Factors specific to age and sex were also included in the model. The classification function of the random forest model was used to classify sarcoidosis and TB. The individual contribution value of each diagnostic factor was measured by mean decrease in accuracy. The diagnostic efficacy of each indicator was tested and shown by the area under the ROC curve. $P<0.05$ was considered statistically significant difference.

Results

Basic characteristics of the sarcoidosis and TB groups

Results of the independent samples *t* test showed that statistically significant differences were found between the two groups in Hb, RBC, lymphocyte count, IgG, IgA, CRP, PT-s,

Table 1. Basic characteristics of the sarcoidosis and TB groups

Index	Total (n=252)	Sarcoidosis (n=123)	Tuberculosis (n=129)	P
Age	46.37±12.21	46.31±12.04	46.42±12.41	0.9433
Sex				0.8240
Male	96 (38.10)	46 (37.40)	50 (38.76)	
Female	156 (61.90)	77 (62.60)	79 (61.24)	
Hb	126.48±16.97	132.15±16.22	121.08±15.92	<.0001
RBC (10^9/L)	4.48±0.56	4.64±0.46	4.33±0.6	<.0001
WBC (10^9/L)	6.04±1.97	5.91±1.99	6.17±1.95	0.2887
Neutrophil count (10^9/L)	3.95±1.78	3.93±1.85	3.97±1.71	0.8515
Lymphocyte count (10^9/L)	1.44±0.48	1.36±0.42	1.53±0.51	0.0045
NLS	3.04±1.79	3.13±1.71	2.95±1.87	0.4210
Monocytes (10^9/L)	0.48±0.21	0.46±0.2	0.51±0.22	0.0856
MLS	0.36±0.19	0.36±0.16	0.37±0.21	0.8016
IgG (ng/L)	13.63±3.78	12.87±3.24	14.35±4.12	0.0018
IgA (ng/L)	2.93±1.2	2.66±0.91	3.2±1.37	0.0003
IgM (ng/L)	1.21±0.61	1.17±0.58	1.25±0.63	0.3028
CRP (mg/L)	11.85±17.25	8.45±11.5	15.09±20.87	0.0021
Complement C3 (g/L)	1.26±0.24	1.24±0.26	1.28±0.22	0.1942
Complement C4 (g/L)	0.32±0.09	0.32±0.08	0.32±0.1	0.5256
PT-s	11.43±1.1	11.1±0.77	11.74±1.26	<.0001
INR-s	1.1±0.67	1.03±0.09	1.18±0.93	0.0833
FIB-s	3.46±1.02	3.13±0.85	3.78±1.08	<.0001
APTT-s	31.2±3.88	30.1±3.51	32.24±3.94	<.0001
TT-s	15.16±2.36	15.57±2.27	14.77±2.38	0.0066
AT3-s	101.35±18.84	98.38±19.87	104.18±17.41	0.0142
D-Dimer-s	291.11±347.32	270.4±282.79	310.85±399.41	0.3564
FDP-s	1.81±2.25	1.49±1.35	2.12±2.82	0.0246
SACE	56.73±29.52	70.46±33.24	43.63±17.38	<.0001
CD3-/CD16+/CD56	11.9±6.59	12.52±6.15	11.32±6.95	0.1476
CD3++	65.37±11.75	63.02±11.86	67.62±11.24	0.0018
CD16+/CD56+	12.98±7	13.68±6.68	12.32±7.26	0.1212
CD3+	64.28±11.29	61.65±11.36	66.79±10.67	0.0003
CD3+CD8+/CD3+	0.32±0.11	0.31±0.12	0.32±0.1	0.3407
CD4+/CD8+	2.28±1.36	2.47±1.7	2.1±0.9	0.0321
CD45+	90.4±15.47	89.9±14.18	90.89±16.64	0.6119
CD8+	20.32±7.85	18.99±7.82	21.59±7.68	0.0081
CD3+CD4+/CD3+	0.58±0.12	0.59±0.13	0.58±0.11	0.6279
CD4+	37.84±9.86	36.44±9.94	39.17±9.64	0.0275

Fib-s, APTT-s, TT-S, AT3-s, FDP-s, SACE, CD3++, CD3+, CD4+/CD8+, CD8+, and CD4+ (**Table 1**).

Computational flow of the random forest model

Statistically significant indicators were shown in **Table 1**, sex and age were included and processed in the random forest model. Results in **Figure 1** revealed a differentiation error rate of 24.9% for sarcoidosis and TB, 27.6% for sarcoidosis and of 22.3% for TB.

Individual contribution value of each index in the model and mean decrease in accuracy

The mean decrease in accuracy and mean decrease in Gini for all indicators included in the random forest model were analyzed, and strong evidence of a relatively higher individual

```
Call:
 randomForest(formula = tuberclenodule ~ SEX + AGE + HGB + RBC +      WBC + NeuT + Lym + Mono + IgG + IgA + IgM + CRP + C3
 + C4 +      PTS + INRS + FIBs + APTTS + TTs + AT3S + DDimerS + FDPS +      SACE + CD31656 + CD32 + CD1656 + CD31 + CD383
+ CD481 + CD8 +      CD343 + CD4, data = mydata.train, importance = TRUE, na.action = na.roughfix)
               Type of random forest: classification
                     Number of trees: 500
No. of variables tried at each split: 5

        OOB estimate of  error rate: 24.9%
Confusion matrix:
    No Yes class.error
No  71  27       0.276
Yes 23  80       0.223
```

Figure 1. Computational flow of the random forest model.

Table 2. Individual contribution value of each index in the model

	Mean Decrease in Accuracy		Mean Decrease in Gini	
Sex	2.20	-0.29	1.57	0.25
Age	-0.42	0.11	-0.26	1.9
Hb	3.47	6.19	6.42	4.42
RBC	5.96	4.7	6.89	4.15
WBC	2.49	1.23	2.71	2.87
NeuT	1.54	-0.82	0.49	2.5
Lym	2.55	3.9	4.58	3.53
Mono	-0.42	0.52	0.09	2.09
IgG	2.17	1.05	2.37	2.86
IgA	4.49	1.54	4.42	3.77
IgM	-0.24	3.25	2.38	2.45
CRP	-0.12	3.52	2.92	2.26
C3	5	2.12	5.02	3.36
C4	2.56	1.24	2.63	2.38
PT-S	7.47	8.07	10.29	4.64
INR-S	5.6	3.8	6.54	3.44
FIB-s	4.6	5.27	6.82	4.68
APTT-S	5.06	4.44	6.78	4.03
TT-s	2.37	2.75	3.44	2.75
AT3-s	4.53	6.96	7.68	3.7
D-Dimer-S	-0.37	0.63	0.41	1.94
FDP-s	2.82	2.08	3.56	2.57
SACE	12.81	17.05	18.56	12.27
CD31656	2.02	2.08	2.96	2.06
CD32	4.8	4.19	6.77	3.03
CD1656	1.47	1.11	2.1	2.32
CD31	0.46	2.32	2.12	3.41
CD383	0.93	1.77	1.71	1.83
CD481	1.78	0.38	1.43	2.15
CD8	2.98	4.35	5.3	2.86
CD343	2.54	3.04	3.68	1.61
CD4	-0.78	3.22	2.05	1.88

Mean decrease in accuracy and mean decrease in Gini for each index in the forest model.

contribution value of SACE and PT-s than the other indicators included in the model was found, as shown in **Table 2** and **Figure 2**, with a mean decrease in accuracy for SACE of 18.56 and for PT-s of 10.29.

Area under the ROC curve of the random forest model

To verify the diagnostic efficacy of the forest model, the remaining 51 serum samples (25 cases of pulmonary sarcoidosis and 26 cases of TB) that were not involved in establishing the random forest model were also processed. The area under the ROC curve was 0.915, as shown in **Figure 3**.

Discussion

The similar clinical, imaging, and pathologic manifestations of sarcoidosis and TB are prone to a misdiagnosis which may result in serious consequences as their treatment methods are completely different. China has a high prevalence of TB. Currently, approximately 4.99 million patients are diagnosed with active TB, among which the number of sputum smear/culture positive pulmonary TB patients only reaches around 790,000. That is, clinically, patients with smear-negative TB, even without mucus, account for the vast majority of cases, increasing the difficulty of identifying the two kinds of diseases. Thus, it is particularly important to explore an efficient differential method for sarcoidosis and TB.

By examining blood samples in patients with pulmonary sarcoidosis and TB, we found that the statistically significant indicators included Hb, RBC, lymphocyte count, IgG, IgA, CRP, PT-s, Fib-s, APTT-s, TT-s, AT3-s, FDP-s, SACE, CD3++, CD3+, CD4+/CD8+, CD8+, and CD4+. Most coagulation function tests, including PT-s, Fib-s, APTT-s, TT-s, AT3-s, and FDP-s, showed statistical significance, whereas no differences were detected in INR-s and d-dimer. Some studies have shown that patients with TB suffer from coagulation dysfunction [21-23], which

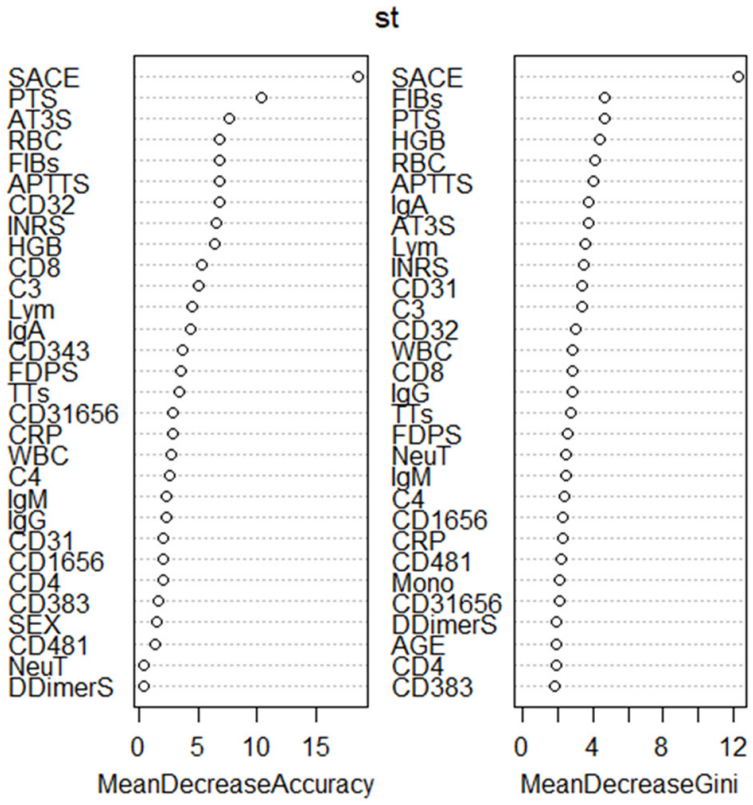

Figure 2. Mean decrease in accuracy.

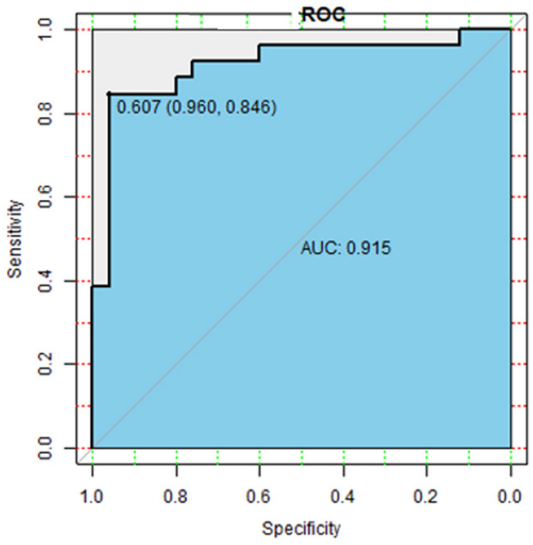

Figure 3. Area under the ROC curve of the random forest model.

may be attributed to the activation of complement by endotoxin, M. tuberculosis metabolites, and decomposition products after M. tuberculosis infection, resulting in the accumulation of inflammatory cells and release of histamine, prostaglandin, and other substances that can damage the capillaries and vascular endothelial cells [23].

By detecting the indices in 201 blood samples, the indices with statistically significant difference were identified and processed in the random forest model, and we found that the random forest model exerted a superior identification effect on sarcoidosis and TB. The differentiation error rate of TB and sarcoidosis was 24.9%, with a rate for sarcoidosis of 27.6% and a rate for TB of 22.3%. However, the overall difference was not statistically significant, which was in consequence of the coagulation dysfunction triggered by M. tuberculosis infection. Although the etiology of sarcoidosis is unknown, the prevailing view is that genetic susceptibility, which does not affect the coagulation function, is responsible for the occurrence and development of the disease. Therefore, in the random forest model, TB can be classified better according to coagulation function, whereas sarcoidosis fails to meet an accurate identification.

The mean decrease in accuracy showed that the value of SACE was the highest, followed by PT-s. It refers to the degree of decrease in accuracy without the presence of this diagnostic factor in the random forest model, which is equivalent to the concept of classification contribution. The higher the value, the more important the contribution. It also indicates that both factors played an important role in the differentiation of sarcoidosis and TB. The greatest contribution was achieved by SACE, also called excitation peptidase II (kinanese II), which is a type of hydroxyl that contains zinc hydrolase with a molecular weight of 14,000 to 15,000 kD. Its main physiologic function is to decrease the activity of angiotensin (Ang I) and convert it into a highly active 8-peptide angiotensin II

(Ang II). The product, Ang II, is a powerful vasoconstrictor that is contained in almost all vascular endothelial cells [24]. Because the blood supply is extremely rich in pulmonary capillaries, a change in the serum ACE level is closely related to lung disease [25]. Most studies have found increased ACE levels in patients with sarcoidosis, possibly in consequence of the existence of granulomatous epithelial cells and macrophages [26-28]. On the other hand, with the progression of TB, the local renin-angiotensin system (RAS) can promote the formation of pulmonary fibrosis, leading to increased concentrations of ACE and Ang II. The increase in ACE can also regulate the inflammatory response of the host and decrease the reactivation of latent TB [29]. Further, the detection of coagulation function allows PT-s to better enable the random forest model for the differentiation of sarcoidosis from TB.

We used data from 201 blood samples to establish the random forest model and tested the diagnostic performance of the model in the remaining 51 cases (25 cases of pulmonary sarcoidosis and 26 cases of TB). The results showed that the area under the ROC curve is 0.915, which means that this model can accurately classify pulmonary sarcoidosis and TB. This will play an important clinical role in differentiating pulmonary sarcoidosis from pulmonary TB. Prior studies have shown that it is better to use a random forest model to classify sarcoidosis and tuberculosis, based on pathological features and improved random forest lung nodule classification algorithms, and the research needs to pay attention to solve boundary problems [30, 31]. If the width and height of the pulmonary nodule or tuberculosis area exceed the boundary of the CT image, offset processing is required to make the center points of different areas coincide [32]. However, blood vessels and lung tissues with similar gray values beside the nodules may also be selected for regional growth. Therefore, a 3×3 template needs to be corroded and expanded once to remove the connectivity of the surrounding tissues. Corrosion and expansion are only performed once, which can well avoid burrs and other features from being discarded in the process of corrosion and expansion. Finally, the region is grown again to obtain the final segmentation result of lung nodules or tuberculosis.

Our study is limited by the absence of control group. By comparing various laboratory findings between pulmonary sarcoidosis and TB, we used statistically significant diagnostic factors to establish the random forest model. However, no control group was used for comparison. By using blood samples from healthy subjects as a control group, multiple random forest models can be used to identify differences among three groups (healthy control group, sarcoidosis group, and TB group), which should be advocated in clinical practice.

Conclusion

The random forest model can be used to distinguish sarcoidosis from tuberculosis by incorporating statistically significant diagnostic factors, which is of potential clinical application values.

Acknowledgements

This work is supported by Shanghai clinical research center for infectious disease (tuberculosis, 19MC1910800).

Disclosure of conflict of interest

None.

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