Original Article

Immunity status of invasive pulmonary aspergillosis patients with structural lung diseases in Chinese adults

Shuo Liang, Rong Jiang, Hai-Wen Lu, Bei Mao, Man-Hui Li, Cheng-Wei Li, Shu-Yi Gu, Jiu-Wu Bai, Jin-Fu Xu

Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China

Contributions: (I) Conception and design: S Liang, R Jiang, HW Lu, JF Xu; (II) Administrative support: JF Xu; (III) Provision of study materials or patients: S Liang, HW Lu, B Mao, MH Li, CW Li, SY Gu, JW Bai; (IV) Collection and assembly of data: S Liang, HW Lu, B Mao, MH Li, CW Li, SY Gu, JW Bai; (V) Data analysis and interpretation: S Liang, R Jiang, HW Lu, JF Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jin-Fu Xu. Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, No. 507 Zhengmin Road, Shanghai 200433, China. Email: jfxucn@gmail.com.

Background: Invasive pulmonary aspergillosis (IPA) is a fungal infection frequently observed in patients with immune dysfunction, such as those suffering from structural lung diseases. Nevertheless, studies assessing IPA combined with other common respiratory diseases remain scarce, particularly those regarding the immune status of its patients. Different structural lung diseases are known to differently affect patient immune status; however, the mechanisms by which this is conferred have yet to be determined. Thus, our study aims to compare the immune status of IPA patients with the structural lung diseases chronic obstructive pulmonary diseases (COPD), interstitial lung disease (ILD) and non-cystic fibrosis bronchiectasis (NCFB).

Methods: This study was performed retrospectively with data collected over the years 2004 to 2013 at Shanghai Pulmonary Hospital, Tongji University, and included 77 patients whose lower respiratory tract (LRT) samples tested positive for. Our analysis considered blood examinations of CD3+, CD4+, CD8+, CD4+/CD8+, IgG, IgA and IgM levels.

Results: CD4+/CD8+ double positive cells, representing cell-mediated immunity, were less abundant in IPA patients with COPD than those with ILD and NCFB (0.81±0.09 *vs.* 1.39±0.25 and 0.81±0.09 *vs.* 1.57±0.06, respectively, P<0.001). In agreement with this result, corticosteroid and broad-spectrum antibiotic use were most common in individuals with COPD (57%). IgA levels, which indicate humoral immunity, were lower in IPA patients with NCFB than those with COPD or ILD (0.95±0.28 *vs.* 1.64±0.40 g/L and 0.95±0.28 *vs.* 3.16±0.83 g/L, respectively, P<0.001).

Conclusions: Immunity status differs between IPA patients with different structural lung diseases. Among IPA patients with COPD, ILD and NCFB, those with COPD have the lowest cell-mediated immunity, while those with NCFB have the lowest humoral immunity.

Keywords: Invasive pulmonary aspergillosis (IPA); chronic obstructive pulmonary diseases (COPD); interstitial lung disease (ILD); non-cystic fibrosis bronchiectasis (NCFB)

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Introduction

Aspergilli are respiratory pathogens acquired through the inhalation of *Aspergillus* conidia, the spores of which are universally present in unfiltered air. While generally not harmful for immunocompetent hosts, colonization and infection of the lungs can occur in those with weakened immune systems, leading to the development of invasive pulmonary aspergillosis (IPA). As the disease is difficult to diagnose early and lacks effective treatment options, the

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survival rate of IPA patients is very poor.

IPA is well-recognized as a severe fungal lung infection, frequently observed in patients following procedures such as allogeneic bone marrow transplantation and solid organ transplantation, as well as alongside conditions including hematologic malignancies, late-stage HIV infection, and chronic granulomatosis (1-3). The disease has also grown in prevalence as a comorbidity in patients with structural lung diseases such as chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and non-cystic fibrosis bronchiectasis (NCFB)—all of which confer different immune dysfunctions to their patients.

Due to the significance of immunology in fungal infection, IPA has been an area of focus for many experts. Several studies have described an increase of IPA incidence in COPD patients (3-7); however, IPA assessments in relation to other common respiratory diseases remain scarce, particularly those evaluating patient immune status. Therefore, this study aims to assess the immune status of IPA patients with COPD, ILD, and NCFB while excluding the presence of basic diseases.

Methods

Study design and diagnostic procedure

Our study retrospectively assessed patients treated at Shanghai Pulmonary Hospital, Tongji University, between 2004 and 2013. Diagnosis of IPA was classified as proven, probable, or possible in accordance with the revised EORTC and MSG criteria (8,9). Consequently, a diagnosis of "proven IPA" was established by both (I) the presence of hyphae compatible with *Aspergillus* in specimens collected from a pulmonary lesion sample; and (II) isolation of *Aspergillus* species in cultures from any lower respiratory tract (LRT) sample, mainly sputum and bronchial secretions, including bronchial brush and bronchial alveolar lavage fluid, etc. combined with evidence of associated tissue damage or two sequential positive serum galactomannan (GM) tests.

COPD diagnosis was established according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (10). In patients with COPD, Bulpa criteria were used for IPA diagnosis (5). NCFB diagnosed routinely and confirmed through high-resolution computed tomography (HRCT) chest imaging and patient history of the syndrome (11,12). ILD diagnosis was established according to the American Thoracic Society Clinical Practice Guideline published in 2012 (13).

Inclusion criteria and data collection

We examined the data on *Aspergillus* isolation from LRT taken at chest and infectious disease clinics in Shanghai Pulmonary Hospital between January 2004 and December 2013. Patient inclusion criteria required both *Aspergillus* isolation (colonization alone being insufficient), and a diagnosis of either "proven IPA" or "probable IPA". As only patients with a positive *Aspergillus* culture were enrolled, no cases of "possible IPA" were obtained. Medical files, discharge reports and CT images from the hospital data processing system were reviewed for each patient in order to obtain data on their demographic features, smoking history, and comorbidities.

Laboratory methods

Following direct microscopic examination, all LRT specimens were cultured on Sabouraud dextrose agar (SDA) either with or without antibiotics. Peripheral blood samples (2.0 mL) were collected in anticoagulation tube containing EDTA to determine CD3+ T lymphocyte, CD3+/CD4+/CD8– lymphocyte (abb.CD4+), CD3+/CD4–/CD8+ lymphocyte (abb.CD8+), CD4+/CD8+ T lymphocyte counts (Shanghai Huizhong Cellular Biotechnology Co., Ltd.). The whole blood samples were also collected to test IgA, IgM and IgG by Immune scatter turbidity method (Siemens Corporation, Germany). All laboratory examinations were performed according to the manufacturers' directions.

The study was approved by institutional ethics committee board of the Shanghai Pulmonary Hospital (No. K16-322) and was consistent with the principles outlined in the Declaration of Helsinki.

Statistical analyses

All statistical analyses were carried out with SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are described with mean ± SD or median (IQR) for normal distributed variable and skewed distributed variable respectively. Categorical variables are expressed as percentages. Comparisons of serum immune levels among patients with COPD + IPA, ILD + IPA, NCFB + IPA and IPA were made using one-way analysis of variance (ANOVA). $P<0.05$ was considered statistically significant.

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Table 1 Clinical and demographic characteristics of 77 patients with IPA

Characteristics	No. (%) or mean ± SD
Male	47 (61.0)
Age (years)	56.2±3.2
Smoking history	
Yes	49 (63.6)
>40 pack years	19 (24.7)
Complication in disease	
Diabetes	6 (7.8)
Cardiovascular disease	3 (3.9)
Corticosteroid use	33 (42.9)
Antibiotics frequently use	39 (50.6)

Data are presented as number (percent) or mean ± SD.

Table 2 Concomitant therapy for the 77 IPA patients

Patients	n	Corticosteroid	Antibiotics	C + A
IPA with COPD (n, %)	26	23 (88.5)	18 (69.2)	41 (57.0)
IPA with ILD (n, %)	15	10 (66.7)	8 (53.3)	18 (23.0)
IPA* (n, %)	21	0	0	0 (0)
IPA with bronchiectasis	15	0	13 (86.7)	13 (17.0)

Data are presented as number (%). *, IPA without structural lung diseases. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPA, invasive pulmonary aspergillosis; C, corticosteroid; A, antibiotics.

Results

Patient characteristics

In total, aspergillum was isolated and identified as proven IPA in the LRT samples of 77 patients. Among them, forty-seven (61%) were male and 30 (39%) were female, with a mean age of 56. A history of smoking was present in 49 (64%) cases. Thirty-three patients (43%) included reported corticosteroid use over the previous 3 weeks, and 39 (51%) reported frequent antibiotic use (*Table 1*).

Of 26 IPA patients with COPD, 23 (89%) used corticosteroids and 18 (69%) used antibiotics. Of 15 IPA patients with ILD, 10 (67%) used corticosteroids and 8 (53%) used antibiotics. Of 15 IPA patients with bronchiectasis, 13 (87%) used antibiotics (*Table 2*).

Cell-mediated immunity analysis

For CD3+ T lymphocyte, there are abundant differences between COPD + IPA, ILD + IPA, NCFB + IPA and IPA (all P<0.001) indicating significant immune differences among these four diseases (*Table 3*) (*Figure 1A*).

CD4+ T cell and CD8+ T cell are the constituents of CD3+ T cell. From *Table 3* and *Figure 1B,C*, CD4+ and CD8+ T cells also have significant differences between patients with COFP + IPA, ILD + IPA, NCFB + IPA and IPA (P<0.05).

Compared with IPA patients with ILD and NCFB, CD4+/CD8+ double positive cells, a marker of cell-mediated immunity, were less abundant in patients with COPD + IPA [(0.81%±0.09% *vs.* 1.39%±0.25% and 0.81%±0.09% *vs.* 1.57%±0.06%), P<0.001, respectively] (*Table 3*) (*Figure 1D*). There is trend of increase of cell-mediated immunity status in patients with COPD + IPA, ILD + IPA, NCFB + IPA and IPA (*Figure 1D*).

Humeral immunity analysis

In with respect to humeral immunity, IgA, IgM and IgG had significant differences between these four diseases (*Figure 2A,B,C*). IgA levels, which indicate respiratory humoral immunity, were lower in IPA patients with NCFB than those with COPD + IPA and ILD + IPA (0.95±0.28 *vs.* 1.64±0.4 g/L and 0.95±0.28 *vs.* 3.16±0.83 g/L, respectively, all P<0.001) (*Table 3*) (*Figure 2B*).

Discussion

An increasing number of studies have reported the emergence of IPA in critically ill, immunocompromised patients, whose immune statuses are characterized by multifactorial impairments in their local defenses, i.e., cell-mediated and humoral immunity. The major parameters affecting immunocompetence in these patients are systemic steroid use and the administration of broad-spectrum antibiotics, particularly in those with COPD, ILD, and NCFB.

We found that CD4+/CD8+ positive cells, a marker of cell-mediated immunity, are less abundant in IPA-infected individuals with COPD (0.81) than those with ILD (1.39) and NCFB (1.57, *Table 3*, *Figure 1D*). These findings corroborated the use of corticosteroid and broad-spectrum antibiotics, both of which were most common in individuals with COPD among all IPA patients (41/72, 57%, *Table 2*)

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Table 3 Immune states in IPA patients with COPD, ILD, NCFB, and control patients

Variables	COPD + IPA (N=26)	ILD+IPA (N=15)	NCFB + IPA (N=15)	IPA (N=21)	F	P
CD3+,%	63.08±3.25*	41.71±3.01*	60.46±2.95*	67.92±10.37*	60.04	<0.001
CD4+, %	27.85±2.82**	23.16±2.23**	36.53±2.30**	34.41±8.95**	23.18	<0.001
CD8+, %	34.10±1.81§	16.89±1.99§	23.18±1.40§Δ	28.02±12.97§Δ	21.25	<0.001
CD4+/CD8+	0.81±0.09¶£	1.39±0.25	1.57±0.06¶	1.78±1.69£	5.06	<0.001
IgG, g/L	6.49±0.66¦	24.34±3.24¦	6.65±0.80¦	14.98±5.82¦	114.71	<0.001
IgA, g/L	1.64±0.40¦¦	3.16±0.83¦¦	0.95±0.28¦¦	2.40±1.35¦¦	21.70	<0.001
IgM, g/L	0.39±0.12§§	0.38±0.15§§	1.60±0.14§§	1.34±0.92§§	32.56	<0.001

Correlations between cellular immunity (CD3+, CD4+, CD8+ and CD4+/CD8+ positive cell numbers) and humoral immunity (IgG, IgA, and IgM levels) in IPA patients with COPD, ILD, and NCFB. Data are presented as average ± SD (for abbreviations, see *Table 2*). *, P<0.001 COPD + IPA *vs.* NCFB+IPA, COPD + IPA *vs.* IPA, ILD + IPA *vs.* NCFB + IPA, ILD + IPA *vs.* IPA, NCFB+IPA *vs.* IPA; **, P <0.001 COPD+IPA *vs.* NCFB+IPA, COPD + IPA *vs.* ILD + IPA, COPD + IPA *vs.* IPA, ILD + IPA *vs.* NCFB + IPA, ILD + IPA *vs.* IPA; §, P<0.001 COPD + IPA *vs.* NCFB + IPA, COPD + IPA *vs.* ILD + IPA, COPD+IPA *vs.* IPA, ILD+IPA *vs.* IPA; Δ, P <0.05 ILD + IPA *vs.* NCFB + IPA, NCFB + IPA *vs.* IPA; ¶, P <0.05 COPD + IPA *vs.* NCFB + IPA; £, P<0.001 COPD + IPA *vs.* IPA; ¦, P<0.001 COPD + IPA *vs.* ILD + IPA, COPD + IPA *vs.* IPA, ILD + IPA *vs.* NCFB + IPA, ILD + IPA *vs.* IPA, NCFB + IPA *vs.* IPA; ¦¦, P<0.001 COPD + IPA *vs.* ILD + IPA, COPD + IPA *vs.* NCFB + IPA, COPD + IPA *vs.* IPA, ILD + IPA *vs.* NCFB + IPA, ILD + IPA *vs.* IPA, NCFB + IPA *vs.* IPA; §§, P<0.001 COPD + IPA *vs.* NCFB + IPA, COPD + IPA *vs.* IPA, ILD + IPA *vs.* NCFB + IPA, ILD + IPA *vs.* IPA. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NCFB, non-cystic fibrosis bronchiectasis; IPA, invasive pulmonary aspergillosis.

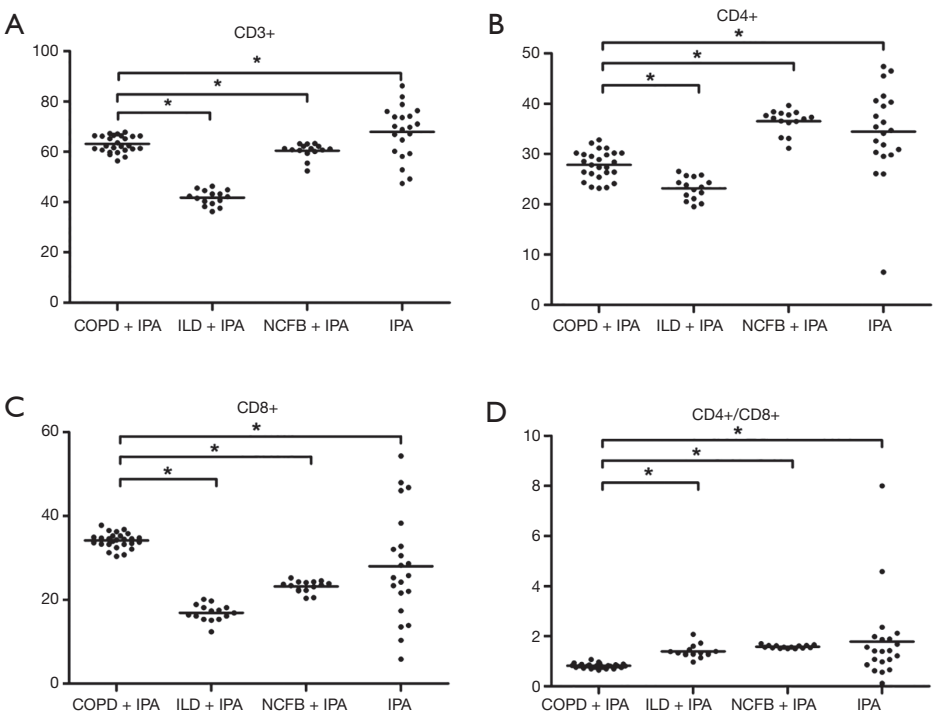

Figure 1 Correlations between CD3+, CD4+, CD8+ and CD4+/CD8+ levels in IPA patients with COPD, ILD, and NCFB. Relationships between continuous variables (F and P values) were evaluated with the Bonferroni method. CD4+/CD8+ amounts in IPA patients with COPD were reduced compared to those with ILD and NCFB. (A) CD3+ T cell; (B) CD4+ T cell; (C) CD8+ T cell; (D) CD4+/CD8+ T cell. *, IPA without structural lung diseases. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NCFB, non-cystic fibrosis bronchiectasis; IPA, invasive pulmonary aspergillosis.

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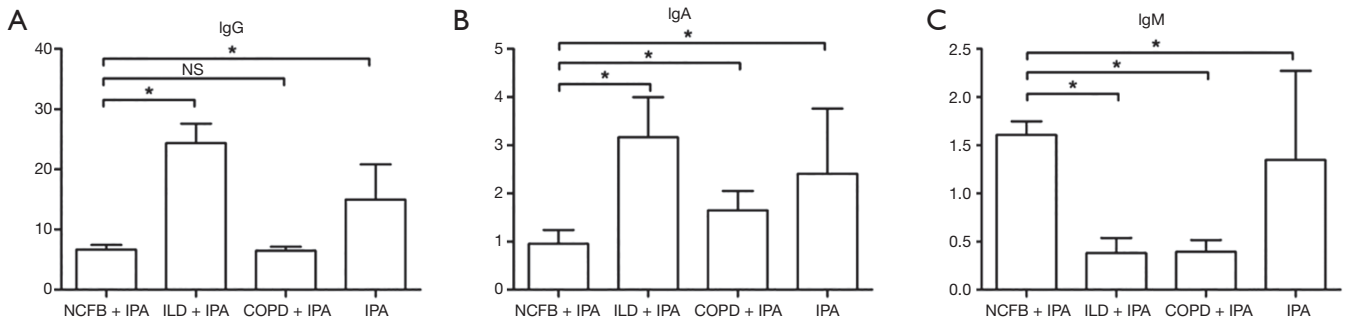

Figure 2 Correlations between IgG, IgA and IgM levels in IPA patients with COPD, ILD, and NCFB. Relationships between continuous variables (F and P values) were evaluated with the Bonferroni method. IgA levels in IPA patients with NCFB were reduced compared to IPA patients with COPD and ILD. (A) IgG; (B) IgA; (C) IgM. *, IPA without structural lung diseases. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NCFB, non-cystic fibrosis bronchiectasis; IPA, invasive pulmonary aspergillosis.

(see previous note on this statistic). Thus, one mechanism how structural lung disease confers immune dysfunction may be through long-term treatment with corticosteroids and broad-spectrum antibiotics.

Among IPA patients with COPD, 89% used corticosteroids (23/26), as opposed to only 67% of IPA patients with ILD (10/15). Corticosteroid use is known to affect IPA incidence in COPD cases (5,6): receiving accumulated doses of corticosteroids (e.g., >700 mg of prednisone) during the 3 months preceding hospital admission has been shown to significantly increase the risk of IPA occurrence in COPD patients (14). Studies by He *et al.* have suggested that cumulative doses of corticosteroids exceeding 350 mg are highly related to IPA occurrence in COPD patients (14,15), and some reports have even evoked a plausible role for inhaled steroids in its emergence (16-18). It has also been shown that immune dysfunction and bacterial persistence in NCFB are associated with the use of anti-inflammatory agents, such as inhaled corticosteroids (19), and long-term antibiotic treatment (20,21).

We also found that 69% of the COPD group used broad-spectrum antibiotics (18/26) (*Table 2*), as opposed to 53% (8/15) of those with ILD and 86.7% (13/15) of those with NCFB (*Table 2*). Both the use of broad-spectrum antibiotics to treat an acute bacteria exacerbation within the 3 months before hospital admission and the prescription of three or more broad-spectrum antibiotics in hospital are significant predictors of IPA in patients with COPD (6,15). These risk factors led Bulpa *et al.* to propose an adapted version of IPA diagnostic criteria in 2007, standardizing the definitions of the non-immunocompromised population with a focus on COPD patients (22).

The impairment of host immune defense plays a major role in IPA pathogenesis. Airway macrophages ingest and destroy A. conidia cells, and germinating spores and hyphae are attacked by polymorphonuclear neutrophils (PMNs) (23). In COPD, although there is increased recruitment and activation of eosinophils, pulmonary alveolar macrophages (PAMs), and lymphocytes within the lungs, their immune functions of phagocytosis and chemotaxis are qualitatively altered (24,25). Evidence now shows that COPD progresses to systemic autoimmunity, possibly through spillover from the primary pulmonary inflammatory input (26-28). The recognition of pathogen-associated molecular patterns by host cell pattern recognition receptors (PRRs) is the first step of phagocytosis, leading to a pro-inflammatory response characterized by the production of cytokines and chemokines. Toll-like receptor 2 (TLR2) and 4 (TLR4) are among the PRRs most recognized by the body, and a decrease in their expression in COPD patients (29,30) could diminish the initial innate immune response against *Aspergillus*. Corticosteroids also contribute to the development of IPA by inhibiting the phagocytosis functions of PAMs and PMNs (31,32), and may also stimulate *Aspergillus fumigatus* (*A. fumigatus*) growth via action from a sterol-binding protein (33).

As shown in *Table 3* and *Figure 2*, IgA levels were lowest in IPA patients with NCFB (0.95) compared to those with COPD (1.64) and ILD (3.16) (*Table 3*, *Figure 2*). Decreased sIgA levels lead to immunocompromisation and result in critical LRT infections that prompt the use of broad-spectrum antibiotics, which in turn bolsters fungal emergence in the airways (34). *Pseudomonas aeruginosa* (*P. aeruginosa*), a Gram-negative non-fermenting bacterium found in bronchiectasis patients with severely affected pulmonary function (e.g., requiring mechanical ventilation), is known

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for its mutational and biofilm producing abilities, conferring it resistance to antibiotics (35). As *A. fumigatus* is known to grow as a biofilm *in vivo*, the possibility of an interaction between these two species has been suggested, with *P. aeruginosa* providing biofilm niches that allow the expansion of invasive fungal colonies (36).

Conclusions

Despite the high mortality rate of IPA patients, the sensitivity of LRT cultures and serology remain poor. We show herein that cellular and humoral immunity parameters vary with the degree of damage induced by invasive pulmonary fungal infections when combined with structural lung disease, and establish a foundation for future inroads into IPA immunotherapy research. In-depth studies should be carried out to further assess IPA, with the aim of characterizing its genesis, occurrence, development, and effects on the immune system, thereby clarifying its immune pathogenesis and providing important theoretical bases for immune intervention. Immune status should be taken into account in the differential diagnosis of IPA, especially in patients with COPD and NCFB under treatment with broad-spectrum antibiotics and steroids.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by institutional ethics committee board of the Shanghai Pulmonary Hospital (No. K16-322) and was consistent with the principles outlined in the Declaration of Helsinki.

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