

A NOVEL MULTI-PARAMETER SCORING SYSTEM FOR DISTINGUISHING SARCOIDOSIS FROM SPUTUM NEGATIVE TUBERCULOSIS

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ABSTRACT. *Background:* Sarcoidosis is a granulomatous disorder of unknown cause, affecting multiple organs. Tuberculosis is the world's second most common cause of death from infectious diseases. Due to the similar clinical, radiological and histopathological pictures in sarcoidosis and tuberculosis, *Mycobacterium tuberculosis* has been considered as potential infectious factor. However, it remains difficult to distinguish sarcoidosis from tuberculosis, especially when sputum examinations for mycobacterium are negative. *Methods:* 1. to establish a scoring system for differentiating sarcoidosis and tuberculosis: We collected the risk factors, laboratory data and the data of clinical, radiographic, pathological manifestations from the 117 of sarcoidosis patients and 181 of sputum negative tuberculosis patient. And we put them into the designed form. Based on the results of univariate analysis, clinical experience and the literature, we further selected 13 variables that were more supportive to distinguish the two diseases. Finally 9 variables were selected based on logistic regression to establish the scoring systems with significant differences between the two diseases. The β -coefficient from the logistic regression were used to calculate the weight of each variable. Four types of comprehensive scoring models were established in the end (clinical - radiographic; clinical - radiographic - radionuclide; clinical - radiographic - pathological and clinico - radiographic - radionuclide - pathological group). Receiver operating characteristics (ROC) analysis was used to determine an optimal cutoff point for each scoring system. 2. to validate the accuracy of the established scoring system: 73 of new sarcoidosis patients and 57 of new tuberculosis patients were chosen to assess the diagnosis accuracy of the four scoring systems. *Results:* 1. we established four types of comprehensive scoring models, included clinical - radiographic; clinical - radiographic - radionuclide; clinical - radiographic - pathological and clinico - radiographic - radionuclide - pathological scoring models, the optimal cutoff values respectively were 9, 17, 18 and 22, the sensitivity and specificity of the four scoring system to distinguish the two diseases respectively were: 93.16% (109/117) and 97.79% (177/181), 92.31% (108/117) and 98.90% (179/181); 93.16% (109/117) and 98.90% (179/181); 94.87% (111/117) and 98.90% (179/181). 2. Validation of the scoring systems with 130 new patients (73 of sarcoidosis and 57 of tuberculosis);, the sensitivity and specificity of CR, CRE, CRP, CREP were 91.78% (67/73) and 87.72% (50/57), 97.26% (69/73) and 98.25% (56/57), 94.52% (71/73) and 96.49% (55/57), 98.63% (72/73) and 98.25% (56/57) respectively. **Conclusions:** The four scoring systems established by this study can be utilized to differentiate sarcoidosis and sputum negative tuberculosis effectively.

Based on the availability of clinical-radiographical/histopathological data, any of the four diagnostic scoring systems were reliable tools for differential diagnosis, with increased information leading to better discrimination. (*Sarcoidosis Vasc Diffuse Lung Dis* 2012; 29: 11-18)

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Abbreviations:

CI:	confidence interval
CR:	clinical - radiographic group
CRE:	clinical - radiographic - radionuclide group
CRP:	clinical - radiographic - pathological group
CREP:	clinical - radiographic - radionuclide - pathological group
CT:	chest computed tomography
ECT:	emission computed tomography
LR:	likelihood ratio
ROC:	receiver operating characteristics
SA:	sarcoidosis
SPSS:	Statistical Product and Service Solutions
TB:	tuberculosis
TST:	the results of the tuberculin skin test

INTRODUCTION

Sarcoidosis (SA) is an enigmatic multisystem disease most commonly involving the lungs and lymphatic system (1, 2). The major histological feature of affected tissues is granuloma, which is similar to that of TB. Moreover, similarities in the clinical, pathological, and immunologic abnormalities between SA and TB have raised the suspicion that SA may be a specific kind of TB. The etiology of SA is still unknown more than 100 years after the first clinical description in 1899 (3). Extensive publications revealed that exposure of genetically susceptible subjects to a specific environmental agent(s) could be the main cause of SA (2). A variety of infectious agents involved in SA, including mycobacterial infection, have been reported in patients with SA (4, 5). Other studies have proposed that the *Mycobacterium tuberculosis* (*MTB*) complex was responsible for the disease (5-7). Current diagnosis of SA is established on the basis of compatible clinical and radiological findings, supported by histological evidence in one or more organs of noncaseating epithelioid cell granulomas in the absence of organisms or particles (2). However, without a definitive diagnostic imaging study, fluid analysis, or blood test, SA remains a diagnosis of exclusion (8).

Tuberculosis is the second leading cause of death worldwide, killing nearly 2 million people each year (9). It is also a multisystem disease, caused by *MTB*. The typical histological feature of affected tissues of TB patients is caseating granuloma, which

makes it distinguishable from that of SA. In typical cases, SA and TB can be distinguished based on cultures and histological examination (9). However, when caseous necrosis is absent and sputum examinations of *mycobacterium* are negative in patients with TB, discriminating TB from SA is quite difficult. This poses a diagnostic challenge to physicians, especially in a high TB prevalence country (like in China).

As the treatment of TB and SA differs greatly (2, 10, 11), establishment of a specific and effective method to distinguish SA and smear-negative pulmonary TB is of critical importance. In this study, we developed a multivariable scoring system with a combination of clinical, radiographic and histological data for more effective and definitive diagnosis of SA and TB. Since reliable determination of radionuclide remains difficult to obtain in some hospitals, four models were developed, with and without it. The four groups were: clinical-radiographic (CR), clinical-radiographic-pathological (CRP) and clinical-radiographic-radionuclide (that is, emission computed tomography, ECT) (CRE), clinical-radiographic-radionuclide-pathological (CREP) group. In a cohort of 298 patients (117 with SA and 181 with smear-negative TB) and 130 validation cases (73 with SA and 57 with smear-negative pulmonary TB), high sensitivity and specificity in discriminating the two diseases were obtained with the scoring system, suggesting it could be used to differentiate SA from TB.

METHODS

Study design and subjects

A retrospective study was carried out comparing clinical - radiographical/histopathological manifestations in TB patients and SA patients who underwent pulmonary or lymphoid biopsy in Shanghai Pulmonary Hospital from January 1998 to December 2004. The study was approved by the Tongji University ethics review board. All individuals gave informed consent. The inclusion criteria of TB patients (12, 13) were: a) negative sputum smears for *MTB* at least three times and negative sputum culture at least once; and b) presence of granulomas with caseous necrosis of affected tissues; or c) no

caseous necrosis in necrotic histological specimens or no necrosis in affected tissues and d) response to anti-TB drugs as the only therapy. The inclusion criteria of SA patients (2, 14, 15) were: a) presence of noncaseating granulomas in biopsy specimens of affected tissues and no evidence of current infection by *M. tuberculosis* or other organisms known to produce granulomatous disease; and b) response to treatment with corticosteroids without anti-TB drugs.

We reviewed the case reports of all included patients and designed a table to input the data for evaluation, including: a) general information: sex, age, occupation, major diagnosis, stage of the disease, family history, past history of TB, allergies, the results of the tuberculin skin test (TST); b) clinical presentations: fever, cough, expectoration, chest distress, bloody phlegm, chest pain, tachypnea, night sweats, fatigue, weight loss, extrathoracic presentations (changes in eyes, joints, skin, etc.), dry and/or moist rales of the lung; c) radiographic data: chest radiograph, chest computed tomography (CT) before and after treatment; d) emission computed tomography (ECT)(⁶⁷Ga citrate scintigraphy or ¹⁸Fluorine-2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography) before and after treatment (16). e) biochemical or instrumental examination data: routine blood tests, serum calcium, urine calcium, serum Anti-TB, serum angiotensin converting enzyme, serum and bronchoalveolar lavage fluid CD3, CD4, CD8, CD4/CD8, electrocardiogram, lung function, and ultrasound examination; and f) histological data of lung or lymphatic tissue biopsy.

Statistical analysis

Univariate comparisons between SA and TB were performed using Chi square tests (χ^2) to screen the candidate variables that could be applied in the scoring system. A logistic regression analysis with backward conditional method was used to choose the final variables and to develop the scoring systems.

The numerical values of the score developed were based on the β -coefficient divided by the minimum β value obtained from the logistic regression models. The sum scores of the four groups were calculated and their statistic significances between the two diseases were tested by the Mann-Whitney U test. Receiver operating characteristics (ROC)

analysis was used to decide the optimal cutoff point for each scoring system based on its highest diagnostic accuracy. How well these scoring systems distinguish between sarcoidosis and tuberculosis patients were evaluated by the areas under the ROC curve, which ranges from 0 to 1, with 0.5 corresponding to no discrimination (i.e., random performance) and 1.0 to perfect discrimination. Sensitivity and specificity ratings for the derived sum score were calculated. Once the cutoff point was developed, we conducted a validation phase to assess its diagnosis accuracy in the collected new sample of 130 patients.

Missing data were managed using two different analytical methods. We ran our logistic regression (1) by excluding subjects who were missing variables necessary to enter the model, (2) by creating an indicator variable to represent the missing data (17, 18). We found that the two techniques yielded similar multivariate results.

Statistical analyses were performed with the SPSS (Statistical Product and Service Solutions) 13.0 statistical package. A *P* value less than 0.05 was considered statistically significant unless specified. All *P* values are two-sided.

RESULTS

Characterizing of study population

Two hundred ninety-eight patients were included in the study. There were 181 patients with a final diagnosis of TB, including 110 male and 71 female, with a mean age of 47 years (range from 16 to 81). One hundred seventeen patients met the criteria for SA, including 43 male and 74 female, with an average age of 47 years (range 18 to 68). Patient numbers for stage 0, stage I, stage II, stage III and stage IV of SA were 0, 49, 65, 2 and 1, respectively.

Screening of variables

A retrospective study was carried out comparing CR, CRE, CRP and CREP manifestations in TB patients and SA patients. Based on the results of Chi square test (χ^2), clinical experience and the literature, we further selected 13 variables that were more supportive to distinguish the two diseases. Finally 9 variables (Table 2) were selected based on logistic re-

Table 1. The selected 13 variables in establishing the scoring systems*

Variables		SA (N=117)	TB (N=181)	The χ^2 test value	P value
Clinical expression	Gender (female/male)	74/43	71/110	16.57	<0.0001
	TST [#]	20 (17.10)	150 (82.87)	134.39	<0.0001
	Dry cough	53 (45.30)	54 (29.83)	7.33	0.007
	Bloody phlegm	7 (5.98)	25 (13.81)	4.88	0.027
	Chest distress	42 (35.90)	18 (9.94)	29.34	<0.0001
	Tachypnea	30 (25.64)	11 (6.08)	22.59	<0.0001
	Extrathoracic presentations	44 (37.61)	13 (7.18)	42.44	<0.0001
Radiological expression	Symmetrical lymphadenopathy [†]	103 (88.03)	17 (9.39)	203.28	<0.0001
	Cavity or calcification	0 (0.00)	22 (12.15)	23.06	<0.0001
	Lesion location in radiography ^{**}	52 (44.44)	9 (4.97)	69.76	<0.0001
	ECT manifestations ^{**} (normal)	2 (1.71)	80 (44.20)	81.93	<0.0001
Pathological manifestation	Necrosis in histological specimens	12 (10.26)	158 (87.29)	191.95	<0.0001
	Reticular fiber stain in histological specimens	93 (79.49)	23 (12.71)	141.8	<0.0001

* Data are presented as No. (%) unless otherwise indicated

[#] Data stands for the largest diameter of TST in one patient (the unit is mm)

[†] Bilateral hilar lymphadenopathy or symmetrical lymphadenopathy in mediastinum in radiography

^{**} Distribution of the lesion in radiography includes usual localization of TB (L0), other positions in two lungs (L1), other positions in single lung (L2) and normal (L3); the χ^2 value was 124.13, $P < 0.0001$. ECT manifestations include normal (E0), single lung or unilateral hilar (E1), typical or atypical panda or λ sign (E2); The χ^2 value was 250.68, $P < 0.0001$

gression to establish the scoring systems with significant differences between the two diseases ($p < 0.005$) (The χ^2 value, P value, and value assignment of the variables are summarized in Table 1). The proportion of patients with missing TST and ECT varied between the SA and TB (17.95% vs. 23.20% and 17.09% vs. 32.60%, respectively). The other variables in Table 1 had no missing data. The variables of age and smoking were removed in further analysis based on clinicians' experience and the literature (19, 20). Gender was selected as a variable because we observed that the number of male patients with TB was larger than that of female patients, with a male-to-female ratio of 110:71, while in SA, the ratio was 43:74. The cutoff point for TST in differentiating the two diseases was set as 9 mm based on the ROC curve. The area under the ROC curve was 0.887 (95% CI 0.845-0.928). A cut-off point of 9 gives the best result in terms of combined sensitivity (84.5%) and specificity (82.9%). These two parameters, together with dry cough, bloody phlegm, chest distress, tachypnea, extrathoracic presentations, symmetrical lymphadenopathy, reticular fiber stain in histological specimens, cavity or calcification, the lesion location in radiography, ECT manifestations, and necrosis in histological specimens were collected for the establishment of a scoring system in our study.

Establishment of scoring system

CR scoring system

In the CR group, the β -coefficients of logistic analysis and scores of the final variables were shown in Table 2. The median of the sum score in SA was 15, 25th~75th (12~16) and the median in TB was 3, 25th~75th (2~6) ($U=282.50$, $p=0.000$). A cut-off point of 9 is associated with a sensitivity and specificity of 93.16% (109/117) and 97.79% (177/181) to distinguish the two diseases and with a LR (likelihood ratio) of 42. This scoring model had an area under the ROC curve (Figure 1) of 0.987 (95% CI: 0.977-0.996).

CRE scoring system

In the CRE group, the β -coefficients and the scores of the final variables were shown in Table 2. The medium of the sum score in SA was 24, 25th~75th (21~29) and in TB was 7, 25th~75th (5~11) ($U=106.0$, $p=0.000$). With a cutoff point of 17, the sensitivity and specificity were 92.31% (108/117) and 98.90% (179/181) respectively, with LR at 84. The area under the ROC curve (Figure 1) was 0.995 (95% CI, 0.990-1.000). The CR and CRE system is applied when the patient has normal body check, such as X-ray, chest CT or ECT, and has no typical symptoms to confirm the diagnosis.

Table 2. The scores of the four scoring systems*

Variables	CR		CRE		CRP		CREP	
	β	Score	β	Score	β	Score	β	Score
TST	3.752	4	4.442	5	3.695	5	4.796	6
Tachypnea (Tac)	2.173	2	0.847	1	2.124	3	1.427	2
Extrathoracic presentations (Extr)	1.966	2	2.036	2	2.022	3	2.37	3
Symmetrical lymphadenopathy (SLym)	4.657	5	3.152	4	4.76	6	3.071	4
Cavity or calcification (CC)	3.284	3	4.179	5	4.295	5	4.37	5
Lesion location in radiography (L)								
L ₁	-0.003	-1	-0.925	-1	0.789	1	0.982	1
L ₂	0.951	1	-0.072	0	0.929	1	1.839	2
L ₃	3.977	4	4.073	5	5.163	7	5.81	7
ECT manifestations (ECT)								
E ₁			2.219	3			0.899	1
E ₂			6.465	8			5.799	7
Necrosis (Nec)					3.985	5	4.792	6
Increase of reticular fiber (Fib)					1.011	1	-0.85	1

* The four groups were: CR = TST + Tac + Extr + SLym + CC + L1 + L2 + L3, CRE = TST + Tac + Extr + SLym + CC + L1 + L2 + L3 + E1 + E2, CRP = TST + Tac + Extr + SLym + CC + L1 + L2 + L3 + Nec + Fib, CREP = TST + Tac + Extr + SLym + CC + L1 + L2 + L3 + E1 + E2 + Nec + Fib

CRP scoring system

The scoring systems in the CRP and CREP groups were shown in Table 2. In the CRP group, the medium of sum scores in SA and TB was 26, 25th~75th (21~27) and 6, 25th~75th (4~9), respectively ($U=94.50$, $p = 0.000$). With a cutoff point of 18, the sensitivity and specificity were 93.16% (109/117) and 98.90% (179/181), with LR at 84. The area under the ROC curve (Figure 1) was 0.996 (95% CI, 0.990-1.001).

CREP scoring system

In the CREP group, the medium of sum scores in SA and TB was 32, 25th~75th (27~36) and 7, 25th~75th (5~12), respectively ($U=38.000$, $p=0.000$). With a cutoff point of 22, the sensitivity and specificity were 94.87% (111/117) and 98.90% (179/181), with LR at 86. The area under the ROC curve was 0.998 (95% CI 0.996-1.000) (Figure 1). The CRP or CREP system could be applied for discrimination of SA and TB when no caseous necrosis is observed in tissue biopsy.

Comparison of the four groups

There was no significant difference in the proportion of patients correctly classified by the four scoring systems (Chi square=0.908) (Table 3).

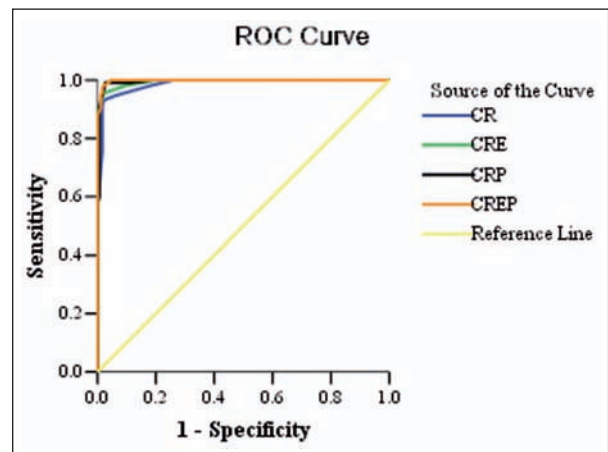


Fig. 1. The ROC curves of four groups, CR = clinical-radiographic group, CRE = clinical-radiographic-radionuclide group, CRP = clinical-radiographic-pathological group and CREP = clinical-radiographic-radionuclide-pathological group. The area under the ROC curve increased gradually with the increasing variables

Validation of the scoring system

Seventy-three patients with SA and 57 TB patients from January 2006 to December 2007 entered this phase of the study. The number of cases of misdiagnosed TB was 4, 2, 2, 2 in scoring systems, all less than 5% of total cases of SA. That ratio was less

Table 3. Comparison of the four groups

Group	Correctly classified	Misclassified	Ratio of correctly classified (%)	The χ^2 test value	P value
CR	286	12	95.97	0.908	0.824
CRE	287	11	96.31		
CRP	288	10	96.64		
CREP	290	8	97.32		

CR vs. CRE ($\chi^2=0.045$, $p=0.832$), CR vs. CRP ($\chi^2=0.189$, $p=0.664$), CR vs. CREP ($\chi^2=0.833$, $p=0.361$), CRE vs. CRP ($\chi^2=0.049$, $p=0.824$), CRE vs. CREP ($\chi^2=0.491$, $p=0.483$), CRP vs. CREP ($\chi^2=0.230$, $p=0.632$). α' in partitions of χ^2 method of 0.007 and $p<0.007$ is considered to have statistical significance

Table 4. The number of misdiagnosed cases and the ratio of correctly diagnosed

Disease	CR	CRP	CRE	CREP	Sum
SA	6 (91.78%)	4 (94.52%)	2 (97.26%)	1 (98.63%)	73
SA	3 (94.55%)	2 (96.36%)	2 (96.36%)	1 (98.18%)	55
TB	7 (87.72%)	2 (96.49%)	1 (98.25%)	1 (98.25%)	57
TB	4 (84.00%)	1 (96.00%)	1 (96.00%)	1 (96.00%)	25

than 10% in validation group (Table 4). There were 55 SA and 25 TB patients who had ECT examinations. The rates of correctly diagnosed were similar to that observed in the first group (Table 4). Therefore, the scoring system provides a satisfactory, predictive value in the validation group.

DISCUSSION

Diagnosis of SA typically requires a compatible clinical picture, histological evidence of epithelioid noncaseating granulomas, and the exclusion of other diseases that may produce similar clinical or histological features (e.g., TB, lymphoma, or fungal infection) (2, 21). The clinical picture of the disease depends on ethnicity, duration of the illness, site and extent of organ involvement, and activity of the granulomatous process (22). Nonspecific constitutional symptoms such as fever, fatigue, malaise, and weight loss may occur in one-third of patients with SA. In Table 1, the clinical symptoms such as dry cough, chest distress, tachypnea are more likely to happen in SA. The thoracic involvement include pulmonary and generally manifests as asymptomatic mediastinal adenopathy. Intrathoracic lymphadenopathy is the most com-

monly encountered radiological finding in SA (88.03% of cases in our study as symmetrical lymphadenopathy) and typically manifests as bilateral hilar adenopathy with right paratracheal adenopathy (23). However, the radiological findings are atypical in some patients. In some cases, radiography may be the only method used to exclude TB (24). Although the panda sign and/or lambda sign are classic features of SA (21, 25), they may also occur in other diseases, such as carcinoma and TB (21).

TB can be easily diagnosed by the conventional method when smear examination for acid bacilli or culture identification was positive for *MTB* from sputum, bronchoalveolar lavage samples, and affected tissue samples. Moreover, the diagnosis of TB was made if granulomas with caseous necrosis appeared in a histological examination (9). However, in patients with a negative mycobacterial culture of sputum and absence of caseous necrosis, exclusion of SA is critically important for the diagnosis due to the similarity of TB and SA in clinical and pathological features. This differential diagnosis is especially important in countries such as China, where there is a high incidence of TB (26).

Treatment of TB mainly depends on antituberculous therapy supplemented by a low dose of corticosteroids in select cases (10). SA treatment primarily consists of administration of long-term and high dose corticosteroids, though alternative drugs are also available (2, 27). If a patient with TB is misdiagnosed with SA, treatment with high doses of corticosteroids may lead to the dissemination of lesions, which can be life threatening. On the other hand, if antituberculous therapy is used for patients with SA, spontaneous remission could occur in some patients. However, progressive symptoms could develop due to delayed corticosteroid therapy. The number of cases of misdiagnosed of TB with scoring systems was less than 5% of total cases of SA. That ratio was less than 10% in the validation group. Therefore, we currently apply the scoring systems to distinguish SA from sputum negative TB routinely in practice in our hospital.

Despite extensive research efforts in differentiating TB and SA, covering etiology (5-7, 27-31), genetic features (32, 33), immunopathogenesis (34-37), pathology (38), and morphology (11), studies to date have not identified specific markers for discriminating the two diseases, and few efforts have been

made to group them in order to improve their individual predictive power. Evaluation systems have been developed for TB (39-41) and in SA (42, 43), respectively. In the current study, we analyzed clinical, radiographic and histological findings and established the scoring system to distinguish between TB and SA. Based on the results of the Chi square test and logistic analysis, 13 variables with statistical significance in distinguishing the two diseases were selected. Using different combinations of these variables, four different scoring systems (CR, CRE, CRP, and CREP) were established by logistic regression analysis. We have made a computer program to apply the scoring systems to aid in differentiating these two diseases. We are currently continuing to perform a prospective analysis of suspicious cases between the two diseases to test the scoring systems in our hospital.

We selected the scoring system to aid in the decision-making process because of its simple design and application. In the four groups, the overall score was significantly higher in SA than in TB by scoring systems. The sum scores were all double-digit and easy to calculate. In clinical practice, especially when physicians come to a dilemma in diagnosing SA and TB with current methods, one of the four scoring systems may be used for discriminating the two diseases in terms of data availability. In our hospital, the scoring systems are currently applied and have given a satisfactory result for diagnosis. The scoring systems have a very good diagnosis value (Table 3). The ratio of correct classification between the four groups have no statistical significance. But the data (Table 3 and Table 4) suggest that the ECT examination and tissue biopsy did not add weight in the discrimination of SA and TB. However, the ratio of correct classification increased gradually as more variables were included, especially when we had ECT data. In some cases, we have averted thoracotomy and other operations when adequate information was available for the application of the CR/CRE scoring system. Also, appropriate treatment may be applied as a result of the application of the scoring system. Since different hospitals may have different equipment, we have established four scoring systems depending on what information is available. However, the establishment of the scoring system is an exploratory study and further effort is warranted for the improvement and wide application

of the system in the differential diagnosis of SA and atypical TB.

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