

# High-Resolution Computed Tomography (HRCT) Disease Patterns and Survival Times in Patients with Interstitial Lung Disease at a University Tertiary Hospital in Southern Thailand from 2006 to 2012

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## Abstract

**Background:** The aim of our study is to assess the high-resolution computed tomography (HRCT) patterns and survival times in patients with interstitial lung disease (ILD) during 2006-2012. **Subjects & Methods:** Sex, age, HRCT disease patterns and severity, pathologic results, year of diagnosis, and year of death in 249 patients with ILD were analysed and described descriptively. **Results:** The patients were 76 (30.5%) men and 173 (69.5%) women with a mean age of 54.3 years old. The most common HRCT pattern was the non-specific interstitial pneumonia (NSIP)-possible usual interstitial pneumonia (UIP) pattern (126 patients, 50.6%) which were connective tissue disease (CNT)-related in 86 patients (34.5%) and idiopathic in 40 patients (16.1%). The second most common HRCT pattern was UIP (61 patients, 24.5%) which was idiopathic in 34 patients (13.7%) and CNT-related in 27 patients (10.8%). The HRCT pattern from which a diagnosis could not be made was the third most common (39 patients, 15.7%). The survival time was longest in the CNT-related-NSIP pattern cases followed by idiopathic NSIP-possible UIP, CNT-related-UIP, and idiopathic UIP. **Conclusion:** The survival times were shortest in idiopathic cases whose HRCT patterns were UIP, possible UIP or NSIP, and longest in CNT-related NSIP.

**Keywords:** Thailand, interstitial lung disease, survival time, high-resolution computed tomography, HRCT pattern.

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## Introduction

Interstitial lung disease (ILD) is a group of assorted parenchymal lung disorders, most of which are chronic. This term covers hundreds of disease entities. However, only 8 of these disease entities are considered to be idiopathic,<sup>[1]</sup> while the others are secondary to various causes including connective tissue disease (CNT), smoking, environmental exposures, infection, and malignancy.

A specific diagnosis of ILD requires a multidisciplinary discussion (MDD) involving pulmonologists, radiologists and pathologists introduced in 2013 and accepted as the current diagnostic standard for ILD in many societies.<sup>[1-3]</sup> However, because of inadequate pathologic data, diagnoses in many patients are mainly based on clinical and radiological findings.

In addition to being more sensitive than chest radiographs in the detection of ILD, HRCT findings correlate well with histopathologic patterns.<sup>[4]</sup> Confident diagnoses of several disease entities can be made if the HRCT findings and clinical context are typical, such as usual interstitial pneumonia (UIP), lymphangitic carcinomatosis, lymphangioleiomyomatosis, Langerhans cell histiocytosis, pulmonary alveolar proteinosis, subacute hypersensitivity pneumonitis, asbestosis, and pulmonary oedema.<sup>[5]</sup> In many institutions, it is recommended that surgical biopsy or invasive diagnostic procedures could be obviated in these circumstances.<sup>[6-9]</sup>

Lung involvement in connective tissue disease (CNT-ILD) 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. Lung biopsies are rarely performed to define the pattern of injury for many reasons: no pathologic findings are pathognomonic

for CNT, the usefulness of a biopsy in predicting prognosis and management decisions is controversial, and there is a tendency to treat all CNT patients with immunosuppressive therapies if they are clinically impaired by the ILD or the ILD is progressive on HRCT regardless of the histopathologic findings.<sup>[10]</sup>

Among idiopathic interstitial pneumonias (IIP), idiopathic pulmonary fibrosis (IPF) is the most common and is likely to have the worst prognosis.<sup>[1,11]</sup> There is a guideline for the diagnosis and 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 surgical lung biopsy (SLB).<sup>[12]</sup>

In spite of advances in the classification of IIP and the development of MDD, a proportion of patients remain unclassifiable because of inadequate data or major discordance among the clinical, radiological or pathological findings. Various studies have reported that the survival time of patients with IPF was the shortest, while unclassifiable ILD was between that of IPF and non-IPF.<sup>[13,14]</sup>

The prevalence or the distribution of disease entities causing ILD varies among studies from different countries. Data regarding ILD in Southeast Asia are scarce. We report our experience in patients diagnosed as having ILD during 2006-2012 prior to routine practice of prospective MDD,<sup>[1-3]</sup> prospective disease registries<sup>[15,16]</sup> and antifibrotic therapies<sup>[17,18]</sup> in a large community with lower diversity in health care resources and utilization of those resources here, focusing on HRCT patterns and the survival time of patients with ILD.

## Subjects and Methods

### Patients

Patients older than 15 years who were diagnosed as having interstitial lung disease in the 900-bed Songklanagarind Hospital, the university tertiary medical centre in Southern Thailand, from January 2006 to December 2012 were included in this historical cohort study. The patients' data were retrieved from the computerized hospital information system (HIS), using ICD-10 (J84 interstitial lung disease) and all cases with HRCT consistent with ILD. Diagnoses of ILD were determined by a multidisciplinary approach.

The study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University.

### Measurements

HRCT patterns were grouped into 3 categories: confident diagnosis, likely diagnosis and diagnosis cannot be made. The confident diagnoses are a UIP pattern (according to the ATS/ERS/JRS/ALAT statement),<sup>[12]</sup> lymphangitic carci-

nomatosis, lymphangioliomyomatosis, Langerhans cell histiocytosis, pulmonary alveolar proteinosis, asbestosis, subacute hypersensitivity pneumonitis, alveolar microlithiasis, and pulmonary oedema. The likely diagnoses are possible UIP (according to the ATS/ERS/JRS/ALAT statement), NSIP, respiratory bronchiolitis interstitial lung disease (RB-ILD), silicosis, coal worker pneumoconiosis, sarcoidosis, and desquamate interstitial pneumonia (DIP). A diagnosis is recorded as 'could not be made' with HRCT findings of bronchiolitis, diffuse groundglass opacities or consolidations, or any HRCT findings that were not consistent with those in the first 2 categories.

The severity of each HRCT pattern was graded according to the International Classification of HRCT for Occupational and Environmental Respiratory Diseases (ICOERD).<sup>[19]</sup>

The patients who were diagnosed as having ILD were followed after their original diagnosis for at least 5 years to obtain mortality rate data; we also recorded the date of last follow up in surviving patients. The date of death of those who died was obtained from the HIS or the government death registry.

### Statistical Analysis

Analysis of the data was conducted using the EpiData and R programs for Windows. The findings are presented using descriptive statistics and Kaplan-Meier curves.

Data from medical records and laboratory and CT findings of patients with ILD (ICD 10 J84) were extracted and recorded in EpiData. All of the analyses were conducted with Stata/MP (College Station, TX). Continuous variables are presented as mean ( $\pm$ SD) or median (IQR) as appropriate. Categorical variables are presented as n (%). Student's t-tests or Mann Whitney Wilcoxon tests were used to show differences between continuous variables. Chi-square or Fisher's exact tests were used to show differences between categorical variables. Time-to-event calculations are presented with Kaplan-Meier curves. Log-rank tests were used to show differences in time-to-event analyses. Cox-proportional hazard regression was used to calculate hazard ratios. Proportional hazards assumptions were used to determine the Cox regressions.

## Results

### Patient Characteristics

Of the 249 patients included in this study, 76 (30.5%) were men and 173 (69.5%) were women with a mean age of 54.3 years old (range 17-87 years) [Table 1].

### Comparisons among ILD Categories

Ninety-five (38.2%) patients had pathologic results and 154 (61.8%) did not [Table 1]. Only one case was from a

surgical lung biopsy while the others were from bronchoscopic biopsies.

Confident HRCT diagnoses were made in 73 cases (29.3%) while likely HRCT diagnoses were made in 132 cases (53.0%) and diagnoses could not be made in 40 cases (16.1%). Three cases (1.2%) had normal HRCTs and 1 case (0.4%) had a poor quality HRCT. The most common HRCT pattern was NSIP-possible UIP (126 patients, 50.6%), which were CNT-related in 86 patients (34.5%) and idiopathic in 40 patients (16.1%). The second most common HRCT pattern was UIP (61 patients, 24.5%), which were idiopathic in 34 patients (13.7%) and CNT-related in 27 patients (10.8%). Comparisons of these patterns are shown in [Table 1 & Figure 1].

The severity scores of each pattern from the first HRCT study are presented as severe and non-severe cases in [Table 1]. Multiple lesions in all lung zones (grade 2 for 6 zones) or numerous findings in most of both lungs (grade 3 for 4 zones) were considered severe.

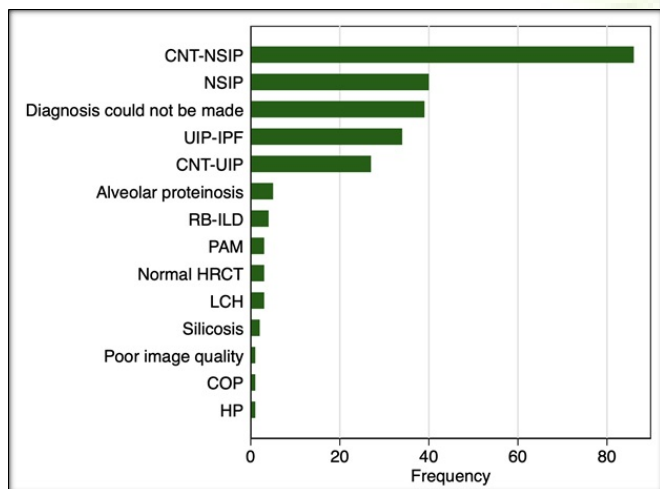


Figure 1: Comparing the number of patients in each HRCT pattern CNT-NSIP: Connective tissue disease-related nonspecific interstitial pneumonia/ possible usual interstitial pneumonia, NSIP: Idiopathic nonspecific interstitial pneumonia/ possible usual interstitial pneumonia, Cannot dx: Diagnosis could not be made (unclassifiable), UIP-IPF: Idiopathic usual interstitial pneumonia, CNT-UIP: Connective tissue disease-related usual interstitial pneumonia, RB-ILD: Respiratory bronchiolitis interstitial lung disease, LCH: Langerhans cell histiocytosis, COP: Cryptogenic organizing pneumonia, HP: Hypersensitivity pneumonitis

### Survival Analysis

The survival time in patients with idiopathic UIP was shorter than in those with other types of ILD as shown in [Table 2

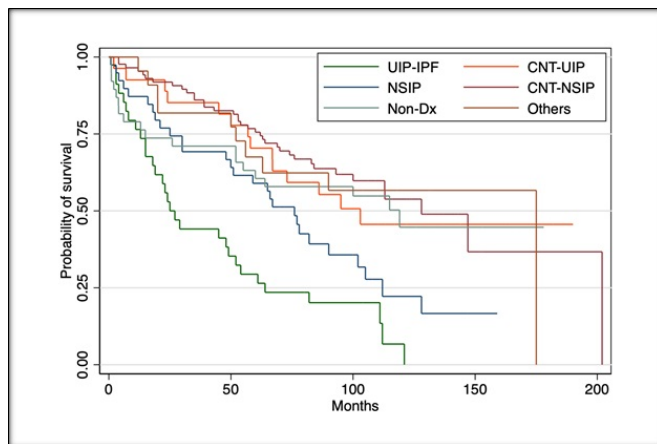


Figure 2: Kaplan-Meier curves showing overall survival of patients with each HRCT pattern UIP-IPF: Idiopathic usual interstitial pneumonia, CNT-UIP: Connective tissue disease-related usual interstitial pneumonia, NSIP: Idiopathic nonspecific interstitial pneumonia/ possible usual interstitial pneumonia, CNT-NSIP: Connective tissue disease-related non-specific interstitial pneumonia/ possible usual interstitial pneumonia, Non-Dx: Diagnosis could not be made (unclassifiable).

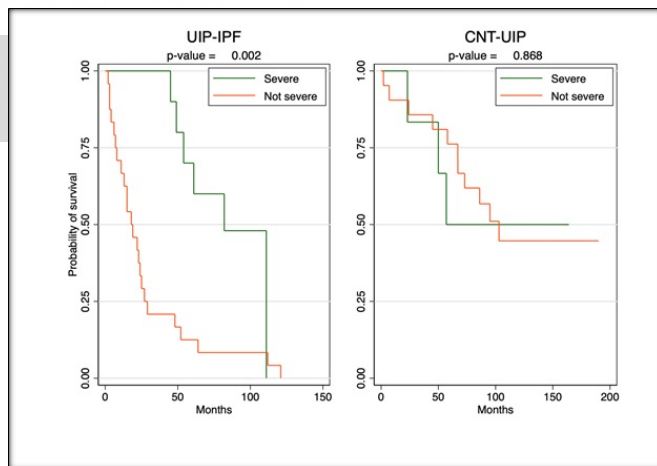


Figure 3: Kaplan-Meier curves comparing the survival of patients with severe and non-severe UIP patterns in the idiopathic and CNT-related groups, UIP-IPF: Idiopathic pulmonary fibrosis, CNT-UIP: Connective tissue disease-related usual interstitial pneumonia

**Table 1: Demographic data, availability of pathologic results and severity of each HRCT pattern**

	Total (N=249)	UIP-IPF (N=34)	CNT-UIP (N=27)	NSIP (N=40)	CNT- NSIP (N=86)	Non-Dx (N=40)	Others (N=22)	p-value
Age (mean ± SD)	54.3 ± 15.2	69.1 ± 10.8	52.9 ± 12.1	59.2 ± 15.2	48.3 ± 12.5	53.5 ± 15.4	48.7 ± 16.7	<0.001
Sex								<0.001
Male	76 (30.5%)	23 (67.6%)	4 (14.8%)	13 (32.5%)	17 (19.8%)	7 (17.5%)	12 (54.5%)	
Female	173 (69.5%)	11 (32.4%)	23 (85.2%)	27 (67.5%)	69 (80.2%)	33 (82.5%)	10 (45.5%)	
Status								<0.001
Death	138 (55.4%)	30 (88.2%)	14 (51.9%)	28 (70.0%)	37 (43.0%)	19 (47.5%)	10 (45.5%)	
Alive	108 (43.4%)	4 (11.8%)	13 (48.1%)	11 (27.5%)	49 (57.0%)	19 (47.5%)	12 (54.5%)	
Lost	3 (1.2%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	2 (5.0%)	0 (0.0%)	
Pathology								<0.001
Yes	95 (38.2%)	11 (32.4%)	8 (29.6%)	24 (60.0%)	20 (23.3%)	17 (42.5%)	15 (68.2%)	
No	154 (61.8%)	23 (67.6%)	19 (70.4%)	16 (40.0%)	66 (76.7%)	23 (57.5%)	7 (31.8%)	
Severity								<0.001
Severe	95 (38.2%)	10 (29.4%)	6 (22.2%)	10 (25.0%)	48 (55.8%)	17 (42.5%)	4 (18.2%)	
Not severe	154 (61.8%)	24 (70.6%)	21 (77.8%)	30 (75.0%)	38 (44.2%)	23 (57.5%)	18 (81.8%)	

UIP-IPF: Idiopathic usual interstitial pneumonia, CNT-UIP: Connective tissue disease-related usual interstitial pneumonia, NSIP: Idiopathic nonspecific interstitial pneumonia/ possible usual interstitial pneumonia, CNT-NSIP: Connective tissue disease-related non-specific interstitial pneumonia/possible usual interstitial pneumonia, Non-Dx: Diagnosis could not be made (unclassifiable).

**Table 2: Survival data of each HRCT pattern**

	Time at risk (months) 18290.8	Incidence rate 0.008	No of sub- ject 246	25% sur- vival (months) 35.0	50% sur- vival (months) 95.0	75% survival (months) 202.0	p-value (Log rank)
UIP-IPF	1469.2	0.020	34	13.0	25.0	64.0	0.000
CNT-UIP	2395.4	0.006	27	57.0	103.0	.	
NSIP	2576.3	0.011	39	25.0	76.0	112.0	
CNT-NSIP	7101.3	0.005	86	62.0	128.0	202.0	
Non-Dx	2985.5	0.006	38	14.9	119.1	.	
Others	1763.1	0.006	22	52.0	175.0	175.0	

UIP-IPF: Idiopathic usual interstitial pneumonia, CNT-UIP: Connective tissue disease-related usual interstitial pneumonia, NSIP: Idiopathic nonspecific interstitial pneumonia/possible usual interstitial pneumonia, CNT-NSIP: Connective tissue disease-related non-specific interstitial pneumonia/possible usual interstitial pneumonia, Non-Dx: Diagnosis could not be made (unclassifiable).

& Figure 2]. The median survival times were 25, 103, 76, 182, 119 and 175 months in idiopathic UIP (UIP-IPF), CNT-related UIP (UIP-CNT), idiopathic NSIP-possible UIP (NSIP), CNT-related NSIP-possible UIP (NSIP-CNT), diagnosis could not be made (Non-Dx) and others, respectively.

Compared with UIP-IPF, the hazard ratios were 0.42, 0.58, 0.48, 0.47 and 0.32 for UIP-CNT, NSIP, NSIP-CNT, diagnosis could not be made, and others, respectively, all with statistical significance. Survival times were shorter in patients with a 'severe' ICOERD severity score, with HR 2.44 (95% CI 1.62–

**Table 3: Results of the adjusted Cox regression model**

Parameter	Haz. Ratio	Std. Err.	z	p-value	[95% Conf. Interval]	
Sex						
Female	0.60	0.12	-2.58	0.01	0.41	0.89
age	1.02	0.01	2.98	0.00	1.01	1.04
ILD pattern						
CNT-UIP	0.42	0.15	-2.43	0.01	0.21	0.84
NSIP	0.58	0.16	-1.98	0.05	0.33	0.99
CNT-NSIP	0.48	0.14	-2.55	0.01	0.27	0.84
Non-Dx	0.47	0.15	-2.37	0.02	0.25	0.88
Others	0.32	0.12	-2.96	0.00	0.15	0.68
Severity						
Severe	2.44	0.50	4.30	0.00	1.62	3.66

UIP-IPF: Idiopathic usual interstitial pneumonia, CNT-UIP: Connective tissue disease-related usual interstitial pneumonia, NSIP: Idiopathic nonspecific interstitial pneumonia/possible usual interstitial pneumonia, CNT-NSIP: Connective tissue disease-related non-specific interstitial pneumonia/possible usual interstitial pneumonia, Non-Dx: Diagnosis could not be made (unclassifiable).

3.66) as shown in [Table 3], with prediction of survival by this severity score most marked in idiopathic UIP (UIP-IPF) as shown in [Figure 3].

## Discussion

Southern Thailand is located on the Malay peninsula which separates its population from another parts of the country. This study is from its only tertiary care provider which could mirror a picture of mortality in patients with interstitial lung disease in the large community with lower diversity in health care resources and utilization of those resources. Its geographic uniqueness also allows access to health data easier and more reliable.

Even though less than half of the patients had pathologic results available and most pathologic results were from bronchoscopic biopsies (except for one surgical biopsy), categorization of HRCT patterns into 3 groups has proven its value. Diseases that are confidently diagnosed on HRCT usually require no lung biopsy.<sup>[5,8]</sup> In our study, confident HRCT diagnoses were made in 73 cases (29.3%). Together with CNT-related NSIP-possible UIP (86 cases, 34.5%), which requires no lung biopsy, diagnoses were confidently made in 159 cases (63.8%).

Idiopathic NSIP-possible UIP was the most common diagnosis among IIP patients and the second most common diagnosis after CNT-NSIP-possible UIP, a finding that is different from other reports.<sup>[11,13,14]</sup> This relatively high proportion of diagnoses in our study could be because almost all of the pathologic findings in our study were from bronchoscopic biopsies. The MDD of idiopathic NSIP-possible UIP in our cohort was based on HRCTs showing the possible UIP pattern

(according to the ATS/ERS/JRS/ALAT statement) or bibasilar subpleural reticulation/groundglass opacities with immediate subpleural sparing, consistent with the NSIP pattern (likely diagnosis pattern),<sup>[5]</sup> in patients whose clinical findings and pathologic results were not diagnostic of other diseases. The survival time of the patients with idiopathic NSIP-possible UIP in this series was shorter than in the report of an American Thoracic Society project in which 82.3% of patients were alive at 5 years and 73.2% at 10 years.<sup>[20]</sup>

It is widely accepted that only around half of UIP cases show the typical UIP pattern on HRCT and idiopathic NSIP is rare.<sup>[21,22]</sup> It is highly possible that some of the 40/249 (16.1%) patients with idiopathic NSIP-possible UIP in our study actually had IPF. The survival time of this group in our study, ranging from 23 days to 3,410 days with an average of 1,422 days, similar to those of IPF and CNT-UIP, could support this possibility. In one study, 79/84 (94%) patients who had an HRCT pattern of possible UIP, according to the 2011 international guideline, had histopathological findings of UIP and 81.7% of the patients with suspected IPF whose HRCT were inconsistent with UIP had histopathologically proven UIP.<sup>[23]</sup> The revised diagnostic criteria for idiopathic pulmonary fibrosis that upgrades a possible UIP pattern to the probable UIP CT pattern, which may obviate the need for a lung biopsy, will help include more cases of idiopathic pulmonary fibrosis.<sup>[2]</sup>

Similar to prior studies,<sup>[13,14]</sup> our study found that 15.7% were unclassifiable ILD, the third most common diagnosis in this series. The clinical and pathological findings of the patients in this group were not suggestive of any specific disease and their HRCTs were inconsistent with UIP (according to the ATS /ERS/JRS/ALAT statement) or not diagnostic of any disease,

or the multidisciplinary findings were discordant. The survival time of patients with unclassifiable ILD was better than that of idiopathic UIP, idiopathic NSIP-possible UIP and CNT-UIP but worse than CNT-NSIP-possible UIP.

As in other studies,<sup>[10,13,14,24]</sup> the survival time in our patients was longest in the cases with CNT-related NSIP-possible UIP and worst in idiopathic UIP (IPF). The idiopathic NSIP-possible UIP and unclassifiable ILD had survival times between IPF and CNT-related ILD.

## Conclusion

Survival times were similarly short in patients with interstitial lung diseases who have unknown causes plus HRCT patterns of either UIP, possible UIP or NSIP. It is highly probable that some of the patients with idiopathic NSIP-possible UIP in our study actually had IPF. The revised diagnostic criteria for idiopathic pulmonary fibrosis that upgrades a possible UIP pattern to the probable UIP CT pattern, which may obviate the need for a lung biopsy, will help (enhance to) include more cases of idiopathic pulmonary fibrosis.

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