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Multidisciplinary working group for interstitial lung disease in Thailand: Part 1- rationale in developing a guide to estimate the global disease and fibrotic extents on high-resolution computed tomography

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Introduction

Interstitial lung diseases (ILDs) comprise a diverse group of diffuse lung parenchymal disorders, which are classified together due to similar clinical, radiologic, physiologic, or pathologic manifestations (Table 1) [1]. As shown in Table 1, most ILDs are caused by either known or unknown pathogens and are usually chronic. These include idiopathic interstitial pneumonias (IIPs; particularly idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia (NSIP)), connective tissue disease-associated ILDs (CTD-ILDs), chronic hypersensitivity pneumonitis, familial pulmonary fibrosis, sarcoidosis, and other exposure-related diseases. Based on previous literature [2-5], the two most common ILDs in Western countries are idiopathic pulmonary fibrosis (IPF) and sarcoidosis, while the two most common ones in Asia are CTD-ILDs and IPF.

Table 1. *Clinical classification of diffuse lung parenchymal disorders [1].*

Idiopathic interstitial pneumonias (IIPs): idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia NSIP, cryptogenic organizing pneumonia (COP), respiratory bronchiolitis-interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), lymphangitic carcinomatosis (LIP), acute interstitial pneumonia (AIP)
Connective tissue disease-associated ILDs (CTD-ILDs): rheumatoid arthritis (RA), systemic sclerosis (SSc), mixed connective tissue disease (MCTD), myositis, systemic lupus erythematosus (SLE), sjögren's syndrome
Eosinophilic lung disease: chronic eosinophilic pneumonia
Chronic lung disorders from drug reaction
Interstitial lung disease with granuloma: chronic granulomatous infections, sarcoidosis, hypersensitivity pneumonitis, berylliosis, etc.
Diffuse alveolar hemorrhage
Pneumoconiosis
Pulmonary hypertension and related disorder
Miscellaneous diseases: Langerhans cell histiocytosis, lymphangioleiomyomatosis, pulmonary alveolar proteinosis, amyloidosis, pulmonary alveolar microlithiasis, etc.
Malignant neoplasms: lymphangitic carcinomatosis, etc.

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ILDs can be suspected or diagnosed based on clinical and radiologic manifestations. The patients with ILD often present with dyspnea at rest or on exertion and has abnormal lung sounds on lung auscultation [6]. The two main physiologic changes on pulmonary function tests are restrictive pulmonary defect and decreased carbon monoxide diffusion capacity [7]. Chest radiography remains the most commonly performed primary imaging tool. However, the low sensitivity and specificity hinder its use [6]. Hence, high-resolution computed tomography (HRCT) has become a cornerstone for evaluating the morphology and distribution and diagnosing various ILDs [6].

At times, a confident diagnosis of several ILD entities can be made when patients have typical clinical and imaging findings, for example, usual interstitial pneumonia (UIP), lymphangitic carcinomatosis, lymphangioleiomyomatosis, Langerhans cell histiocytosis, pulmonary alveolar proteinosis, subacute hypersensitivity pneumonitis, asbestosis, and pulmonary edema [8]. The diagnosis of CTD-ILDs usually relies on clinical, physiologic, and radiologic data to define the presence of the disease, determine the clinical course, and assess the prognosis of the lung involvement [9].

Despite advances in knowledge, a significant proportion of ILDs remains complex and challenging to diagnose. Various ILDs often share common histological features and pathological mechanisms regardless of their causes. When the specific diagnosis cannot be entertained based on clinical, physiologic, and radiologic data, surgical lung biopsy (SLB), a gold standard tool for ILD diagnosis, may be required [10]. However, the procedure carries a high risk, especially in old or frail patients. The 30-day mortality is approximately 2.4% [11], comparable to the 2.3% 30-day mortality of lobectomy [12]. Hence, SLB is not a commonly performed procedure. As shown in previous studies, SLBs were performed in 1.8% in Indian National Registry [3], 8% in the previous study from a single center in Singapore [4], and less than 1% in the study from a single center in Southern Thailand [5].

Furthermore, SLBs are rarely performed in CTD-ILDs because there are no pathognomonic pathologic findings in CTD-ILDs, and the usefulness of a biopsy in predicting prognosis and management decisions is controversial. There is a tendency to treat all CTD patients with immunosuppressive therapies if they develop progressive clinical impairment or ILD on HRCT regardless of the histopathologic findings [8].

Due to inadequate pathologic data, a proportion ILDs remain unclassifiable because of insufficient data or significant discordance among the clinical, radiological or pathological findings. A specific diagnosis of ILD requires a multidisciplinary discussion (MDD), which has generally been accepted as the current diagnostic process for ILDs in many societies [13-15] since its introduction in 2004 [16]. The dynamic interaction and information exchange between physicians (pulmonologists and rheumatologists), radiologists, and pathologists help improve the diagnosis and management of ILD patients.

Progressive fibrosing interstitial lung disease (PF-ILD)

A proportion of ILD patients can have a progressive fibrosing clinical phenotype, termed progressive fibrosing interstitial lung disease (PF-ILD). PF-ILD is characterized by symptom worsening, a decline in lung function, and an increase to the extent of fibrosis on HRCT, which eventually leads to decreased quality of life and early death despite current therapy [17]. PF-ILD can also occur in patients with IPF, CTD-ILD, chronic hypersensitivity pneumonitis, familial pulmonary fibrosis, and unclassifiable ILDs.

Among IIPs, IPF is the most common and likely to have the worst prognosis [13,18]. Various studies [19-20], including a retrospective study from a single center in Southern Thailand [5], have reported that the survival time of patients with IPF was the shortest, while that of unclassifiable ILD cases was between that of the IPF and non-IPF patients. There is a guideline for the diagnosis and

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management of IPF providing levels of certainty for patterns of UIP based on HRCT and pathologic findings. The presence of the UIP pattern on HRCT in patients with clinically suspected IPF could guide a diagnosis if they are not subjected to SLB [10].

Previous studies [21-24] have found that antifibrotic therapies effectively slow down disease progression when lung fibrosis has become progressive. These included nintedanib and pirfenidone in IPF [21, 22] and nintedanib in systemic sclerosis-associated ILD (SSc-ILD) [23, 24]. In Thailand, nintedanib has been approved to treat patients with IPF diagnosed by MDD in 2016 and patients with SSc-ILD diagnosed by MDD, who has the fibrotic extent of more than 10% on HRCT and with PF-ILD feature in 2020. Moreover, the Thoracic Society of Thailand under Royal Patronage, the Thai Rheumatism Association, and the Thai Society of Pediatrics Respiratory and Critical Care Medicine recommend immunosuppressive therapies in SSc-ILD patients with the disease extent of more than 20% on HRCT.

A multidisciplinary working group in Thailand

At present, a clear definition of the ILD severity and fibrotic extent has become mandatory for the diagnosis, management, and treatment of patients with PF-ILDs. To facilitate communication among members and practitioners regarding the disease severity and fibrotic extent appearing on HRCT, the Royal College of Radiologists of Thailand and the Foundation for Orphan and Rare Lung Disease invited Thai thoracic radiologists and physicians (pulmonologists and rheumatologists) (Figure 1) to discuss the proposed method for estimation of ILD extent on December 3rd, 2021.

Figure 1. *Multidisciplinary working group on global disease and fibrotic extents on HRCT on December 3rd, 2021.*

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Our working group agreed that the ILDs should be estimated regarding all radiological features related to ILDs found on HRCT. These mainly include coarse reticulation, honeycombing, and traction bronchiectasis, considering the essential HRCT features of the UIP pattern since they are well correlated with fibrosis at histology and associated with increased mortality and poor prognosis [25-30]. Other CT findings suggesting non-ILD findings, such as cancer, pneumonia, or aspiration, are excluded from the estimation.

The extent of HRCT findings in each level can be determined by visually estimating the percentage to the nearest 5% parenchymal involvement. Minor interobserver variation or more reproducibility in estimation can be achieved by drawing a horizontal line on each level, leaving a measurable area of 50%, and then a second line, which runs perpendicularly to the horizontal one leaving a 25% assessable area of each lung. Each 25% is subdivided into five portions, corresponding to an area of 5% each [31] (Figure 2).

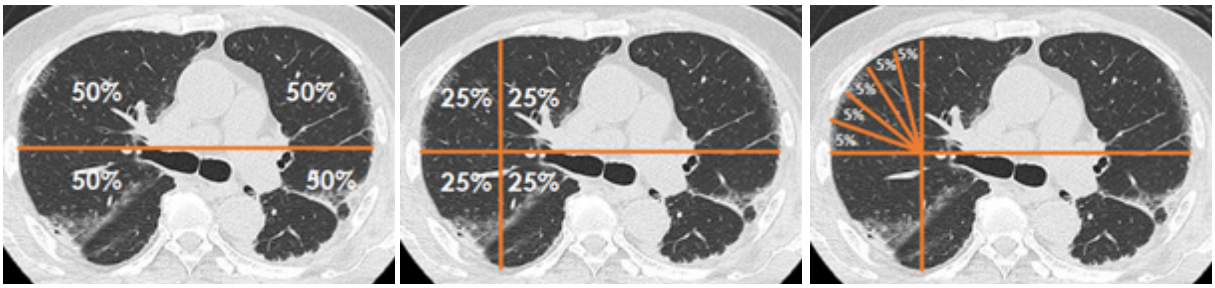

Figure 2. *Extent of disease assessment on HRCT using estimated to the nearest 5% method. This figure represents a cut of HRCT of a patient with SSc, at the level of the main carina. A drawing a horizontal line; leaving a measurable area of 50%, and then a second line, which runs perpendicularly to the horizontal line; leaving a 25% assessable area of each lung. Each 25% is subdivided into five portions, corresponding to an area of 5% each.*

Estimation of the global disease and fibrotic extents of ILD in both lungs can be quantified by averaging the summation of all three or five chosen HRCT levels previously described in the literature [29, 32]. The three-level method included the three selected HRCT levels from the upper, middle, and lower lung zones [32] (Figure 3). The five-level method included the HRCT levels at 1) the origin of

the great vessels; 2) the main carina; 3) the pulmonary venous confluence; 4) the halfway between levels 3 and 5; 5) immediately above the right hemidiaphragm dome [29]. However, the anatomical level defined in these methods, particularly the three-level method, is deemed unclear about which level to be assessed.

Estimation of ILD extent			
Level	Right lung (%)	Left lung (%)	Sum at each level (%)
Level 1 in upper zone	5%	10%	15%
Level 2 in middle zone	0%	5%	5%
Level 3 in lower zone	5%	5%	10%
Sum % (of all 3 levels or 6 areas)	30%		
Average extent (Sum% /6)	5%		

Figure 3. *Estimation of ILD extent.*
An example of a table demonstrates a calculation technique regarding the three-level method. Each side of HRCT level, the right and left lungs, was separately scored to the nearest 5%. The extent of disease (either global disease extent or fibrotic extent) is derived from the summation of all chosen HRCT levels divided by a number of areas of the lungs (total of 6 selected areas).

Noteworthy, many ILDs, especially IPF and SSc-ILD, are basal predominant. Moreover, patients with early ILD often have interstitial abnormalities confined to lung bases, specifically below the right hemidiaphragm dome. Hence, the global disease and fibrotic extent can be underestimated.

Since there are no clear description of how the level should be selected and the potentially inadequate inclusion of ILD extent, we have proposed the six-level method by modifying the original five-level method and adding level 6 (2-3 cm above the posterior costophrenic angle). The details regarding the six-level method will be further discussed in the upcoming article in the following journal issue. Nevertheless, the proposed method requires further validation to confirm its usefulness in evaluating ILDs in routine clinical practice. At present, the methods for estimating the ILD extent can still be based on personal preference.

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