ERJ Express. Published on August 2, 2018 as doi: 10.1183/13993003.01554-2017

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Spectrum of Interstitial Lung Disease in China from 2000 to 2012

Ban Chengjun, Yan Wei, Xie Bingbing, Zhu Min, Liu Yan, Zhang Shu, Ye Qiao, Ren Yanhong, Jiang Dingyuan, Geng Jing, Dai Huaping, Wang Chen

Please cite this article as: Chengjun B, Wei Y, Bingbing X, *et al*. Spectrum of Interstitial Lung Disease in China from 2000 to 2012. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01554-2017).

Spectrum of Interstitial Lung Disease in China from 2000 to 2012

Ban Chengjun [1. 2*], Yan Wei [1. 3*], Xie Bingbing [4], Zhu Min [1], Liu Yan[1], Zhang Shu [1], Ye Qiao [1], Ren Yanhong [4], Jiang Dingyuan [4], Geng Jing [4], Dai Huaping [1.4], Wang Chen [4]

1. Department of Pulmonary and Critical Care Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

2. Department of Respiration of Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China

3. Fu Xing Hospital, Capital Medical University

4. Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital; National Clinical Research Center for Respiratory Diseases, Beijing, China

*Both contributed equally to this study.

Correspondence to: Dai H, MD, Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China–Japan Friendship Hospital, National Clinical Research Centre for Respiratory Medicine, Beijing, 100029, P.R. China.

E-mail: daihuaping@ccmu.edu.cn

Funding/Support: Supported by the Key Program of National Natural Science Foundation of China (No. 81430001) and National Key Technologies R & D Program Precision Medicine Research (No.2016YFC0901101)

Take-Home Message: Hospital admissions of patients for ILD increased in China from 2000 to 2012 and IPF was the most frequent type. This suggests an increasing recognition of ILD and/or increased burden of disease.

Authors' contributions

Yan W contributed to the data collection and analysis and the draft of the manuscript; Ban C contributed to the construction of database, collection of clinical data and the revision of the manuscript; Xie B, Zhu M, Liu Y, Zhang S, Ye Q contributed to the collection and explanation of clinical data; Ren Y, Jiang D, Geng J contributed to the data analysis and the revision of manuscript; Wang C contributed to the construction of database and study design, the revision of the manuscript. Dai H contributed to the construction of ILD database, study design, the revision of the manuscript, and final approval of the version to be published. All authors read and approved the final manuscript.

Epidemiological data on interstitial lung disease (ILD) are very limited in China. This study describes the distribution of ILD in China based on data from a large ILD center.

All patients admitted to the Department of Pulmonary and Critical Care Medicine of Beijing Chao-Yang Hospital, affiliated to Capital Medical University, for further diagnosis of suspected ILD from January 1, 2000 to December 31, 2012 were included in the analysis.

Patients suspected with ILD underwent a standard investigation protocol as described previously [1]. The diagnosis of ILD and idiopathic interstitial pneumonia (IIP) was based on the international ILD guidelines and ATS/ERS international consensus classification of IIP [2, 3]. Clinical data were recorded, including demographic information, environmental and occupational exposure, symptoms, physical examination, laboratory tests, pulmonary function tests, arterial blood gas analysis, imaging, and pathology if available.

The study protocol was approved by the Institutional Human Ethics Review Committee. Statistical analyses were performed with SPSS 18.0 software package (SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables were presented as mean ± standard deviation (SD). Non-normally distributed variables were presented as median and interquartile ranges (IQR).

In total, there were 3,568 hospital admissions for further workup of ILD from 2000 to 2012. Number of admissions per year significantly increased from 43 in 2000 to 732 in 2012. The percentage of hospital admissions for ILD increased in the Department of Pulmonary and Critical Care (from 2.8% in 2000 to 10.5% of all admissions in 2012) and in the whole hospital (from 0.2% to 1.4%).

Patients newly diagnosed with ILD (total 2615) were further analyzed after exclusion of repeated admissions (n=621), non-Chinese ethnicity (n=3), lack of critical diagnostic tools such as HRCT, pulmonary function tests and blood gas analysis (n=329). The number of ILD increased from 12 cases in 2000 to 532 in 2012. Similarly, number of patients with IIP increased from 9 in 2000 to 246 in 2012. The proportion of IIP to all ILD decreased from 75% to 46.2%. The proportion of ILD secondary to connective tissue disease (CTD) increased from 8.3% to 28.6% of all ILD (one case in 2000 to 152 in 2012). Details of ILD subtypes and demographic characteristics of all patients are shown in table 1. More than half (52.3%) of ILD patients were diagnosed with IIP. In the entire cohort, the most common entity was idiopathic pulmonary fibrosis (IPF; 26.5%), followed by CTD-ILD (24.1%), unclassifiable IIP (UC-IIP; 13.2%), cryptogenic organizing pneumonia (COP; 8.8%), vasculitis (6.2%), and sarcoidosis (5.6%).

Table 1. ILD Types and Demographic characteristics

Types of ILD	N (%*)	Male N (%§)	Female N (%§)	Age at diagnosis (years)
ILD of known causes	952(36.4)	387(40.7)	656(59.3)	61.1±12.5
CTD-ILD	631(24.1)	198(31.4)	433(68.6)	60.9±12.2
pSS	294(11.2)	74(25.2)	220(74.8)	60.9±11.9
RA	121(4.6)	56(46.3)	65(53.7)	67.1±10.4
PM/DM	46(1.8)	16(34.8)	30(65.2)	52.4±12.3
SS-c	18(0.7)	1(5.6)	17(94.4)	55.7±11.8
SLE	6(0.2)	0(0)	6(100.0)	56.0 (54.8,64.5)
AS	1(0)	1(100.0)	0(0)	(61.0)
MCTD	19(0.7)	4(21.1)	15(78.9)	59.1±11.1
UCTD	126(4.8)	46(36.5)	80(63.5)	58.9±12.4
Vasculitis	161(6.2)	79(49.1)	82(50.9)	65.0 (54.5,72.0)
Pneumoconiosis	58(2.2)	55(94.8)	3(5.2)	58.1±12.8
Asbestos lung	23(0.9)	9(39.1)	14(60.9)	63.4±9.1
Drug induced ILD	28(1.1)	17(60.7)	11(39.3)	63.0±12.3
Radiation pneumonia	21(0.8)	13(61.9)	8(38.1)	64.8±9.8
Gastroesophageal reflux	18(0.7)	11(61.1)	7(38.9)	64.3±12.7
Others#	12(0.5)	5(41.7)	7(58.3)	57.3±15.4
IIP	1367(52.3)	898(65.7)	469(34.3)	64.0 (55.0,72.0)
IPF	692(26.5)	551(79.6)	141(20.4)	65.0 (58.0,72.0)
COP	230(8.8)	107(46.5)	123(53.5)	57.3±13.6
NSIP	55(2.1)	19(34.5)	36(65.5)	56.8±10.7
RB-ILD	30(1.1)	24(80.0)	6(20.0)	61.4±11.1
AIP	10(0.4)	6(60.0)	4(40.0)	57.0±12.0
LIP	4(0.2)	0(0)	4(100.0)	67.5 (54.3,74.0)
DIP	2(0.1)	0(0)	2(100.0)	55.0 (34.5,58.0)
Unclassifiable IIP	344(13.2)	191(55.5)	153(44.5)	66.0 (55.0,74.0)
Granulomatous	209(8.0)	82(39.2)	127(60.8)	53.5±11.1
Sarcoidosis	147(5.6)	54(36.7)	93(63.3)	53.1±10.4
HP	62(2.4)	28(45.2)	34(54.8)	54.5±12.8
Miscellaneous	87(3.3)	53(60.9)	34(39.1)	44.0±15.9
Total	2615(100.0)	1420(54.3)	1195(45.7)	62.0 (53.0,71.0)

Data were presented as mean ± standard deviation (SD)/medians and interquartile range (IQR) or number (%);* Proportion of ILD entity in all the ILD patients;§ Proportion of male or female patients with ILD subtype in the same subtype of ILD patients.# Including alveolar carcinoma and lymphangitis carcinomatosa; ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; COP: cryptogenic organising pneumonia ; NSIP: nonspecific interstitial pneumonia; AIP: acute interstitital pneumonia; RB-ILD: respiratory bronchiolitis associated interstitial lung disease; DIP: desquamative interstitital pneumonia; LIP: lymphoid interstitial pneumonia; CTD-ILD: connective tissue disease - interstitial lung disease; MCTD: mixed connective tissue disease; UCTD: undifferentiated connective tissue disease; pSS: primary sjoren's syndrome; RA: rheumatoid arthritis; PM/DM: Polymyositis/Dermatomyositi; SSc: systemic sclerosi; SLE: systemic lupus erythematous; AS:ankylosing spondylitis; HP: hypersensitivity pneumonitis

There is limited epidemiological data about the prevalence of ILD in China [4]. Our study is the first study describing the proportion of different subtypes

of ILD in China based on the current classification and definition of IIP. One major finding of our study is that hospital admissions of patients for diagnostic workup of ILD significantly increased from 2000 to 2012 in China, which has also been observed in Western countries [5, 6]. There are several possible reasons for this observation. First, the increasing awareness on ILD and the broader access to new and more sensitive clinical tools such as HRCT-scans has probably improved diagnostic accuracy of ILD subtypes [2]. Second, the older population is at higher risk of developing ILD and the Chinese population is aging, similar to the Western population. This may have resulted in a real numerical increase of ILD. Third, even if it is speculative, the incidence of ILD in China might also have been rising because of environmental factors such as pollution, tobacco smoking, bird breeding, and viral infection [3].

The distribution of ILD subtypes varies between different studies and countries because of differences in studied populations, research methods, and practical approaches of establishing a clinical diagnosis. However, one consistent finding is that IPF is typically the most common subtype of ILD, which was also confirmed in our large cohort in China.

One rather unexpected finding from this study was that CTD-ILD was the second most commonly diagnosed ILD after IPF (24.1%). The reason for this dramatic increase of patients with CTD-ILD in recent years, particularly pSS as most common CTD-ILD is unclear. We suspect that the broader awareness of ILD, and a more standardized ILD diagnostic approach in China, together with the use of sensitive diagnostic technologies, more and more ILD were accurately diagnosed and subtypes identified. Additionally, the majority of patients with pSS-ILD had lung dominant diseases and came directly to our department, which might explain the higher frequency of these patients in our cohort. In our study, there were 13.2% unclassifiable ILD, which is similar to previous studies that showed that the proportion of unclassifiable ILD was between 5% to 15% [7]. The proportion of sarcoidosis was 5.6%, which was

much lower than in the US and Europe [8-12], where sarcoidosis was the frequent entity with the proportion of 20% to 42%. The variation of ILD subtypes in different countries is certainly affected by ethnic and geographic factors [13], besides the differences in the diagnostic awareness and approaches, and study population.

Our study has several strengths. We obtained data from large number of patients in a major ILD center managing Chinese patients from across the country. Further, it was relatively easy to achieve a strict internal quality control through standard diagnostic protocols in a single center. Therefore, the ILD spectrum in this study was more accurate and a reflection of a “real world” scenario in China. Several similar studies from the past years also reported a detailed break down of subtypes of ILD, but they were limited by their observational / questionnaire based nature and would not have captured all cases like we did in our study [10-12].

Obviously, our study has several limitations. First, data were only from one major ILD centre and were retrospectively analyzed, even if we collected all patients admitted with a working diagnosis of ILD. Second, we missed the majority of patients with pneumoconiosis, because in China, these patients would typically be assessed in a specialized hospital for occupational diseases. Only a prospective, multicenter study can provide more accurate breakdown of the different ILD subtypes in China.

In summary, we show that hospital admissions of patients for detailed workup of ILD increased in China from 2000 to 2012. IPF was the most frequent type, followed by CTD-ILD. It suggests an increasing recognition of ILD as well as increased burden of disease**.**

References:

1. Cai M, Zhu M, Ban C, Su J, Ye Q, Liu Y, Zhao W, Wang C, Dai H. Clinical features and outcomes of 210 patients with idiopathic pulmonary fibrosis. *Chin Med J (Engl)* 2014: 127(10): 1868-1873.

2. American Thoracic S, European Respiratory S. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002: 165(2): 277-304.
3. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TJ, Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011: 183(6): 788-824.
4. Richeldi L, Rubin AS, Avdeev S, Udwadia ZF, Xu ZJ. Idiopathic pulmonary fibrosis in BRIC countries: the cases of Brazil, Russia, India, and China. *BMC MED* 2015: 13: 237.
5. Navaratnam V, Fleming KM, West J, Smith CJ, Jenkins RG, Fogarty A, Hubbard RB. The rising incidence of idiopathic pulmonary fibrosis in the U.K. *THORAX* 2011: 66(6): 462-467.
6. Raghu G, Chen SY, Hou Q, Yeh WS, Collard HR. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old. *EUR RESPIR J* 2016: 48(1): 179-186.
7. Skolnik K, Ryerson CJ. Unclassifiable interstitial lung disease: A review. *RESPIROLOGY* 2016: 21(1): 51-56.
8. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. *N Engl J Med* 2018: 378: 1811-1823.
9. Duchemann B, Annesi-Maesano I, Jacobe De Naurois C, Sanyal S, Brillet PY, Brauner M, Kambouchner M, Huynh S, Naccache JM, Borie R, Piquet J, Mekinian A, Virally J, Uzunhan Y, Cadranel J, Crestani B, Fain O, Lhote F, Dhote R, Saidenberg-Kermanac'H N, Rosental PA, Valeyre D, Nunes H. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. *EUR RESPIR J* 2017: 50.
10. Musellim B, Okumus G, Uzaslan E, Akgun M, Cetinkaya E, Turan O, Akkoclu A, Hazar A, Kokturk N, Calisir HC, Turkish Interstitial Lung Diseases G. Epidemiology and distribution of interstitial lung diseases in Turkey. *CLIN RESPIR J* 2014: 8(1): 55-62.
11. Karakatsani A, Papakosta D, Rapti A, Antoniou KM, Dimadi M, Markopoulou A, Latsi P, Polychronopoulos V, Birba G, Ch L, Bouros D, Hellenic Interstitial Lung Diseases G. Epidemiology of interstitial lung diseases in Greece. *Respir Med* 2009: 103(8): 1122-1129.
12. Xaubet A, Ancochea J, Morell F, Rodriguez-Arias JM, Villena V, Blanquer R, Montero C, Sueiro A, Disdier C, Vendrell M, Spanish Group On Interstitial Lung Diseases S. Report on the incidence of interstitial lung diseases in Spain. *Sarcoidosis Vasc Diffuse Lung Dis* 2004: 21(1): 64-70.
13. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 1999: 160(2): 736-755.