Prevalence, incidence, and survival analysis of interstitial lung diseases in Hong Kong: a 16-year population-based cohort study

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Summary

Background Published data on the epidemiology of interstitial lung disease (ILD) in Asia is scarce. Understanding the epidemiology is important for authorities in the health management planning. This study aimed to estimate the prevalence, incidence, and survival of ILD in Hong Kong from 2005 to 2020 and evaluate the change of trend over time.

Methods In this retrospective cohort study, we identified ILD patients between 2005 and 2020 using a territory-wide electronic health record database. Prevalence, incidence rates, and age- and sex-standardised incidence rates with United Nations population in 2020 as a reference were estimated. Trends in prevalence and incidence were analysed using joinpoint regression and the average annual percent change (AAPC) was estimated. Median survival, and risk factors of mortality were evaluated using Cox proportional hazard regression.

Findings We identified 5924 patients and included 5884 of them for analysis. The prevalence of ILD increased from 24.7 to 33.6 per 100,000 population from 2005 to 2020 with an AAPC of 1.94 (95% confidence interval, CI: 1.69–2.34). The standardized incidence rate decreased from 5.36 to 2.57 per 100,000 person from 2005 to 2020 (AAPC –3.56, 95% CI, –4.95 to –1.78). The median survival of ILD was 2.50 (95% CI, 2.32–2.69) years. Male, older age, higher Charlson comorbidity index, and IIP subtype were associated with increased mortality with statistical significance.

Interpretation This study provided the first epidemiological evaluation of ILD in Hong Kong. Further studies on ILD in multiple Asian cities and countries are warranted.

Funding None.

Keywords: Electronic health record; Interstitial lung disease; Idiopathic interstitial pneumonia; Mortality; Epidemiology

Introduction

Interstitial lung disease (ILD) is a complex group of disorders encompassing over 200 entities,[1–4] some of which share common clinical features of progressive inflammation with variable lung fibrosis resulting from damage to the lung parenchyma. The mortality rate differs by types of ILD, the lowest being observed in sarcoidosis and the highest in idiopathic pulmonary fibrosis (IPF),[5] with a median survival of two to three years.[6,7] The recent introduction of new pharmacological agents, such as pirfenidone and nintedanib, has been shown to improve the patient prognosis.[8]

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Research in context

Evidence before this study

We searched PubMed and Embase from the inception of the database to Aug 1st, 2022, without regard to language, using the key words ("interstitial lung disease" OR "ILD" OR "idiopathic pulmonary fibrosis" OR "IPF" OR "connective tissue disease interstitial lung disease" OR "CTD-ILD" OR "IIP") AND ("epidemiology" OR "incidence" OR "prevalence" OR "survival" OR "mortality" OR "risk factor" OR "electronic health record" OR "EHR" OR "electronic medical record" OR "EMR"). Studies on interstitial lung disease (ILD) were mostly conducted in the Europe and North America. There was a paucity of studies in Asia and no study was conducted in the Chinese population. In the reported data, the geographical variation was wide. The prevalence of ILD were reported ranging from 6.27 per 100,000 persons in North Belgium, to 97.9 per 100,000 persons in Greater Paris. The incidence was reported to be 1 to 32 per 100,000 person-years in Europe, United States, Middle East and Asia. Some studies have shown an increasing incidence of ILDs, while others have suggested otherwise. Previous studies typically had a small sample size and a short study period, and were based on questionnaires filled out by physicians or on single-center studies. Few population-based studies have evaluated the secular trends in the incidence of ILD and its subtypes.

Added value of this study

This is the largest epidemiology study on ILD in Asia with the longest studied period in the world, filling the knowledge gap by providing insights into the prevalence, incidence, secular trends, and geographical differences in the landscape of ILD. Our study showed that the prevalence of ILD had increased, while the incidence had decreased over 16 years in Hong Kong The median survival of ILD was 2.50 (95% CI, 2.32–2.69) years. Male, older age, and higher Charlson comorbidity index were associated with increased mortality with statistical significance. The risk of mortality among ILD subtype, using PiPF as a comparison group, was estimated for the first time and we found that IIP was associated with an increased mortality risk.

Implications of all the available evidence

Our study provides valuable information in the epidemiology perspective of ILD for health authorities and drug development institute on resources planning. More efficient clinical management and research are needed to improve poor prognosis in this vulnerable population.

Understanding the epidemiology of ILD is important for governments and health authorities in the ILD management planning. However, there is limited epidemiological data on ILD, particularly in Asia.

Wide geographical variations in the prevalence of ILD have been reported, ranging from 6.27 per 100,000 population in North Belgium,[9] to 97.9 per 100,000 population in Greater Paris.[10] Similarly, the incidence has been reported to be 1 to 32 per 100,000 person-years in previous studies conducted in Europe,[3,4,9–15] United States,[1] Middle east,[16] and Asia.[17] Some studies have shown an increasing incidence of ILDs,[14,15,18] while other studies suggested otherwise.[13,17] The discrepancies could be attributed to the geographical difference in demographics, lifestyle, living, and working environment. Furthermore, heterogeneity in the study design and data source may have also led to such variation. Previous studies on ILDs usually had a small sample size, with a short study period, based on the questionnaire filled by physicians[3,9–12] or a single center study.[14,16,17,19] Discrepancies in ILD incidence might also be affected by the multiple updates in diagnosis and classifications in international consensus over the last two decades.[6,7,20–22] Few population-based studies evaluated the secular trends in the incidence of ILD and its subtypes.

Population-based electronic health record (EHR) provides important information for clinical management and research, particularly for rare diseases like ILD. In the current study, we utilized a territory-wide EHR of a previously validated dataset to characterize the prevalence, incidence, survival, and risk factors of mortality of ILD over 16 years.

Methods

Data source

This is a retrospective cohort study. Data used in the current study was retrieved from the EHR of the Clinical Data Analysis and Reporting System (CDARS), a territory-wide electronic database managed by the Hospital Authority of Hong Kong Special Administrative Region (HKSAR) of China with a population size of 7.58 million. The Hospital Authority of Hong Kong is a public healthcare statuary body that manages all the 43 public hospitals and health care institutions, as well as 122 general and specialist outpatient clinics. The specialist outpatient clinics (SOPCs) are located in and managed by the public hospitals. Thus, ILD cases from in-patients and SOPCs are diagnosed by the same specialist teams. The public hospitals and outpatient clinics are organized into seven hospital clusters based on the geographic location, offering a comprehensive and complementary range of services to patients within the same geographic settings and throughout their episode of illness. Data from all institutions were automatically uploaded to the data warehouse and centralized in the CDARS for report, audit, and research purposes. As such, the CDARS captures more than 90% of the population in Hong Kong, comprising medical

information since 1993, including diagnosis, drug prescription, demographic, admission, and laboratory records.[23] All diagnoses were recorded by physicians. The CDARS data has been validated in many therapeutic areas and utilized in high-quality population-based studies,[24–26] Data generated from the CDARS showed similar results as what were reported in subsequent randomized control studies.[27,28] CDARS links to the Death Registry where the date of death is recorded with high accuracy.

Data, including demographics, diagnosis, in-patients admission, and out-patients visit were extracted from CDARS. The extracted data were then merged into analytical datasets using a unique patient identifier. To ensure data quality, a cleaning process was performed to screen for outliers and inappropriate date formats.

Case identification

We used CDARS to identify ILD records between 1 January 2005 and 31 December 2020 and we used records from 2000 to 2004 as the screening period to identify new ILD cases. A prevent case was defined as both new and pre-existing ILD during the study year, whereas a new case was defined when a patient first ever diagnosed with ILD during the study period and had no record of ILD in the screening period. The diagnosis was coded based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Mappings to ICD-10-CM diagnostic codes were conducted (Supplementary Table S1). The diagnostic coding of ILD was previously validated by reviewing the chest imaging reports, physician medical notes, and clinical examination reports in accordance with the latest guidelines, conducted by a specialist of respiratory medicine.[7,26] ILD was defined as post-inflammatory pulmonary fibrosis (PiPF; ICD-9-CM: 515), idiopathic interstitial pneumonia (IIP; ICD-9-CM: 516.3), connective tissue disease-associated interstitial lung disease (CTD-ILD; ICD-9-CM: 517.2, 517.8, 714.81), sarcoidosis (ICD-9-CM: 135), and hypersensitivity pneumonitis (ICD-9-CM: 495). Patients who were diagnosed with more than one type of ILD was considered a ILD case with multiple subtype. Patients with missing information on gender, age below 20 years at the first diagnosis of ILD were excluded to maintain the consistency with earlier studies and to ensure data quality.[29,30]

Sample size

Sample size calculation is not applicable given the descriptive nature of the study. We identified a total of 5924 patients with a diagnosis of ILD between 1 January 2005 and 31 December 2020. Of these, 5884 patients were included in the analysis.

Outcomes

The primary outcomes for the study were the prevalence, incidence, and median survival of ILD in Hong Kong. Additional outcomes were the change of trend over time and the risk factors of mortality.

Statistical analysis

Descriptive statistics for the cohort were presented as mean ± standard deviation (SD) for continuous variables and as number and percentage for categorical variables.

The total population size was obtained from Census and Statistics Department of the HKSAR.[31] The crude prevalence was estimated as the proportion of the total number of ILD cases over the total population in each given year. The crude incidence was estimated as the proportion of new ILD cases over the total population in each given year. The standardized incidence was estimated with direct standardization to account for changes in sex and age distribution of the United Nations standardized population of 2020. The age- and sex-specific prevalence and incidence rates were calculated with age groups over a 5-year interval for aged between 20 and 84, and aged 85 or above. All prevalence and incidence rates were presented as number of cases per 100,000 population. The rates between females and males were compared using a two-sample z-test for proportion.

Joinpoint regression was used to analyse the trends in prevalence and incidence rates over time using the joinpoint software developed by the U.S. National Cancer Institute (Joinpoint Regression Program, Version 5.0.1. April, 2023; Statistical Research and Applications Branch, National Cancer Institute). Natural logarithmic transformation was applied to the rates, which were modeled as dependent variable, while the calendar year was modeled as independent variable. The joinpoint model detected the number and location of joinpoints, where a statistically significant change over time occurred in the linear slope of the trend. Weighted Bayesian Information Criteria (BIC) was used to select the best-fitting model with a maximum of two joinpoints allowed. Annual percent change (APC) of each linear segment was estimated and average annual percent change (AAPC) of the whole study period, if a turning point was presented, was evaluated as the weighted average of the APCs, with the weights equal to the length of the APC interval. A trend was considered as increase or decrease if the 95% confidence interval (CI) of the APC/AAPC did not cross zero.

The new ILD cases were included in the survival analysis. Median survival with corresponding 95% CI was estimated in all subtypes of ILD. Median survival indicated the time for at least 50% of the patients who survived within each ILD subtype. The mortality rate was the ratio of the number of deaths to total follow-up time within the study period, with respective 95% confidence interval (95% CI) estimated using a Poisson distribution. Univariable and multivariable Cox proportional hazard regression models were used to evaluate risk factors of all-cause mortality following ILD. Age

(categorised into <45, 45–54, 55–64, 65–74, 75–84, ≥85) sex, and comorbidity burden were investigated in the analysis. Comorbidity burden was quantified using the updated Charlson Comorbidity Index (CCI) using ICD-9-CM code of each corresponding comorbidity (categorised into 0, 1, 2, ≥3).[32,33] Given the potential impact of regional variation in clinical practice on patient survival, we performed a sensitivity analysis with additional adjustment for hospital clusters (Hong Kong East, Hong Kong West, Kowloon Central, Kowloon East, Kowloon West, New Territories East, and New Territories West) where the ILD was diagnosed. Hazard ratio (HR), 95% confidence interval (95% CI), and its corresponding p-value were reported. R package 'survival' was used for survival analysis.

A two-tailed p-value <0.05 was considered statistically significant for all statistical analysis. There was no allowance for multiplicity. All statistical analyses were performed using R version 4.1.3.

Ethics approval

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW19-729).

Role of the funding source

This study does not receive any support in the form of grants, gifts, equipment, or drugs.

Results

A total of 5924 patients were identified between 1 January 2005 and 31 December 2020. Of these, one patient with missing information on gender and 57 patients aged below 20 years were excluded from the analysis (Fig. 1 and Supplementary Table S2), leading to 5884 patients in the main analysis. Of these, 4938 patients had new ILD. The mean age of the new ILD cases was 72.52 ± 13.64 years, 42.2% were females (Table 1).

The prevalence of ILD increased from 23.1 per 100,000 population in 2005 to 32.6 per 100,000 population in 2020 (Table 2 and Fig. 2). Similar trends were observed in both female and male subgroups, while a higher prevalence was observed in males (24.7–36.4 per 100,000 population) than in females (21.7–29.5, per 100,000) (Supplementary Table S3 and Fig. 2). Two turning points were identified in 2007 and 2010 by the joinpoint regression analysis. The prevalence remained stable in the early years from 2005 to 2007 (APC 2.55, 95% CI, –0.53 to 7.54), followed by an increase from 2007 to 2010 (APC 11.18, 95% CI, 0.04–13.09) and a slight decrease from 2010 to 2020 (APC –0.44, 95% CI, –0.9 to –0.03) (Table 3). The overall trend in prevalence from 2005 to 2020 was increasing with an AAPC of 2.18 (95% CI, 1.90–2.65). Similar trend pattern was observed in female with an AAPC of 1.99 (95% CI, 1.77–2.31) (Supplementary Table S4). The trend pattern in males was slightly different from that in females, with an increasing trend observed from 2005 to 2011, followed by a stable trend thereafter. However, the overall prevalence of ILD in males was similar to that in females, with an increasing trend observed (AAPC 2.87, 95% CI, 2.50–3.34) (Supplementary Table S4). The trend in prevalence of each ILD subtype was shown in Supplementary Fig. S1.

The crude incidence rate decreased from 5.97 to 3.83 per 100,000 population (Table 2 and Fig. 3). The overall crude incidence rate was 5.21 per 100,000 population, with a higher rate in males (6.62 per 100,000 population) than in females (4.03 per 100,000 population) (Supplementary Table S3 and Fig. 3). This difference was statistically significant (difference = 2.59 per 100,000 population, 95% CI = 2.29–2.89 per 100,000 population, p < 0.001). Similarly, the standardized

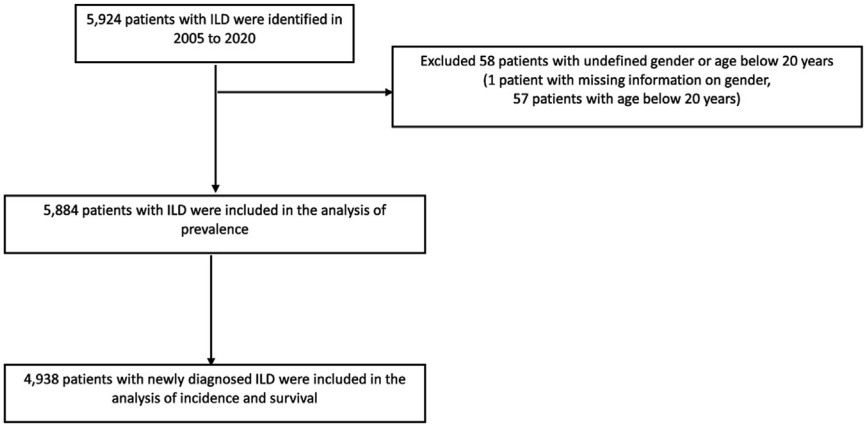

Fig. 1: Flow diagram of patient selection.

	ILD	PiPF	IIP	CTD-ILD	Sarcoidosis	Hypersensitivity Pneumonitis	Multiple subtype
N	4938	3746	588	93	188	81	242
Female (%)	2082 (42.2)	1539 (41.1)	243 (41.3)	68 (73.1)	94 (50.0)	38 (46.9)	100 (41.3)
Age, mean (SD)	72.52 (13.64)	74.13 (12.48)	74.15 (12.17)	54.87 (14.60)	49.93 (13.69)	62.51 (15.74)	71.26 (10.93)
Age group (%)							
<45	208 (4.2)	90 (2.4)	14 (2.4)	20 (21.5)	70 (37.2)	10 (12.3)	4 (1.7)
45–54	333 (6.7)	205 (5.5)	30 (5.1)	25 (26.9)	43 (22.9)	9 (11.1)	21 (8.7)
55–64	671 (13.6)	475 (12.7)	69 (11.7)	22 (23.7)	49 (26.1)	21 (25.9)	35 (14.5)
65–74	1175 (23.8)	883 (23.6)	162 (27.6)	19 (20.4)	18 (9.6)	22 (27.2)	71 (29.3)
75–84	1652 (33.5)	1327 (35.4)	204 (34.7)	6 (6.5)	6 (3.2)	17 (21.0)	92 (38)
≥85	899 (18.2)	766 (20.4)	109 (18.5)	1 (1.1)	2 (1.1)	2 (2.5)	19 (7.9)
CCI, mean (SD)	1.35 (1.62)	1.60 (1.70)	1.43 (1.63)	1.72 (1.64)	0.77 (1.33)	2.74 (2.19)	1.29 (1.6)
CCI (%)							
0	1955 (39.6)	1062 (28.4)	207 (35.2)	12 (12.9)	118 (62.8)	0 (0.0)	97 (40.1)
1	1234 (25)	1170 (31.2)	158 (26.9)	46 (49.5)	35 (18.6)	33 (40.7)	66 (27.3)
2	778 (15.8)	710 (19.0)	103 (17.5)	15 (16.1)	17 (9.0)	18 (22.2)	37 (15.3)
≥3	971 (19.7)	804 (21.5)	120 (20.4)	20 (21.5)	18 (9.6)	30 (37.0)	42 (17.4)
Myocardial infarction	288 (5.8)	231 (6.2)	35 (6.0)	2 (2.2)	4 (2.1)	3 (3.7)	13 (5.4)
Congestive heart failure	862 (17.5)	705 (18.8)	85 (14.5)	7 (7.5)	8 (4.3)	7 (8.6)	50 (20.7)
Peripheral vascular disease	123 (2.5)	88 (2.3)	21 (3.6)	1 (1.1)	3 (1.6)	5 (6.2)	5 (2.1)
Cerebrovascular disease	538 (10.9)	446 (11.9)	51 (8.7)	6 (6.5)	8 (4.3)	9 (11.1)	18 (7.4)
Dementia	89 (1.8)	77 (2.1)	8 (1.4)	0 (0.0)	1 (0.5)	2 (2.5)	1 (0.4)
Chronic pulmonary disease	1507 (30.5)	1196 (31.9)	131 (22.3)	6 (6.5)	16 (8.5)	81 (100.0)	77 (31.8)
Rheumatoid disease	652 (13.2)	450 (12.0)	72 (12.2)	73 (78.5)	8 (4.3)	10 (12.3)	39 (16.1)
Peptic ulcer disease	351 (7.1)	281 (7.5)	42 (7.1)	5 (5.4)	4 (2.1)	4 (4.9)	15 (6.2)
Mild liver disease	330 (6.7)	258 (6.9)	34 (5.8)	7 (7.5)	14 (7.4)	6 (7.4)	11 (4.5)
Diabetes without complications	693 (14)	526 (14.0)	92 (15.6)	7 (7.5)	13 (6.9)	16 (19.8)	39 (16.1)
Diabetes with complications	133 (2.7)	95 (2.5)	20 (3.4)	2 (2.2)	8 (4.3)	1 (1.2)	7 (2.9)
Hemiplegia or paraplegia	78 (1.6)	70 (1.9)	4 (0.7)	1 (1.1)	0 (0.0)	1 (1.2)	2 (0.8)
Renal disease	236 (4.8)	184 (4.9)	26 (4.4)	5 (5.4)	4 (2.1)	7 (8.6)	10 (4.1)
Cancer malignancy	412 (8.3)	320 (8.5)	57 (9.7)	6 (6.5)	10 (5.3)	5 (6.2)	14 (5.8)
Moderate or severe liver disease	27 (0.5)	24 (0.6)	1 (0.2)	0 (0.0)	1 (0.5)	1 (1.2)	0 (0)
Metastatic solid tumour	83 (1.7)	56 (1.5)	9 (1.5)	3 (3.2)	3 (1.6)	8 (9.9)	4 (1.7)
AIDS/HIV	1 (0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0)

Table 1: **Basic demographic characteristics and comorbidities of patients who were newly diagnosed with ILD in Hong Kong, 2005–2020.**

incidence rate decreased from 5.36 to 2.57 per 100,000 population in 2005–2020 (Table 2 and Fig. 3). There were statistically significant changes in the trend in standardized incidence in 2010 and 2013 (Table 3). The standardized incidence increased initially from 2005 to 2010 with an APC of 6.77 (95% CI, 2.14–16.50) and then decreased from 2010 to 2013 with an APC of –20.34 (95% CI, –25.74 to –10.79). The trend became stable after 2013 (AAPC –2.66, 95% CI, –6.24 to 9.01). The overall trend was decreasing with an AAPC of –3.56 (95% CI, –4.95 to –1.78). Similar trends were observed in female and male (Supplementary Table S4). The trend in incidence of each ILD subtype was shown in Supplementary Fig. S2.

Among the incident ILD cases, PiPF was the most frequent subtype of ILD, accounting for 79.8% (n = 3746) of all ILD cases, followed by IIP (n = 588, 12.5%), sarcoidosis (n = 188, 4.0%), CTD-ILD (n = 93, 2.0%), and hypersensitivity pneumonitis (n = 81, 1.7%). Among CTD-ILD, the most common subtype was polymyositis with lung involvement (n = 52, 55.9%), followed by lung involvement in systemic sclerosis (n = 36, 38.7%), and rheumatoid arthritis associated ILD (n = 5, 5.4%) (Supplementary Table S4). The mean age of IIP was the highest (74.15 ± 12.17 years), followed by PiPF (74.13 ± 12.48 years), hypersensitivity pneumonitis (62.51 ± 15.74 years), CTD-ILD (54.87 ± 14.60 years), and sarcoidosis (49.93 ± 13.69 years). Baseline demographics of the patients were reported in the Table 1.

The overall mortality rate of ILD was 196.67 per 1000 person-years (95% CI, 190.09–203.42; Table 4), median survival was 2.50 years (95% CI, 2.32–2.69). Among the subtypes of ILD, IIP had the highest mortality rate of 247.38 per 1000 person-years (95% CI, 224.55–272.52), and shortest median survival of 1.84 years (95% CI, 1.35–2.27), followed by PiPF, hypersensitivity pneumonitis, CTD-ILD, and sarcoidosis (Table 4). Among the subtypes of CTD-ILD, polymyositis with lung

Year	Per 100,000 population				
	Prevalence		Crude incidence rate		Standardised incidence rate[a]
	N	Rate (95% CI)	N	Rate (95% CI)	Rate (95% CI)
2005	1251	23.1 (21.9, 24.4)	323	5.97 (5.34, 6.66)	5.36 (4.78, 6.01)
2006	1304	23.8 (22.5, 25.1)	273	4.98 (4.41, 5.61)	4.31 (3.80, 4.88)
2007	1363	24.5 (23.2, 25.9)	289	5.20 (4.62, 5.84)	4.39 (3.89, 4.96)
2008	1495	26.6 (25.3, 28.0)	367	6.53 (5.88, 7.23)	5.38 (4.83, 5.99)
2009	1726	30.4 (29.0, 31.9)	469	8.26 (7.53, 9.04)	6.81 (6.19, 7.49)
2010	1904	33.1 (31.6, 34.6)	439	7.63 (6.93, 8.38)	6.14 (5.56, 6.77)
2011	1990	34.2 (32.7, 35.7)	370	6.35 (5.72, 7.03)	4.99 (4.48, 5.56)
2012	2012	34.0 (32.5, 35.5)	329	5.56 (4.98, 6.19)	4.21 (3.76, 4.73)
2013	1948	32.6 (31.2, 34.1)	248	4.15 (3.65, 4.70)	2.99 (2.61, 3.41)
2014	1930	32.0 (30.5, 33.4)	255	4.22 (3.72, 4.77)	3.02 (2.65, 3.45)
2015	1972	32.3 (30.9, 33.8)	257	4.21 (3.71, 4.76)	3.07 (2.69, 3.50)
2016	1998	32.4 (31.0, 33.9)	299	4.85 (4.32, 5.43)	3.33 (2.95, 3.76)
2017	2024	32.5 (31.1, 33.9)	271	4.35 (3.85, 4.90)	2.98 (2.62, 3.39)
2018	2022	32.1 (30.8, 33.6)	242	3.85 (3.38, 4.36)	2.56 (2.23, 2.94)
2019	2042	32.2 (30.8, 33.6)	264	4.16 (3.67, 4.69)	2.81 (2.46, 3.22)
2020	2066	32.6 (31.2, 34.0)	243	3.83 (3.37, 4.35)	2.57 (2.24, 2.96)

CI, confidence interval. [a]Age- and sex-standardisation using United Nations population of 2020 as a reference.

Table 2: **Prevalence and incidence rates of interstitial lung diseases in Hong Kong, 2005–2020.**

involvement had the highest mortality rate, followed by lung involvement in systemic sclerosis, and rheumatoid arthritis associated ILD, with the mortality rate of 77.84 (95% CI, 52.59–115.19), 70.68 (95% CI, 39.14–127.62), 22.54 (95% CI, 3.18–160.04) per 1000 person-years, respectively. Median survival of lung involvement in systemic sclerosis and polymyositis with lung involvement were 10.85 and 10.81 years, respectively. The median survival of rheumatoid arthritis associated ILD were undetermined due to insufficient deaths (Table 4).

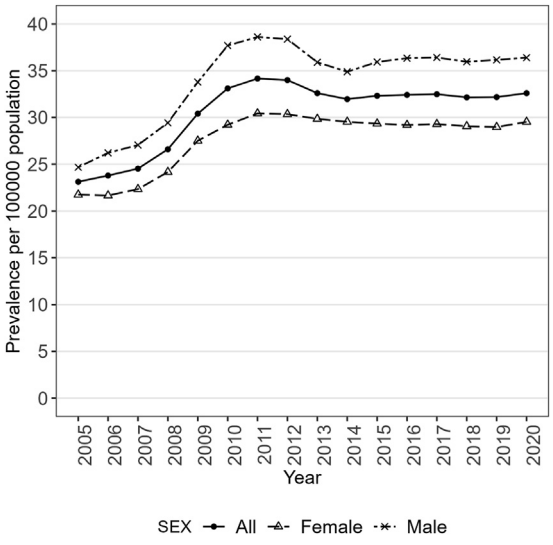

Fig. 2: Prevalence of ILD in Hong Kong, 2005–2020.

The results from Cox regression analysis showed male, older age, and higher CCI were associated with increased risk of mortality with statistical significance in the crude model (all $p < 0.001$) (Table 5). Using PiPF as the reference, IIP was associated with increased risk of mortality with statistical significance (HR: 1.16; 95% CI, 1.04–1.29), while CTD-ILD, sarcoidosis, and hypersensitivity pneumonitis were associated with reduced risk of mortality with an HR of 0.40 (95% CI, 0.29–0.56), 0.08 (95% CI, 0.05–0.13), and 0.53 (95% CI, 0.38–0.73), respectively (Table 5). In the multivariable model, similar statistically significant associations were observed for male, age, CCI, and subtypes of ILD, except that the association of CTD-ILD and hypersensitivity pneumonitis with reduced mortality was no longer statistically significant (Table 5). Sensitivity analysis with additional adjustment for hospital cluster showed similar findings (Supplementary Table S6).

Discussion

The study reported on the secular trends in prevalence and incidence of ILD, as well as the survival of ILD in Hong Kong over 16 years. This is the largest epidemiology study on ILD in Asia with the longest studied period in the world (epidemiology characteristics of ILD worldwide is shown in Appendix), filling the knowledge gap by providing insights into the prevalence, incidence, secular trends, and geographical differences in the landscape of ILD. Our study showed that the prevalence of ILD had increased, while the incidence had decreased over 16 years in Hong Kong. In the studied population, PiPF and hypersensitivity pneumonitis were the most

	Segment	Period	APC	95% CI	AAPC	95% CI
Prevalence	1	2005–2007	2.55	−0.53 to 7.54	2.18	1.90–2.65
	2	2007–2010	11.18	0.04–13.09		
	3	2010–2020	−0.44	−0.90 to −0.03		
Crude incidence rate	1	2005–2010	8.86	4.37–17.89	−1.66	−2.93 to −0.04
	2	2010–2013	−17.59	−22.59 to −8.59		
	3	2013–2020	−1.34	−4.39–8.07		
Standardised incidence rate	1	2005–2010	6.77	2.14–16.58	−3.56	−4.95 to −1.78
	2	2010–2013	−20.34	−25.74 to −10.79		
	3	2013–2020	−2.66	−6.24 to 9.01		

APC, annual percent change; AAPC, average annual percent change; CI, confidence interval.

Table 3: **Joinpoint analysis of prevalence and incidence in Hong Kong, 2005–2020.**

and least frequent ILD subtypes respectively, with the highest and lowest mortality rate being observed for IIP and sarcoidosis. In the multivariable Cox regression modeling, male, older age, higher CCI, and IIP subtype were associated with higher risk of mortality.

The prevalence of ILD in Hong Kong was similar to Greece,[3] but lower than that of the Greater Paris,[10] and the United States,[1] approximately four-fold higher than Belgium.[9] Our study reported the overall incidence of 5.21 per 100,000 population, which was similar to Greece,[3] Spain,[11,12] and Central Denmark,[34] but lower than that of India,[17] United states,[1] Turkey,[4] Greater Paris,[10] and another Denmark study (Appendix).[13] PiPF (79.8%) was the most frequent subtype in the current study. Compared to Spain/RENIA and two East-Asia studies, the percentage of PiPF was higher (79.8% vs 39.12% vs 43%–52.3%).[11,19,35] Sarcoidosis was the most frequent subtype in Greece,[3] Turkey,[4] Greater Paris,[10] Northam Belgium,[5] and Italy.[36] However, it was the third most frequent subtype in Hong Kong, being six-to-ten-fold less frequent than reported in studies mentioned above. Hypersensitivity pneumonitis was the most frequent subtype in India,[37] but it was least frequent in Hong Kong, same as in the populations of Europe[3,5,11,12,34] and China[19] (Appendix). CTD-ILD was the most frequent subtype in Canada[38] and Saudi Arabia,[16] nevertheless it was one of the least frequent subtypes in Hong Kong (1.9%), same as in Spain (6.31%),[11] Belgium (7.2%),[9] and Germany (7%).[39,40] The differences in frequency unveiled the distinctive distribution pattern of ILD subtypes in Hong Kong versus other populations, which might be attributable to genetic factors, lifestyle, environment, and clinical practice of comorbidity management, as some subtypes of ILD were known to be environment or drug induced. In the study cohort, we found that a small portion of the cases (n = 220, 4.7%) were non-Chinses. We saw it as an interesting opportunity to understand whether the

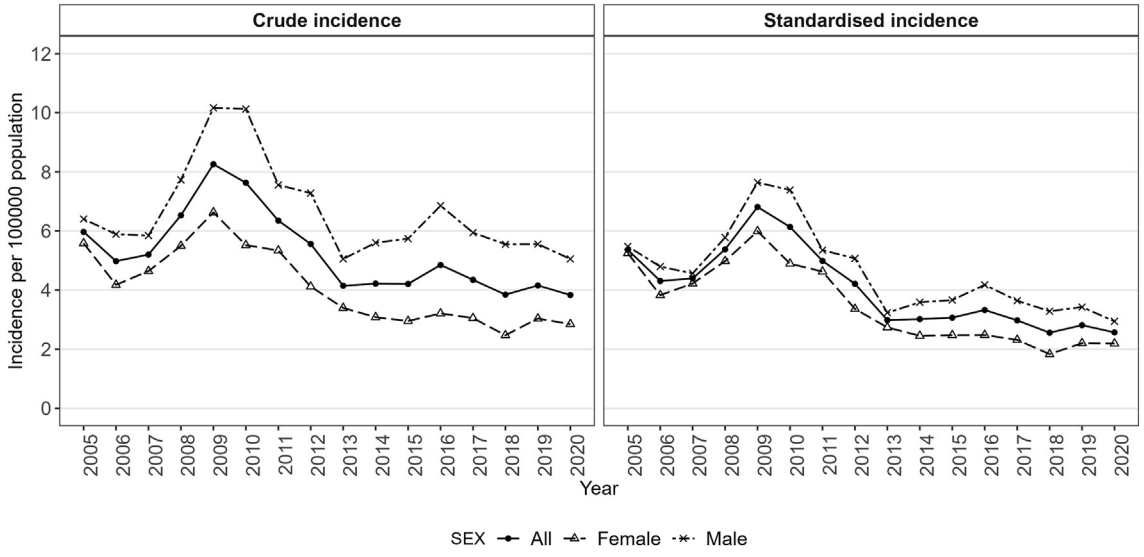

Fig. 3: Incidence rate of ILD in Hong Kong, 2005–2020.

ILD type	Total	Death	Median Survival, year (95% CI)	Mortality Rate, per 1000 person-years (95% CI)
Overall	4938	3376	2.50 (2.32, 2.69)	196.67 (190.09, 203.42)
PiPF	3746	2672	2.26 (2.05, 2.47)	213.64 (205.70, 221.90)
IIP	588	410	1.84 (1.35, 2.27)	247.38 (224.55, 272.52)
CTD-ILD	93	37	12.46 (7.63, NA)[a]	70.99 (51.44, 97.98)
Polymyositis with Lung Involvement	52	25	10.81 (5.93, NA)[a]	77.84 (52.59, 115.19)
Lung Involvement in Systemic Sclerosis	36	11	10.85 (7.05, NA)[a]	70.68 (39.14, 127.62)
Rheumatoid Arthritis associated ILD	5	1	NA[a]	22.54 (3.18, 160.04)
Sarcoidosis	188	17	NA[a]	14.17 (8.81, 22.79)
Hypersensitivity pneumonitis	81	37	11.10 (2.78, NA)[a]	90.22 (65.37, 124.52)

[a]Median survival and confidence interval were undetermined due to insufficient deaths.

Table 4: **Median survival and mortality rates for all ILDs and by subtypes.**

potential distribution pattern of ILD subtypes was ethnic specific or due to external factors. To explore this, we conducted a sensitivity analysis by comparing the ILD subtype distributions pattern between Chinese and non-Chinese patients in the current dataset. PiPF and Sarcoidosis were found to be more and less prevalent in Chinese compared to non-Chinese, respectively. No statistically significant difference was shown in the IIP, CTD-ILD or hypersensitivity pneumonitis which were mostly caused by external factors (Supplementary Table S7). We attempted to examine the pattern in non-Chinese Asian cases. Of 220 non-Chinese cases, only 64 were Asian. Due to the small number of cases, no meaningful conclusion can be drawn. Larger analyses across multiple Asian cities/countries would be warranted to further investigate the ILD subtype distribution pattern. We conducted a cross-study comparison and found that the nomenclature related to the ICD-9-CM codes of 515 and 516.3 were inconsistent. Literature commonly defined IPF or IPF clinical syndrome (IPF-CS) using the ICD-9-CM codes 515 (PiPF) and 516.3 (IIP) collectively.[18,30,41–43] The ICD-9-CM code 515 was likely a common code for patients before a definitive diagnosis of the ILD. Many cases coded as 515 were either IIP or IPF. The ICD-9-CM code 516.3 was the most specific for IPF. Still, this code included other IIPs since October 2011 due to the changes in the definition and diagnosis of ILD over time, and we, therefore,

	Total	Death	Percentage	Crude HR (95% CI)	p-value	Adjusted HR[a] (95% CI)	p-value
Gender							
Female	2082	1291	62.0	1.00		1.00	
Male	2856	2085	73.0	1.44 (1.34, 1.54)	<0.001	1.35 (1.26, 1.45)	<0.001
Age group							
<45	208	36	17.3	1.00		1.00	
45–54	333	115	34.5	2.33 (1.60, 3.39)	<0.001	1.87 (1.28, 2.72)	0.001
55–64	671	318	47.4	3.71 (2.63, 5.24)	<0.001	2.72 (1.92, 3.86)	<0.001
65–74	1175	775	66.0	6.28 (4.50, 8.78)	<0.001	4.10 (2.92, 5.76)	<0.001
75–84	1652	1351	81.8	9.66 (6.93, 13.46)	<0.001	6.09 (4.34, 8.54)	<0.001
≥85	899	781	86.9	14.05 (10.04, 19.66)	<0.001	8.79 (6.24, 12.37)	<0.001
CCI							
0	1955	1181	60.4	1.00		1.00	
1	1234	807	65.4	1.07 (0.97, 1.17)	0.165	1.08 (0.98, 1.18)	0.105
2	778	570	73.3	1.41 (1.28, 1.56)	<0.001	1.25 (1.13, 1.39)	<0.001
≥3	971	818	84.2	2.02 (1.85, 2.21)	<0.001	1.69 (1.54, 1.85)	<0.001
ILD subtypes							
PiPF	3746	2672	71.3	1.00		1.00	
IIP	588	410	69.7	1.11 (1, 1.24)	0.040	1.16 (1.04, 1.29)	0.006
CTD-ILD	93	37	39.8	0.40 (0.29, 0.56)	<0.001	0.85 (0.61, 1.19)	0.35
Sarcoidosis	188	17	9.0	0.08 (0.05, 0.13)	<0.001	0.20 (0.12, 0.32)	<0.001
Hypersensitivity pneumonitis	81	37	45.7	0.53 (0.38, 0.73)	<0.001	0.73 (0.53, 1.02)	0.064

CCI, Charlson comorbidity index; HR, hazard ratio; CI, confidence interval. [a]Adjusted for sex, age, CCI, ILD subtype.

Table 5: **Multivariable analysis on associations with death after ILD diagnosis.**

named this category IIP in accordance with the current practice.[44] To make the cross-study comparison possible, we estimated the incidence of IIP and IPF combined as a group (Supplementary Table S8).[44]

With regards of the secular trend of the incidence of ILD, some studies reported the incidence increased over time,[41,45–47] however our study showed the incidence decreased from 5.36 per 100,000 person-years in 2005 to 2.57 in 2020. Notably, a decreasing trend was also seen in IPF-focused studies in USA.[48] Since PiPF and IIP explained most cases in the current study, we performed a subgroup analysis on the APC of incidence on both PiPF and IIP over time, a consistent decreasing incidence trend was observed (Supplementary Table S9). Nevertheless, a cautious interpretation was required on the secular trend data observed in the current study. The increasing prevalence of ILD may be due to the growing aging population which offsets the impact of the decreasing incidence. The year 2010 was identified as a turning point in the trend of prevalence of ILD, with rates increasing by 11.18% per year before 2010 and then decreasing by 0.44% per year after 2010 (Table 3). This change could be partially attributed to the methodology and improvement in diagnosis, and coding practices following international guideline update in 2011[21] and 2013.[22] The guidelines updated the diagnostic criteria of PiPF and IIP, recommending that diagnosis be made by a multidisciplinary panel. The evolving diagnosis and classification towards higher clarity supported definitive diagnosis and coding practices While the 2013 update did not result in a statistically significant change in the trend of prevalence as shown in the joinpoint analysis, we observed a turning point in incidence in the same year, with the declining trend leveling off after 2013 (Table 3). We further conducted a sensitivity analysis to evaluate the distribution pattern of ILD subtype after 2013, which would more reflect the epidemiological characteristics under the current guideline. The result revealed that the proportion of PiPF among ILD cases decreased from 83.0% in 2005–2013 to 74.4% in 2014–2020, with statistically significant differences (difference = –8.6, 95% CI, –11.1 to –6.1, $p < 0.001$). Conversely, the proportion of IIP and sarcoidosis showed significant increases, while the proportion of CTD-ILD and hypersensitivity remained similar between the two periods (Supplementary Table S10). The finding suggests that more specific types of ILD can be classified under the current classification guideline, thereby highlighting the impact on the changes of guideline on the coding and diagnostic practice for ILD.

Our study showed that male, older age, and higher CCI score were associated with mortality in ILD patients, which was consistent with the previous studies in the United States where male, age, and comorbidities were associated with poor survival.[18,49] Our study further estimated the association of these factors with mortality in multivariable modeling in ILD subtypes for the first time. Among published studies in ILD worldwide, the association of different ILD subtypes with mortality was not commonly explored due to limited number of reported cases in some subtypes. Using a large EHR with PiPF as the reference, it unveiled IIP was associated with an increased mortality risk.

The strength of this study lies in being the largest ILD study in Asia with the longest study period. The data included in this study with minimal selection bias allowed accurate evaluation of the epidemiology of ILD. The prevalence and incidence of ILD, as well as survival data, was estimated for the first time in the population of Chinese dominant. Since we found a small portion of non-Chinese in the ILD cases, we ran sensitivity analysis by only including patients of Chinese ethnicity (94%). We saw similar results and patterns as those of the main analysis (Supplementary Figs. S3 and S4 and Tables S11–S15). Hence the population-based results were representative of Chinese. Given that most ILD epidemiology research were conducted in European and American population, this study provided the important epidemiological data of ILD in Chinese, particularly some subtypes showed strong ethnic-specific result, which would help policy development with drug provision planning. Nevertheless, there were limitations. First, the diagnosis and classification of ILD changed over time. Our validation study used the current international consensus in validating the studied cases, therefore the validity was up to date. Second, pharmacological, and surgical management pattern were not included in the study. Specific drug treatments like pirfenidone and nintedanib were increasingly available at the later part of the study period since 2014 and 2016. 3% of the indicated cases diagnosed after 2014 received the treatments. 1% of overall ILD patients received surgical biopsy. These numbers might imply the need of revisiting the resources planning. Third, we did not include Langerhans cell histiocytosis (LCH, ICD-9-CM: 516.5), which is generally an uncommon lung disease that is mostly seen in young adult smokers. The prevalence and incidence of LCH has been reported as very low. It is unlikely that its exclusion would significantly affect the incidence and prevalence of overall ILD. Forth, our selection of ILD subtypes was based on earlier studies,[11,29] which resulted in other subtypes of ILD and CTD-ILD not being individually reported. For example, acute interstitial pneumonia and drug-induced ILD were reported under IPP (ICD-9-CM: 516.3) and PiPF (ICD-9-CM: 515, Supplementary Table S16), respectively. On the other hand, we used the ICD-9-CM code 517.8, which corresponds to "lung involvement in other diseases classified elsewhere" to identify CTD-ILD. This code may potentially include ILD associated with Sjögren's syndrome and microscopic polyangiitis, among other conditions, but there is no further information available to determine which specific diseases are

associated with ILD. Fifth, we observed that some PiPF and IIP cases had prevalent rheumatoid diseases, which could potentially indicate CTD-ILD. However, due to the lack of consensus on whether the progressive diagnostic criteria for rheumatoid diseases should be classified as CTD-ILD, we did not classify these cases as such. This approach may underestimate the prevalence and incidence of CTD-ILD, while potentially overestimate that of PiPF and IIP. Furthermore, a high proportion of PiPF cases were observed in the study. The coding for PiPF is generally non-specific, which could lead to misclassification. However, our previous validation of diagnostic coding for ILD demonstrated that only 6% of PiPF cases were considered as non-ILD cases, while 20% were classified as other ILD subtypes. Thus, although non-specific coding for PiPF may result in an overestimation of its prevalence and incidence, its impact on the estimation of overall ILD should be minimal. Sixth, ILD cases managed by private institutes might not be included but the number of these cases should be small given the high coverage of population in CDARS. Thus, we expect only a slight underestimation of the prevalence and incidence. Seventh, we did not report cause of death of the ILD cases due to the uncertainty on the accuracy of the information. Lastly, we cannot rule out the possibility of residual confounding in the analysis of risk factors for mortality.

In conclusion, our study provides valuable epidemiological information on ILD in Hong Kong. The findings highlight the importance of monitoring trends in ILD and the potential impact of changes in clinical guidelines on disease diagnosis and coding practice. In addition, understanding the distribution patterns of ILD subtypes is particularly important given the recent availability of drugs for PiPF and IIP, which might help to guide clinical decision-making and resource allocation for ILD management. Furthermore, the short survival of ILD, as shown in our study, underscores the need for early diagnosis, appropriate subtype classification, and timely initiation of treatment. Further studies are necessary to investigate the risk and prognostic factors of ILD, as well as healthcare resources usage and costs associated with ILD management. Additionally, studies on ILD in multiple Asian cities and countries are warranted to facilitate a better understanding of the disease across populations.

Contributors

Study concept and design: Y.Y., C.L.C. Acquisition of data: S.C.H., C.W.S., C.L.C. Analysis and interpretation of data: Y.Y., S.C.H., C.W.S., C.L.C. Drafting of the manuscript: Y.Y., C.W.S. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Y.Y., C.W.S., S.C.H. Guarantors: Y.Y., C.W.S., C.L.C. Approval of final manuscript: All authors.

Data sharing statement

Data presented in this study are available upon reasonable request and conditional on ethics approval and policy of data custodian.

Declaration of interests

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100871.

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