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ORIGINAL ARTICLE

Risk factors of relapse in pulmonary sarcoidosis treated with corticosteroids

Yi Zheng[1] · Hui Wang[1] · Qingqing Xu[1] · Xin Yan[1] · Yi Zhuang[1] · Hanyi Jiang[1] · Fanqing Meng[2] · Yonglong Xiao[1] · Hourong Cai[1] · Jinghong Dai[1]

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Abstract

Objective To evaluate the incidence and risk factors of relapse in pulmonary sarcoidosis treated with corticosteroids.

Methods Medical records of patients with pulmonary sarcoidosis were retrospectively reviewed. Clinical features, chest radiographs, pulmonary function tests, and treatment information were collected. The starting point was the date of diagnosis. Clinical relapse was defined as chest high-resolution computed tomography (HRCT) showing radiographic progression in combination of worsening of clinical symptoms to warrant retreatment following a decrease in dose or discontinuation of corticosteroids, without alternative causes such as infections, heart failure, or pulmonary embolism. Non-relapse was defined as remission of clinical symptoms and chest abnormalities, or clinical syndrome improvement with retention or stability of radiographic abnormalities after corticosteroids were withdrawn for at least 6 months. The primary endpoint was the occurrence of relapse.

Results Two hundred three patients with newly biopsy-proven pulmonary sarcoidosis were enrolled over a 7-year period. Among them, 96 patients received corticosteroids therapy. Relapse occurred in 30 patients with the relapse rate yielding 30/96 (31.25%). After adjustment, multivariate analysis showed that smoking history (HR = 3.674 95% CI 1.573–8.581, $P = 0.003$) and increased percentages of circulating neutrophils (> 70%) (HR = 2.211, 95% CI 1.073–4.557, $P = 0.032$) were the significant predictors of relapse in pulmonary sarcoidosis treated with corticosteroids.

Conclusions This study provided useful information that the relapse and associated risk factors should be taken into considerations when determining treatment strategies for patients with pulmonary sarcoidosis.

Keywords Corticosteroid · Pulmonary sarcoidosis · Relapse · Risk factor

Introduction

Sarcoidosis is a multisystem granulomatous disease with undetermined etiology, which could affect multiple organs, mainly the lungs, eyes, and skin. The clinical course of sarcoidosis is highly variable together with distinct prognosis. To date, there is no standard treatment for patients with sarcoidosis [1, 2]. Some patients did not need active interventions because they were asymptomatic or had a self-limited disease. But for patients with symptoms or impaired quality of life, corticosteroids were the mainstay of therapeutic choice [3]. Although most of patients with sarcoidosis could rapidly respond to corticosteroids, relapse was common when corticosteroids were tapered or discontinued. Published data suggested that relapse rates in patients with sarcoidosis ranged from 37 to 75% [4–6]. However, it was difficult to make a direct comparison and comprehensive analysis among these studies due to the distinct inclusion criteria and definitions of relapse.

Summary at a glance The study showed that relapse for pulmonary sarcoidosis treated with corticosteroids was common. Smoking history and increased percentages of circulating neutrophils were firstly identified to be significantly associated with the relapse. This information would be useful for clinicians to decide the treatment choice for patients with pulmonary sarcoidosis.

✉ Jinghong Dai
daijinghong@nju.edu.cn

[1] Department of Pulmonary and Critical Care Medicine, The Affiliated Drum Tower Hospital of Nanjing University Medical School, No. 321 Zhongshan Road, Nanjing 210008, Jiangsu, China

[2] Department of Pathology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, No. 321 Zhongshan Road, Nanjing 210008, Jiangsu, China

Pulmonary involvement was the most common form of sarcoidosis and relapsing disease was most common among patients with pulmonary involvement [7]. Few studies investigated whether corticosteroids therapy could prevent the relapse or not, and the associated risk factors for relapse in pulmonary sarcoidosis remained largely unknown. Therefore, we conducted this retrospective study in an interstitial lung disease center in China, to investigate the incidence of relapse and associated risk factors in patients with pulmonary sarcoidosis who were treated with corticosteroids.

Methods

Study subjects

Electronic medical records of patients with newly biopsy-proven diagnosis of pulmonary sarcoidosis in the database from January 2012 to December 2018 were retrospectively reviewed. Diagnosis of pulmonary sarcoidosis was established when chest radiography was accompanied by compatible clinical features, supported by the presence of non-caseating granulomas in a biopsy specimen [1]. The biopsy specimens were obtained from pulmonary parenchyma, skin, or lymph nodes. Patients with alternative granulomas diseases such as organisms and particles and combined with other diseases requiring corticosteroid therapy were excluded. Patients with other chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease were also excluded. The ethics approval was acquired according to the policy of the Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School.

In our center, the decision on introducing a patient to receiving corticosteroid therapy was made through a fashion of consultation with an experienced specialist in interstitial lung disease field (H.C.). The following factors should be considered: severity of the clinical symptoms, the radiographic stages, impairment of pulmonary function tests, and the life quality. Based on the international expert panel [2], corticosteroid treatment was initiated from 20 to 40 mg of prednisone per day or its equivalent; higher doses were used infrequently. All patients were informed to visit every 1 to 3 months to evaluate the response. Assessment of response to corticosteroids included physical examinations, chest radiographs, and pulmonary function tests. If there had been a response, the dosage was tapered to 5 to 15 mg per day and continued the minimal effective dose for 9 to 12 months. When corticosteroids were withdrawn, follow-up would last for at least 6 months.

Patients were divided into corticosteroid-treated group and untreated group according to the therapeutic records. The corticosteroid-treated group included patients who were treated with corticosteroids from diagnosis and who were not treated with corticosteroids at diagnosis but initiated corticosteroid therapy when the diseases progressed in follow-up. Clinical relapse was defined as chest high-resolution computed tomography (HRCT) showing radiographic progression (new emerging pulmonary infiltrations or the extent of chest abnormalities becoming widen) in combination with worsening of clinical symptoms to warrant retreatment following a decrease in dose or discontinuation of corticosteroids, without alternative causes such as infections, heart failure, or pulmonary embolism. Non-relapse was defined as resolution of clinical symptoms and chest abnormalities, or clinical syndrome improvement with retention or stability of radiographic abnormalities when corticosteroid treatment was withdrawn for at least 6 months.

Data collection

Clinical information at initial diagnosis was collected via reviewing electronic medical records, including demographics, smoking history, and comorbidities (diabetes mellitus, hypertension and chronic superficial gastritis, etc.). The initial manifestations at presentations and major extra-pulmonary involvements such as eyes and extra-thoracic lymph nodes were recorded. The lab examination data included blood routine, biochemical parameters, and presence of serum autoantibodies. Fasting venous blood sample of every patient was taken at diagnosis before corticosteroid therapy and analyzed in Clinical Laboratory in our hospital. Pulmonary function testing included forced vital capacity (FVC), FVC% predicted, diffusion capacity for carbon monoxide (DLCO), and DLCO% predicted. Chest HRCTs of all patients in supine position were performed at diagnosis, and radiographic staging was recorded according to the previous criteria [8, 9]. Radiographic staging was grouped as stage 1 (lymphadenopathy only), stage 2 (parenchymal abnormalities with lymphadenopathy), stage 3 (parenchymal abnormalities without lymphadenopathy), and stage 4 (pulmonary fibrosis). Treatment information included the initial dose of corticosteroids and treatment duration. When relapse occurred, corticosteroid dose and the duration of discontinuation were recorded.

Follow-up

The starting point of this study was the date of diagnosis. The primary endpoint of this study was the occurrence of relapse. The second endpoint was the risk factors of relapse. The last follow-up was until December 2018. Vital status of all patients was determined based on medical records and telephone communications.

Statistical analysis

Continuous variables were compared using a two-tailed Student's *t* test. Categorical variables were compared using a chi-squared test when needed. Cox proportional hazards model was used for univariate and multivariate survival analyses to calculate the

hazard ratios (HR) and corresponding 95% confidence intervals (CI). *P* values were two-sided and considered significant if less than 0.05. All statistical analyses were performed using the SPSS statistical software, version 22.0 (SPSS Inc., Chicago, IL, USA). The normal range of the percentage of circulating neutrophils was from 40 to 70%, and we used the normal upper value 70% as cut-off. The Omnibus tests of model coefficients showed that Cox proportional hazards models were fit.

Results

Two hundred forty-three patients with biopsy-proven pulmonary sarcoidosis in the database were screened over a 7-year period. Among them, 40 patients who missed data or lost follow-up were excluded. Hence, 203 patients were enrolled in the study. They were 117 (57.64%) females and 86 (42.36%) males with a mean age of 53.22 ± 10.22 years old (range from 22 to 80). Forty-five (22.17%) patients reported a smoking history. All patients presented with pulmonary sarcoidosis. Other organs included ocular involvement in 17 patients and extrathoracic lymph node involvement in 51 patients. The most frequent initial manifestation was coughing presented in 141 (69.46%) patients, followed by dyspnea in 59 (29.06%) patients, and chest pain in 47 (23.15%) patients. Thirty-nine (19.21%) patients were asymptomatic and presented HRCT abnormalities in routine health examinations. Chest radiographs revealed that 39 (19.21%) patients presented with stage 1, 135 (66.50%) patients with stage 2, 14 (6.90%) patients with stage 3, and 15 (7.39%) patients with stage 4 (Table 1).

In total, 96 patients who received corticosteroid therapy were classified as the corticosteroid-treated group; of them, 83 (86.46%) patients were treated from the diagnosis and 13 (13.54%) patients who initially were not treated and received corticosteroid therapy when the diseases progressed in follow-up. One hundred seven patients without corticosteroid treatment were classified as the untreated group (Fig. 1). No patients received other immunomodulatory or cytotoxic drugs such as methotrexate, azathioprine, leflunomide, and mycophenolate. Demographics, clinical features, pulmonary function tests, and CT staging at baseline of two groups were described in Table 1. No significant differences were observed between the two groups.

In the corticosteroid-treated group, the average initial dose was 30.64 ± 8.03 mg (range, 10–60 mg) of prednisone daily or its equivalent. The mean follow-up time was 31.13 months (range, 6–84 months). Sixty-six patients achieved clinical stability lasting more than 6 months after cessations of corticosteroid treatment (Table 2). Thirty (31.25%) patients suffered relapse to warrant retreatment. Relapse occurred in 15 patients when prednisone doses were reduced to 10–15 mg/day. Relapse occurred in 15 patients in 8 months (range, 1–36 months) after discontinuing corticosteroid therapy.

Univariate analysis demonstrated that smoking history (HR = 3.599, 95% CI 1.543–8.395, $P = 0.003$), increased percentages of circulating neutrophils (> 70%) (HR = 2.277, 95% CI 1.106–4.689, $P = 0.026$), and lactate dehydrogenase (LDH) (HR = 1.003, 95% CI 1.001–1.005, $P = 0.011$) were significantly associated with relapse in pulmonary sarcoidosis treated with corticosteroids. After adjusted for sex and age, multivariate analysis showed that smoking history (HR = 3.674, 95% CI 1.573–8.581, $P = 0.003$) and increased percentages of circulating neutrophils (> 70%) (HR = 2.211, 95% CI 1.073–4.557, $P = 0.032$) remained the significantly independent predictors of relapse in the treated group (Fig. 2a, b).

Discussion

In this study, we showed that relapse in pulmonary sarcoidosis treated with corticosteroids was common when the treatment was reduced or discontinued. Smoking history and increased percentages of circulating neutrophils (> 70%) were identified to be significantly associated with the relapse. This study provided valuable information that clinicians should take into considerations when introducing treatment for patients with pulmonary sarcoidosis.

Several studies had demonstrated that relapse was usual in patients with sarcoidosis receiving corticosteroid therapy [4–6]. One of them reported relapse rate was 67% after corticosteroid treatment withdrawal. The inclusion criteria in this study restricted patients to chest radiographs presented as stage 2 and stage 3 [5]. Johns and coauthors reported that the relapse rate was 75% following corticosteroid therapy without providing the details of definitions and criteria for relapse [6]. In a study from Gottlieb and colleagues, relapse was defined as a recurrence of symptoms of sufficient severity to warrant treatment following a remission without treatment lasting more than 1 month [4]. Interestingly, a previous study revealed that relapse occurred more frequently in patients treated with corticosteroids than those who had not been treated with corticosteroids. Did corticosteroid treatment itself, or not, contributed to the propensity for relapse? There was indeed some support for this hypothesis from a future clinical trial [4]. Prolonged maintenance of corticosteroids had ever been recommended to reduce the risk of relapse, but no clinical evidences supported this approach [10]. Furthermore, long-term corticosteroid therapy was associated with toxic effect [3]. Herein, the clinical decision to initiate corticosteroid therapy should be a reflection of weighing the risks of using corticosteroids and the potential benefits.

Smoking was found less common in patients with sarcoidosis than in the control subjects in Western populations [11]. Conversely, a study from Japan showed that increased prevalence of cigarette smoking in Japanese sarcoidosis patients, and lung parenchymal involvement was greater in current smokers

Table 1 Comparisons of demographic, clinical characteristics between the corticosteroid-treated group and untreated group

	Corticosteroid-treated group ($n = 96$)	Untreated group ($n = 107$)	P
Age (years)	54.89 ± 9.85	51.73 ± 10.36	0.965
Follow-up time (months)	32.13 ± 23.48	32.06 ± 21.09	0.480
Gender (female)	51 (53.13%)	66 (61.68%)	0.218
Patients with baseline comorbidities			
Diabetes mellitus at baseline	5 (5.21%)	11 (10.28%)	0.181
Hypertension at baseline	18 (18.75%)	22 (20.56%)	0.746
Chronic superficial gastritis at baseline	4 (4.17%)	8 (7.48%)	0.318
Smoking history	20 (20.83%)	25 (23.36%)	0.665
Radiographic staging			0.066
1	17 (17.71%)	22 (20.56%)	
2	60 (62.50%)	75 (70.09%)	
3	9 (9.38%)	5 (4.67%)	
4	10 (10.42%)	5 (4.67%)	
Pulmonary function at baseline	64 available	88 available	
FVC	2.70 ± 0.87	3.03 ± 0.84	0.435
FVC% predicted	84.38 ± 17.71	92.10 ± 16.09	0.174
DLCO	5.78 ± 2.02	6.89 ± 1.96	0.801
DLCO% predicted	77.30 ± 22.10	91.45 ± 18.70	0.602
Presence of antibody	74 (77.08%)	89 (83.18%)	0.276
Relapse rate	30 (31.25%)	–	–
Mortality	3 (3.13%)	0 (0.00%)	–

Mean ± SD, *n* (%). *FVC* forced vital capacity, *DLCO* diffusion capacity for carbon monoxide of the lung

than in never smokers [12]. Smokers were also found to have a higher incidence of extra-pulmonary involvements and have significantly reduced forced expiratory volume in the first second (FEV_1) and FEV_1/FVC values compared with nonsmokers [13]. In the current study, smoking history was identified as an independent risk factor for relapse in pulmonary sarcoidosis treated with corticosteroids. A previous study indicated that the ratio of CD4:CD8 lymphocytes and the counts of alveolar macrophages were lower in bronchoalveolar lavage fluid (BALF) in smokers compared with non-smokers in patients with

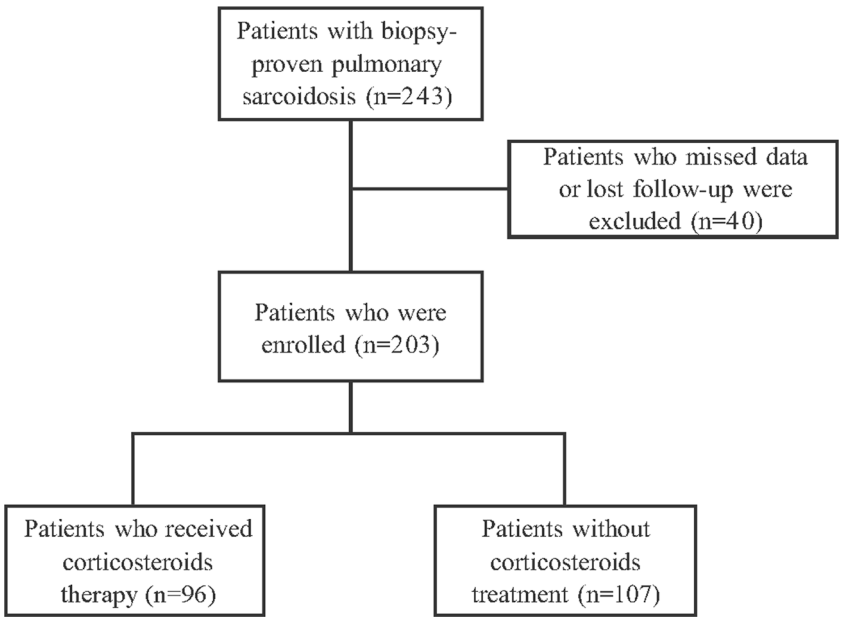

Fig. 1 Flowchart of the patients' selection

Table 2 Comparisons of demographic, clinical characteristics between the non-relapse group and relapse group in corticosteroid-treated group

	Non-relapse group ($n = 66$)	Relapse group ($n = 30$)	P
Age (years)	54.35 ± 9.60	56.07 ± 10.46	0.712
Gender (female)	39 (59.09%)	12 (40.00%)	0.082
Follow-up time (months)	34.52 ± 22.00	26.87 ± 26.05	0.471
Patients with baseline comorbidities			
Diabetes mellitus at baseline	4 (6.06%)	1 (3.33%)	0.181
Hypertension at baseline	16 (24.24%)	2 (6.67%)	0.050
Chronic superficial gastritis at baseline	3 (4.55%)	1 (3.33%)	1.000
Smoking history	11 (16.67%)	9 (30.00%)	0.136
Radiographic staging			0.107
1	11 (16.67%)	6 (20.00%)	
2	46 (69.70%)	14 (46.67%)	
3	5 (7.58%)	4 (13.33%)	
4	4 (6.06%)	6 (20.00%)	
Pulmonary function at baseline	44 available	20 available	
FVC (L)	2.67 ± 0.86	2.78 ± 0.92	0.588
FVC% predicted	84.40 ± 16.24	84.32 ± 21.05	0.168
DLCO (ml/min/kPa)	5.93 ± 1.96	5.46 ± 2.15	0.923
DLCO% predicted	76.56 ± 21.84	78.87 ± 23.23	0.802
Laboratory data			
WBC ($\times 10^9$/L)	5.14 ± 1.76	6.48 ± 2.15	0.154
L %	24.79 ± 7.34	19.60 ± 10.59	0.064
N %	62.25 ± 9.00	69.43 ± 12.01	0.072
HB (g/L)	130.75 ± 15.54	135.30 ± 13.59	0.198
Plt ($\times 10^9$/L)	227.95 ± 127.64	199.27 ± 66.84	0.477
ALB (g/L)	39.48 ± 2.91	37.71 ± 3.87	0.509
LDH (U/L)	204.30 ± 53.17	263.93 ± 179.27	< 0.01
CRP (mg/L)	7.26 ± 9.91	21.71 ± 39.73	< 0.01
GLU (mmol/L)	4.98 ± 1.10	4.84 ± 1.24	0.675
TG (mmol/L)	1.87 ± 1.00	1.57 ± 0.58	0.047
TCH (mmol/L)	4.29 ± 0.63	4.51 ± 0.88	0.095
Presence of antibody	49 (74.24%)	25 (83.33%)	0.326
Extra-pulmonary involvement			
Ocular involvement	8 (12.12%)	4 (13.33%)	1.000
Extra-pulmonary lymph node enlargement	17 (25.76%)	3 (10.00%)	0.078
Initiation dosage(mg)	30.46 ± 7.11	31.03 ± 9.88	0.190
Duration of treatment (months)	18.42 ± 17.82	25.70 ± 25.48	0.095

Mean ± SD, *n* (%). *FVC* forced vital capacity, *DLCO* diffusion capacity for carbon monoxide of the lung, *WBC* white blood cell counts, *L%* lymphocyte percentage; *N %* neutrophil percentage, *HB* hemoglobin, *PLT* platelet, *ALB* albumin, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *GLU* glucose, *TG* triglyceride, *TCH* total cholesterol

sarcoidosis [11]. Further study is still needed to clarify the exact role that smoking intervened in the macrophage-lymphocyte activation process in the granuloma formation.

In this study, increased percentages of circulating neutrophils (when exceeding the upper normal range: 70%) were an independent risk factor for relapse in pulmonary sarcoidosis treated with corticosteroids. Pathologically, sarcoidosis was marked by granulomatous inflammation in the affected organ. Increased neutrophil chemotactic factors in BALF reflected that neutrophils might be involved in non-specific inflammation and induce sustained inflammation in pulmonary sarcoidosis [14]. Drent and colleagues demonstrated that the counts of neutrophils in BALF had significant differences between patients who underwent spontaneous remission and those exhibiting a more severe course of disease [15]. Also, elevated neutrophils in BALF indicated a higher risk of disease progression [16]. Ongoing studies are needed to investigate the mechanisms of cells immune in the pathophysiology of sarcoidosis.

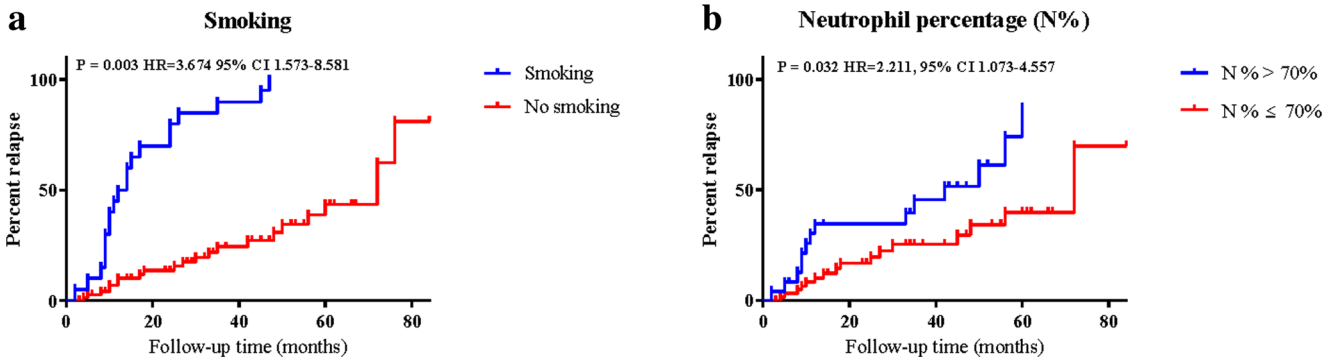

Fig. 2 Time-to-event analysis for development of composite end-point by Cox model between patients with or without smoking history and patients with N % > 70% or N % ≤ 70% in the corticosteroid-treated group. Time is represented in months

An increased level of serum LDH was found in some interstitial pneumonia including cryptogenic fibrosing alveolitis and extrinsic allergic alveolitis [17]. A study from Aubart and colleagues reported serum levels were elevated in patients with spinal cord sarcoidosis [18]. In our study, the value of serum LDH was a significant risk factor for relapse in univariate analysis, whereas it had no significance in the multivariate analysis after adjustment. Pulmonary function testing such as FVC was most commonly used to evaluate response to therapy [19]. We failed to find an association between lung function tests and the occurrence of relapse in sarcoidosis probably due to a small sample size. Several environmental and occupational exposures, including insecticides, agricultural employment, and microbial bioaerosols, had been reported to have positive relationships with sarcoidosis risk [20]. In addition, tuberculosis and sarcoidosis were both granulomatous diseases with some overlapping. A more recent study concluded that tuberculosis was a risk factor for developing sarcoidosis [21]. Unfortunately, all patients in our study denied special occupational exposures or having contact with patients with tuberculosis.

Second-line drugs were generally required for patients who were unresponsive to corticosteroids or who could not tolerate their toxic effects. The most common alternative strategies included antimetabolites and cytotoxic drugs (i.e., methotrexate, azathioprine, leflunomide, and mycophenolate mofetil) [22]. Patients receiving a combination of corticosteroids and methotrexate required significantly smaller dosages of corticosteroids than the control group [23]. The monoclonal anti-TNFα antibody infliximab had been used to treat refractory sarcoidosis with some success [24]. However, most of these published data were based on small numbers of patients. Future collaborative research networks are critical for conducting randomized, controlled trials of novel drugs and improving our understanding of diseases pathogenesis.

The risk of death from sarcoidosis was estimated between 1.0 and 7.6% [25, 26]. Mortality from sarcoidosis appeared to have increased in the past three decades, with respiratory failure being the most common cause of sarcoidosis-related death [9, 27]. In the current study, three patients died and the mortality was 1.48% (3/203). One patient who was treated with corticosteroids died from cryptococcal meningitis. The initial dose of prednisone was 30 mg daily and tapered 5 mg daily every 3 months. He developed fever when the dosage of prednisone was tapered to 20 mg daily in 8 months from diagnosis. *Cryptococcus neoformans* was found in his cerebrospinal fluid examinations. Even we stopped prednisone and gave aggressive anti-fungi therapy, fever persisted and the patients developed coma. Two patients died from respiratory failure. Mortality in this study was low mainly due to the small proportion of patients with staging 4 and a relative shorter follow-up durance.

This study had several limitations that should be acknowledged. First, it was a retrospective single-center study with a small sample size. Selection bias was inevitable. Future study should be prospectively performed in a large cohort from multiple institutions with diverse populations. Second, we considered only the eye and lymph node involvement as extra-pulmonary lesions because the retrospective nature of the data did not reveal exact details for other organ involvements as evaluated by uniform examination, such as abdominal and brain computed tomography. This will result in the underestimation of involvement of extra-pulmonary lesions.

In summary, our study showed that relapse in pulmonary sarcoidosis treated with corticosteroids was common. Smoking history and increased percentages of circulating neutrophils were significantly associated with the relapse. This information would be useful for clinicians to decide treatment strategies for patients with sarcoidosis.

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Compliance with ethical standards

The ethics approval was acquired according to the policy of the Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School.

Disclosures None.

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