SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2017; 34; 209-216 DOI: 10.36141/svdld.v34i3.5727

Clinical characteristics of sarcoidosis patients in the United States versus China

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Abstract. *Objective:* To characterize and compare the disease manifestations between patients with sarcoidosis in China versus the United States using the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) instrument. *Methods:* Clinical data and disease manifestations were reviewed from sarcoidosis patients from the Shanghai Pulmonary Hospital (China) and University of Cincinnati Medical Center (US). *Results:* 481 Chinese patients and 522 US patients with sarcoidosis were studied. Extra-pulmonary sarcoidosis was observed more frequently in US patients than Chinese patients. Chinese patients were more likely to develop hypercalcemia or hypercalcuria (23%) compared to US patients (14%) (χ^2=18.342, P<0.001), and US White patients were more likely to experience hypercalcemia or hypercalcuria (20%) compared to US Black patients (7.6%) (χ^2=16.230, P<0.001). However, Black patients were more likely to have eye involvement (39%) than White patients (26%) (χ^2=10.986, P=0.001). Additionally, US patients witnessed more advanced Stage 3 or 4 chest x-ray patterns and lower predicted FVC% and DLCO% compared to Chinese patients (both P<0.001). *Conclusion:* Compared to US sarcoidosis patients, Chinese patients were older at diagnosis and experienced a lower frequency of extra thoracic involvement, higher incidence of hypercalcemia or hypercalcuria, and less severe lung involvement. These differences were mostly due to the African American patients seen in the US sarcoidosis clinic. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 209-216)*

Key words: sarcoidosis; epidemiology; organ involvement; hypercalcemia

Introduction

The systemic granulomatous disease of unclear etiology, sarcoidoisis, can involve multiple organs. Ethnic differences may account for the some of the various disease manifestations, extent, and severity of sarcoidosis reported globally (1, 2). Studies in the United States have demonstrated that the disease is more common in Black females and the disease severity is worse in Black patients compared to Whites (3-5). Because sarcoidosis was considered very rare in China (6), scant information exists regarding disease manifestations and severity of pulmonary disease for the Chinese Han population.

In 1999 a sarcoidosis specific instrument was developed to standardize the disease phenotypes in newly diagnosed US sarcoidosis patients based on race, sex, and age (7). Using this instrument the A Case Control Etiologic Study of Sarcoidosis (ACCESS) multicenter study characterized the dis-

Received: 2 September 2016
Accepted after revision: 10 August 2017
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ease manifestations of 736 US patients with newly diagnosed sarcoidosis from 10 US clinical centers (3). Cutaneous, ophthalmic, extra-thoracic lymph node, hepatic, and bone marrow involvement were more frequently identified in Black patients; whereas White patients were more likely to develop abnormal calcium metabolism. Although prior reports suggested that patients were rarely diagnosed after age 50 (8), the ACCESS study identified significant phenotypic differences in patients diagnosed before and after age 40 (3). Newly diagnosed women were more likely to be >age 40 years; whereas, men tended to be younger. Younger patients (<age 40) were more likely to develop extra-thoracic lymph node involvement; however, older patients (>age 40) were more likely to have abnormal calcium metabolism.

Recently, the ACCESS disease manifestation instrument was updated by the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) (9). By incorporating newer diagnostic imaging such as positive emission tomography (PET) and magnetic resonance imaging (MRI), this newer version is designed to more precisely define sarcoidosis phenotypes. Using the new WASOG sarcoidosis assessment system, we compared the disease manifestations experienced by US and Chinese sarcoidosis patients to determine whether race, gender, or age influenced the phenotypes.

Methods

Patients with sarcoidosis were enrolled from two clinics: Shanghai Pulmonary Hospital (Chinese patients) and the University of Cincinnati Medical Center (US patients). The diagnosis of sarcoidosis was established based on the presence of clinical symptoms, radiological features compatible with sarcoidosis, and biopsy evidence of noncaseating epithelioid cell granulomas with other known causes of granulomatosis excluded (10). For Chinese patients, the medical records were retrospectively reviewed from patients diagnosed with sarcoidosis between January 2009 and January 2015. In contrast, the medical records were prospectively reviewed for all the US patients seen in clinic during the four month period from July 1, 2015 to October 31, 2015. Additionally, US patients were further characterized by self declared race with further analysis performed for the racial subgroups, Blacks (African Americans) and Whites (Caucasians).

Disease phenotypes were determined for each patient using the revised WASOG instrument described in 2014 (9).

The clinical manifestation for a specific organ system was categorized as: a) highly probable, b) probable, or c) possible. Highly probable lesions were defined when the likelihood of sarcoidosis causing this manifestation was at least 90%; whereas, probable lesions had a likelihood between 50% and 90%. Possible lesions included those in which the likelihood of sarcoidosis causing this manifestation was < 50%. Specific sarcoidosis organ involvement was defined as biopsy confirmation of granulomas or either "highly probable" or "probable" disease category. Fifteen distinct organs or disease manifestations were compared between the Chinese and US groups: pulmonary, neurologic, non-thoracic lymph node, renal, cardiac, cutaneous, ophthalmic, hepatic, hematologic (bone marrow or spleen) bone/joint, head and neck, parotid/salivary, muscle and endocrine (hypercalcemia/hypercalcuric).

Chest imaging and pulmonary function were evaluated and compared between the Chinese and US groups. Using the modified Scadding staging system (11), chest radiography was classified as Stage 0: no adenopathy or infiltrates; Stage 1: hilar and mediastinal adenopathy alone; Stage II: adenopathy and pulmonary infiltrates; Stage III: pulmonary infiltrates alone; and Stage IV: pulmonary fibrosis. Pulmonary function testing included forced vital capacity percent predicted (FVC%) and diffusion lung carbon monoxide percent predicted (DLCO%). Normal values for US patients were calculated using Hankinson, which includes a correction for race (12); whereas, normal values for Chinese patients were calculated according to the Miller and Hankinson standard (13).

Statistics: Chinese-US comparisons between disease manifestations and chest radiographic stages were analyzed by χ^2 test and corrected for continuity using Fisher's exact test if needed. All P values were corrected (Pc) for the number of disease manifestations (fifteen) according to Bonferroni's correction factor. The strength of association was expressed by odds ratio (OR) with 95% confidence interval (95% CI). Pulmonary function differences were analyzed

by Student t test. Statistical analysis was performed using SPSS 19.0 package software with ap value of <0.05 considered statistically significant. Binary Logistic Regression Analysis was utilized to test for possible relationships between demographic variables (race, gender and age) and disease manifestations.

Results

A total of 481 Chinese patients and 522 US patients with sarcoidosis were included in the study. The self-reported race in the US patients included 242 Blacks, 277 Whites, and three Asian. Additional demographic data, including gender and age, are summarized in Table 1. The female to male ratio was 2.41 in Chinese patients versus 2.26 in the US population (P >0.05). There was no significant gender difference between US Black versus White patients (P >0.05). Age distribution varied between the United States and Chinese groups with a diagnostic peak of 45-59 years for Chinese patients versus 35-49 years for US patients. The mean age at diagnosis was significantly older for Chinese (49.45 years) than US patients (44.29 years) (p<0.001). Chinese patients tend to have later age at diagnosis (≥40 years old) than US patients (P<0.001). Age at diagnosis also varied by race with Black patients having an earlier age at diagnosis (<40 years old) compared to White patients, p <0.001. Additionally, the mean age at diagnosis was statistically different for U S Black patients (41.42 years) compared to US White patients (46.77 years), (p<0.001). In contrast, 56.55% of Chinese patients were diagnosed after age 50 while only 32.95% US patients were diagnosed after age 50.

Table 2 summarizes the disease manifestations experienced by Chinese versus US patients. The chest was the most commonly involved organ identi-

Table 1. Demographics of Chinese, US Black and White Patients Studied

	Chinese	US total	US Black	US White
Number	481	522	242	277
Female: Male	340:141	362:160	168:74	193:84
Age (median, range)	49 (19-76)	44 (9-92)	41 (9-78)	47 (18-92)
Age <40ys	90 (18.7) *	190 (36.4)	112 (46.3)	77 (27.8)
≥40ys	391 (81.3)	332 (63.6)	130 (53.7)	200 (72.2)

*Number (percent)

Table 2. Organ manifestation reported by race

	Chinese (Han)	US (all)	Pc[&]	Black	White	Pc
Lung *	475 (98.8)	393 (87.7)	<0.001	187 (88.8)	204 (86.8)	NS[§]
Neurologic	6 (1.2)	75 (14.4)	<0.001	38 (15.7)	37 (13.4)	NS
Non-thoracic lymph node	80 (16.6)	74 (14.2)	NS	28 (11.6)	46 (16.6)	NS
Renal	0 (0.0)	6 (1.1)	NS	2 (0.8)	4 (1.4)	NS
Cardiac	1 (0.2)	31 (6.0)	<0.001	11 (5.2)	19 (8.1)	NS
Skin	51 (10.6)	124 (27.7)	<0.001	66 (31.3)	58 (24.7)	NS
Eye	30 (6.2)	145 (32.4)	<0.001	83 (39.3)	62 (26.4)	0.015
Liver	7 (1.5)	57 (10.9)	<0.001	31 (12.8)	25 (9.0)	NS
Bone marrow	1 (0.2)	11 (2.1)	NS	3 (1.2)	8 (2.9)	NS
Spleen	12 (2.5)	35 (6.7)	0.03	16 (6.6)	19 (6.9)	NS
Bone/joint	10 (2.1)	20 (3.8)	NS	5 (2.1)	15 (5.4)	NS
Head/neck	4 (0.8)	22 (4.2)	0.03	13 (5.4)	9 (3.2)	NS
Parotid/ Salivary	4 (0.8)	6 (1.1)	NS	1 (0.4)	5 (1.8)	NS
Muscle	3 (0.6)	0 (0.0)	NS	0 (0.0)	0 (0.0)	NS
Hypercalcemia/hypercalciuria	115 (23.9)	63 (14.1)	<0.001	16 (7.6)	47 (20.0)	<0.001

*According to WASOG criteria, biopsy confirmed or at least one clinical condition was "at least probable" as representing sarcoidosis.
†Pc: P values were corrected multiple testing of disease manifestations (fifteen tested) according to Bonferroni's correction.
[§]NS: no significant difference.

fied for both countries with 98.8% in Chinese and 87.7% US patients reporting involvement. However, US patients were more likely to demonstrate eye, skin, neurologic, cardiac, liver, spleen, or nasal-sinus involvement. In contrast, hypercalcemia/hypercalciuria was more common in the Chinese population (χ^2=18.342, Pc<0.001). US White patients were more likely to be hypercalcemic/hypercalciuric compared to US Black patients (χ^2=16.230, Pc<0.001). The influence of race on abnormal calcium metabolism was detected only for Black US patients compared to Chinese (χ^2=30.752, Pc<0.001) but not US White patients (χ^2=2.323, P >0.05).

Ocular involvement was more prevalent in US Black patients compared to White patients (χ^2=10.986, Pc=0.015). Table 3 summarizes the disease phenotypes based on gender and age at diagnosis. Men were more likely to be hypercalcemic/hypercalciuric (χ^2=9.643, Pc= 0.002). Although ocular involvement was more common in women than men (χ^2=5.462, P=0.019), this was not significantly different after Bonferroni's correction (Pc>0.05). However, hepatic involvement was more common in patients with earlier age at diagnosis (<40 years old) compared to older age patients (≥40 years old). Figure 1 summarizes the major differences identified between the various groups by ethnicity, race, and reported organ involvement.

Binary Logistic regression analysis demonstrated the race of Han (Chinese patients). US Whites Americans, and men of either ethnicity were independent risk factors for hypercalcemia/hypercalciuria, while US Blacks and female gender were independent risk factors for eye involvement. Earlier age at diagnosis (<40 years old) was an independent risk factor for liver involvement (Table 4).

Only 126 US patients (24.14%) displayed a solitary organ manifestation, with pulmonary involvement noted in 103 and extra-thoracic organs (eye=8; skin=6; neurologic=5; non-thoracic lymph node=2; calcium=1; and liver=1) reported in 23 patients. The remainder of US patients had multiple organs involved (2=210 [40.23%)]; 3=130 (24.90%); 4=36 (6.90%)' and 5+=20 (3.83%) patients. In contrast 267 (55.51%) of Chinese patients experienced only one disease manifestation, thoracic disease. Additional multiple organ Chinese involvement included: 149 (30.98%) with two organs involved, 38 (7.90%) with three organs involved, 19 (3.95%) with four organs involved, and eight (1.67%) with five or more disease sites. US patients were more likely to develop multiple disease manifestations compared to Chinese patients (χ^2=103.386, P<0.001) (Figure 2a), while there was no significant difference for multiple disease sites between US Black and White patients (Figure 2b). Ten cases of Löfgren syndrome were noted including six US White, two US Black and two Chinese patients.

The evaluation for lung involvement included pulmonary function testing (PFT) and chest x-ray examination which was performed and staged in all

Table 3. Disease manifestation by age and gender

	Age<40 (n=280)	Age>=40 (n=723)	Pc[&]	Female (n=702)	Male (n=301)	Pc†
Lung *	256 (91.4)	677 (93.6)	NS[§]	653 (93.0)	280 (93.0)	NS
Neurologic	32 (11.4)	49 (6.8)	NS	54 (7.7)	27 (9)	NS
Non-thoracic lymph node	43 (15.4)	111 (15.4)	NS	111 (15.8)	43 (14.3)	NS
Renal	3 (1.1)	3 (0.4)	NS	4 (0.6)	2 (0.7)	NS
Cardiac	9 (3.2)	30 (4.1)	NS	22 (3.1)	17 (5.6)	NS
Skin	72(25.7)	132 (18.3)	NS	146(20.8)	58 (19.3)	NS
Eye	65 (23.2)	126(17.4)	NS	147 (20.9)	44(14.6)	NS
Liver	30 (10.7)	34 (4.7)	<0.001	48(6.8)	16 (5.3)	NS
Bone marrow	3 (1.1)	9 (1.2)	NS	7 (1)	5 (1.7)	NS
Spleen	19 (6.8)	28 (3.9)	NS	32 (4.6)	15 (5.0)	NS
Bone/joint	7 (2.5)	23 (3.2)	NS	20 (2.8)	10 (3.3)	NS
Head/neck	11 (3.9)	15 (2.1)	NS	16 (2.3)	10 (3.3)	NS
Parotid/ Salivary	4 (1.4)	6 (0.8)	NS	5 (0.7)	5 (1.7)	NS
Muscle	1(0.4)	2 (0.3)	NS	2(0.3)	1 (0.3)	NS
Hypercalcemia/hypercalciuria	43 (15.4)	142 (19.6)	NS	112 (16)	73 (24.3)	0.03

*According to the WASOG criteria, biopsy confirmed or at least one clinical condition was as "at least probable" as representing sarcoidosis.
†Pc: P values were corrected multiple testing of disease manifestations (fifteen tested) according to Bonferroni's correction.
§NS: no significant difference.

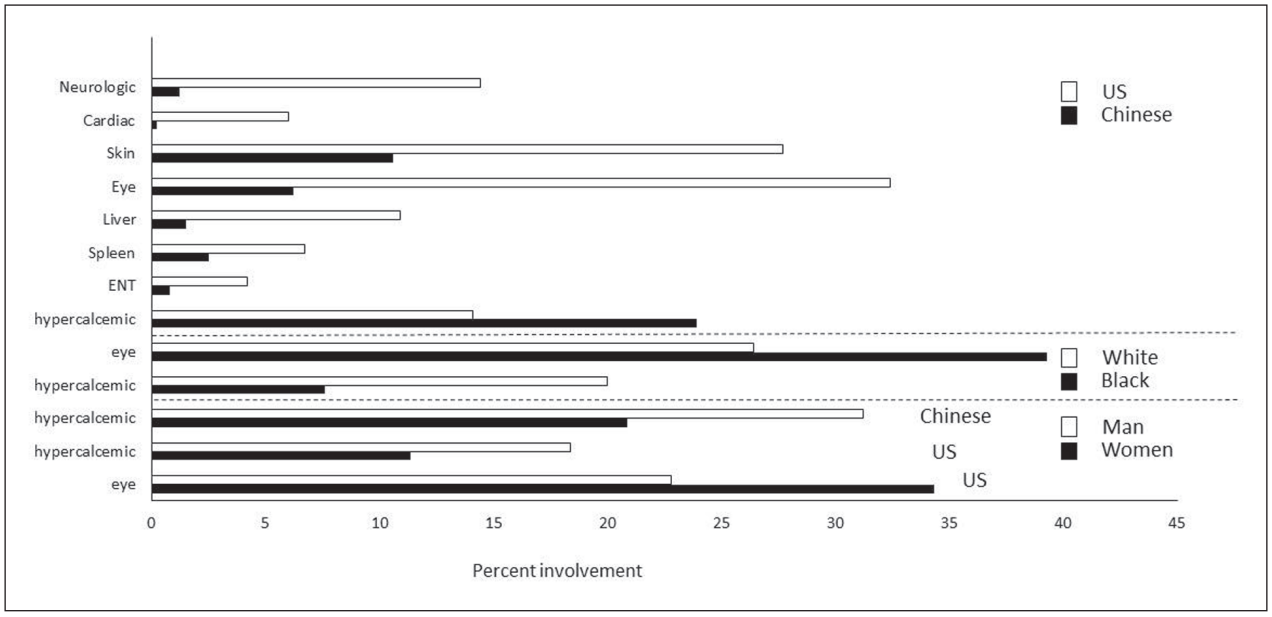

Fig. 1. Comparison of disease manifestation in which there was significant difference between Chinese and US patients

Table 4. Odds ratios for hypercalcemia/hypercalciuria or eye involvement based on race and gender

		OR	95% CI	P
Hypercalcemia/ hypercalciuria	Chinese	4.035	2.340-6.957	<0.001
	White	3.051	1.703-5.465	<0.001
	Men	1.845	1.298-2.623	0.001
Eye	Women	1.635	1.107-2.417	0.014
	Black	9.579	6.002-15.289	<0.001
Liver	Age<40	1.844	1.071-3.176	0.027

patients. There was a significant difference in the Scadding chest x-ray stage between Chinese and US patients (χ^2=347.149, P<0.001). Stages 1 and 2 were the major chest x-ray patterns identified in Chinese patients (27.6% and 60.5% respectively) with only 10.8% of Chinese patients showing a Stage 3 or 4 pattern. In contrast, 30.0% of US patients displayed Stage 3 or 4 patterns. There was no significant difference in the Scadding chest x-ray stage between US Black and White patients (χ^2=3.138, P >0.05) (Figure 3).

Spirometry was available for 388 (80.67%) Chinese patients and 282 (54.02%) US patients with the DLCO recorded in 282 (58.63%) Chinese patients and 125 (23.95%) US patients. The mean predicted FVC% was 94.32±16.92 in Chinese patients and

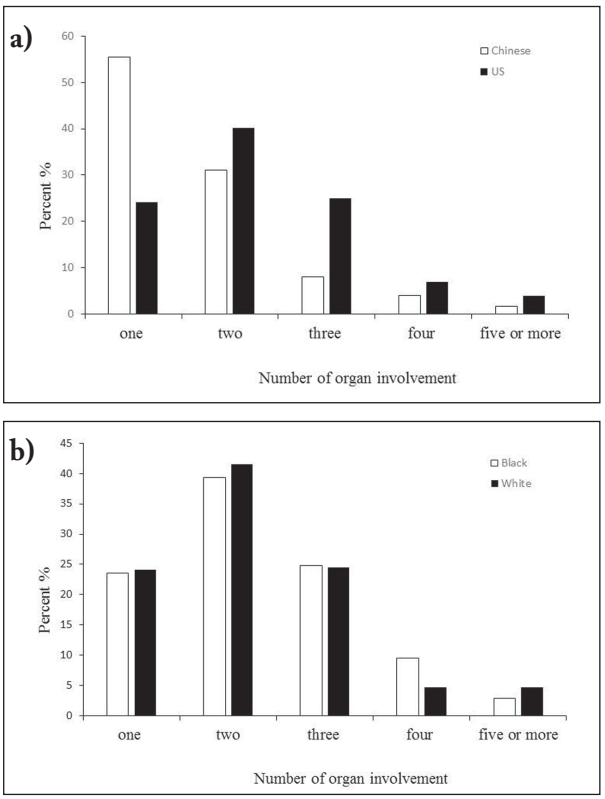

Fig. 2. Comparison of number of organs involved between Chinese and US patients (a) and between US Caucasians and African Americans (b)

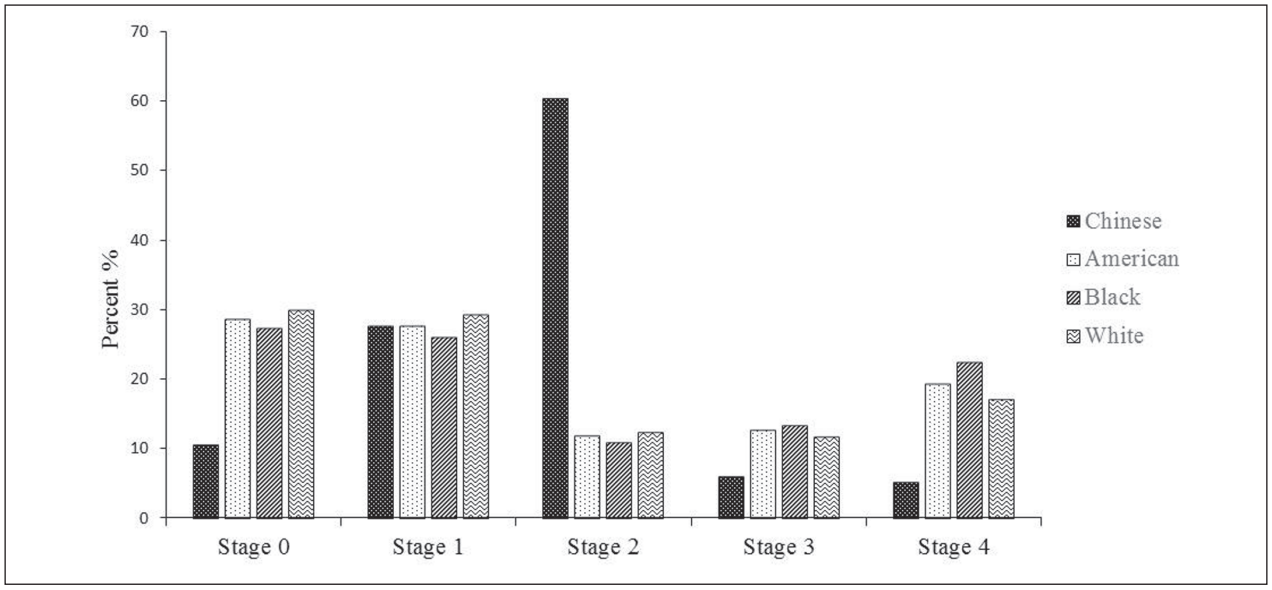

Fig. 3. Comparison of Scadding chest x-ray stage between Chinese and US patients. More advanced stages were experienced by US patient, especially those who were Black

81.49±19.63 in US patients (P<0.001). As shown in Figure 4, significant differences for FVC% were noted between US and Chinese patients in the proportion of patients with normal, mild, moderate, or severe impairment (χ^2=53.655, P<0.001). The mean predicted DLCO% was 86.67±16.55 in Chinese patients and 76.29±24.04 in US patients (P<0.001). Likewise the proportion of patients with normal, mild, moderate, or severe impairment for DLCO% differed between the two groups (Figure 4) (χ^2=49.225, P<0.001). American Whites experienced a higher predicted DLCO% (81.82±22.86) compared to Black patients (67.98±24.17, P=0.002), and the proportion with moderate or severe impairment was higher for US Blacks (Figure 4) (χ^2=6.524, P =0.011). There was no significant difference in percent predicted DLCO between Chinese and White patients.

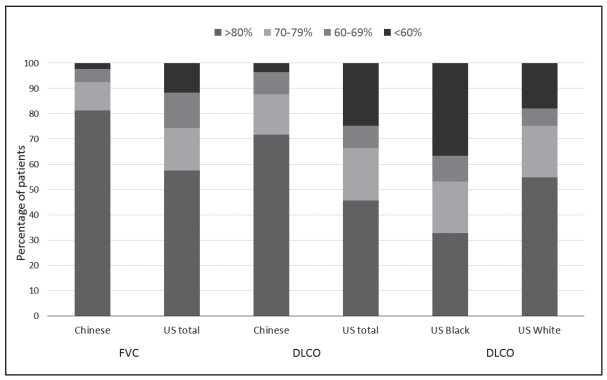

Fig. 4. The percent of Chinese versus total US sarcoid population with normal, mild, moderate, or severe respiratory impairment for % predicted FVC and % predicted DLCO. For the US sarcoidosis patients, the total and values for Blacks and Whites are shown. More severe respiratory impairment was seen in US Blacks compared to US Whites.

Discussion

Although sarcoidosis is a global disease, the prevalence and clinical phenotypes show great geographic variation (10, 14). For example, sarcoidosis is more common in northern European and US Blacks than elsewhere in the world (15-17), while the disease has rarely been reported in China. Japanese patients have a higher likelihood of ocular and cardiac involvement compared to Western populations (14), while Europeans experience a higher proportion of patients with Lofgren's syndrome (2). These racial and geographic differences suggest that a possible genetic and/or environmental exposure may play a role in the development of the disease. Prior studies suggest that some human leukocyte antigens (HLA) are associated with sarcoidosis (18-20).

Limited epidemiological data is available for Chinese (Han) sarcoidosis patients. Some reports suggest that Chinese patients experience less im-

paired spirometry (6, 21). In this study, of 481 Chinese sarcoidosis patients diagnosed between 2009 and 2015 in the Shanghai Pulmonary Hospital, the female to male ratio was 2.41 and the median age of diagnosis was 51 years. The most common manifestation was thoracic involvement which was identified in 98.8% of these patients. The most frequently noted extra pulmonary involvement was hypercalcemia/hypercalcuria followed by non-thoracic lymph node, skin and eye disease. No significant phenotypic difference was detected by gender or age. To our knowledge this report provides specific demographic and clinical information on the largest number of Chinese sarcoidosis patients.

Epidemiologists have reported ethnic age peaks for sarcoidosis. In Japan, incidence rates peak between the ages of 20-34 years with a second peak occurring in women between the ages of 50-60 years (22, 23). Likewise, Scandinavia data discloses a bimodal incidence rates in women with peaks occurring between ages 25 and 29 and 55 to 659 years of age (24). In the current study, the mean age of diagnosis was 49.45 years for Chinese patients with the peak between ages 45 and 60 years versus 44.29 years for US patients with the age peak between 35 and 50 years The age peak age in US patients was similar to the multicenter ACCESS study (3). Although in both groups substantial numbers of patients were diagnosed after age 50, we were unable to detect a bimodal distribution. The later age at diagnosis in Chinese patients may reflect an initial evaluation for tuberculois in patients with Stage 3 or 4 chest roentgenograms. However, this imaging pattern was identified in only 11% of Chinese patients. A delay in diagnosis of a year or more has also been reported for many US patients (25).

Compared to the US patients, Chinese patients witnessed a higher frequency of intrathoracic involvement with a lower prevalence of extra thoracic involvement including neurologic, cardiac, skin, eye, liver, spleen, and head/neck. As previously noted, the most extensive disease was noted in US Blacks (3, 4). Phenotypic manifestations may reflect referral bias. Chinese patients in this study were followed in a specialized pulmonary hospital where the principle investigator was a pulmonologist. Hence patients with thoracic sarcoidosis usually presented to respiratory physicians first, while patients with manifestations of multi-organ sarcoidosis might present to other clinical departments first. In contrast, data on US patients came from a general sarcoidosis clinic, which includes patients with extra-pulmonary or multi-organ symptoms. Despite the potential Chinese referral bias, the prevalence of extra-pulmonary disease for Chinese was similar to that reported in the US ACCESS trial (3).

The higher prevalence of more severe pulmonary disease, including higher Scadding chest roengenogram stage and more severe pulmonary function impairment, identified in US patients was in large part due to the Black patients. Compared to White patients, Black sarcoidosis patients experienced lower percent predicted DLCO and absolute FVC values. However, no change was noted for percent predicted FVC between the groups. In part, this could be attributed to the race correction used to calculate normal values. The finding of Stage IV disease in 5% of Chinese patients compared to 19.6% of US patients may explain some of the differences seen in pulmonary function testing as advanced stage disease has been associated with significant morbidity and mortality (26, 27).

The estimated incidence of hypercalcemia in sarcoidosis patients ranges between 2-27% (3, 22, 28-30). The multicenter US ACCESS study, which evaluated patients within the first six months of diagnosis, detectedmore hypercalcemic/hypercalcuric in men and White patients (3). In the current study, Chinese, White, and male patients were more likely to be hypercalcemic/hypercalciuric compared to Black patients. Binary Logistic regression analysis revealed the race of Chinese, White, and men as independent risk factors for abnormal metabolism. The cause of hypercalcemia/hypercalciuria in sarcoidosis relates to the upregulation of 1- alpha- hydroxylase activity within the granulomas of sarcoidosis which enhances the conversion of 25- (OH) vitamin D3 to 1, 25- (OH) 2 vitamin D3 (31, 32). The increase of 1, 25- (OH) 2 vitamin D3, the active form of the vitamin, can increase gut absorption and renal excretion of calcium which manifests with hypercalcemia or nephrolithiasis.

In the US patients, the eye is one of the more commonly involved organs, and granulomatous disease may cause inflammation within the eye and adnexal structures. Uveitis, the most common manifestation of eye sarcoidosis (4, 33), was reported in 32.4% of US patients, but only 6% of Chinese patients. In 96% of US sarcoidosis patients, uveitis with

or without other eye involvement was commonly seen. Both racial and gender differences were noted with the ORR=9.579 for Black versus White patients and OR=1.635 ocular involvement in women versus men. Prior studies have also reported higher rates of eye involvement in Blacks and women (3, 34).

In conclusion, compared with US patients in this study, Chinese sarcoidosis patients displayed the following clinical characteristics: 1) older age at diagnosis; 2) witnessed higher prevalence of intrathoracic involvement and lower frequency of extra thoracic involvement; 3) developed higher incidences of hypercalcemia/hypercalciuria ; and 4) were more likely to have earlier chest roengenogram stage with less serious PFT abnormalities.

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