Original Article Impact of idiopathic pulmonary fibrosis in lung cancer patients: a systematic review and meta-analysis

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Abstract: Idiopathic pulmonary fibrosis (IPF) is associated with increased risk of lung cancer. However, incidence of lung cancer in IPF patients is uncertain. Moreover, clinicopathological characteristics, clinical outcomes, and risk factors of postoperative deterioration in lung cancer patients with IPF remain unclear. Therefore, the present systematic review and meta-analysis was performed to address these issues. This study systematically searched Embase and PubMed databases, up through May 2, 2016, with a total 52 studies ultimately included. Weighted mean differences are expressed for continuous outcomes, hazard ratios for time-to-event outcomes, and relative risks for other dichotomous outcomes. Study-specific measures were combined using fixed or random effects models. Subgroup analysis was performed to identify sources of heterogeneity. During prospective follow-ups, 995 lung cancer patients with IPF were included, with an incidence of 14%. However, incidence rates were different in different countries. The highest incidence was in Japan, followed by the US. The lowest incidence was in the UK. Lung cancer patients with IPF were more frequently found in male, elderly, and heavy smoking patients. Tumors were usually located in the lower lobe and the major histologic type was squamous cell carcinoma. Patients undergoing surgical treatment showed markedly higher postoperative rates of pulmonary complications and worse prognosis. Patients with a lower preoperative percentage of forced vital capacity and higher serum LDH, CRP, and KL-6 seemed to develop acute exacerbation much easier. This meta-analysis described epidemiological and clinical characteristics in lung cancer patients with IPF. Results suggest that IPF patients may have potential risks of developing lung cancer, especially lower lobe squamous cell carcinoma. Additionally, due to bad prognosis in lung cancer patients with IPF, careful preoperative evaluation and perioperative management are necessary.

Keywords: Lung cancer, meta-analysis, idiopathic pulmonary fibrosis, systematic review, IPF

Background

Idiopathic pulmonary fibrosis (IPF), known as cryptogenic fibrosing alveolitis, is the most important subset of idiopathic interstitial pneumonias, with a histological hallmark of usual interstitial pneumonia (UIP). It is a chronic, progressive, irreversible, and devastating disease of unknown causes, with few treatment options [1-5].

Annual incidence of IPF has been rising and differs in different regions, with higher incidence in Europe and North America but lower incidence in East Asia and South America [6]. Incidence of IPF ranges from 0.48 to 93.7 cases per 100,000 people [7, 8]. Patients with IPF are often comorbid with other pulmonary disorders, including emphysema [9, 10], pneumothorax [11], lung cancer [12, 13], pulmonary hypertension [14, 15], and obstructive sleep apnea [16]. Clinical features of lung cancer patients have high consistency with IPF patients, including occurrence in elderly men, associated with smoking, and with lesions usually located in the lower lobe and periphery. Moreover, based on image examinations, the performance between lung cancer and IPF is similar, thus it is difficult to distinguish between these two diseases. Many patients have experienced missed diagnosis or misdiagnosis until the autopsy. Hironaka and Fukayama found that when patients suffered morphological evaluations in the squamous metaplasia between UIP with lung carcinoma and UIP without lung carcinoma, atypia with no significant differences was observed in both groups. This implies that the fibrosis process itself may be involved in the formation of lung cancer [17].

Based on the above, the present study analyzed the real incidence and evaluated clinicopathological characteristics and clinical outcome indicators in lung cancer patients with IPF. Acute exacerbation (AE) is the most severe pulmonary complication, postoperatively, in lung cancer patients with IPF. The present study analyzed risk factors of postoperative deterioration, establishing operative indications for these patients.

Methods

Search strategy and selection criteria

PubMed and Embase databases were searched using the following terms: pulmonary fibrosis OR fibrosing alveolitis OR usual interstitial pneumonia AND lung cancer OR lung tumor OR lung carcinoma OR lung neoplasm. The search was restricted to systematic reviews, controlled clinical trials, or randomized controlled trials and used "human" and "embase" as the qualifier when searching Embase. Moreover, academic search engines, such as Google, were used to search relevant literature. No restrictions were made regarding publication language.

Two researchers (XZ and LC) worked independently to assess every study. If there were any differences, a third researcher (LZ) was involved until a consensus was reached through group discussion. Inclusion and exclusion criteria were: (1) The etiology of pulmonary fibrosis was not mentioned in the paper; (2) Postoperative pulmonary complications included pneumonia, prolonged air leak, prolonged ventilation, atelectasis, empyema, bronchopleural fistula, and acute lung injury/acute respiratory distress syndrome (ALI/ARDS); (3) Diagnosis of IPF was accepted by histological or clinical or radiological or pathological patterns; (4) When multiple studies were published by the same author or the same agency, the most informative study was chosen for the meta-analysis; (5) Exclusion criteria included letters, editorials, reviews, case reports, and basic research.

Outcomes

Based on results, this study was split into four parts: (1) Determination of whether IPF increased the risk of lung cancer through incidence of lung cancer in IPF patients; (2) Preoperative characteristics of patients with lung cancer and IPF (IPF-LC) and lung cancer only (LC-only) included age, sex (male), smoking status, primary site (left, low), operation performed (pneumonectomy, bilobectomy, lobectomy, limited resection), pathological stage (I, II, III, IV), histological diagnosis (adenocarcinoma, squamous carcinoma, large cell carcinoma, small cell carcinoma), pulmonary function test [percent forced vital capacity (%FVC), percent forced expiratory volume in 1 second (FEV1%), percent diffusing capacity of lung for carbon monoxide (%DLCO)], arterial blood gas analyses [arterial partial pressure of oxygen (PaO₂) (mmHg), and arterial partial pressure of carbon dioxide (PaCO₂) (mmHg)]; (3) Postoperative outcome measurements in IPF-LC and LC-only included postoperative pulmonary complications, recurrence, AE, 30-day mortality, overall survival (OS), and disease free survival (DFS); (4) Preoperative characteristics of IPF-LC patients with or without AE included age, sex (male), surgery time, blood examination (white blood cell count (WBC, 10/UL), lactate dehydrogenase (LDH, IU/L), C reactive protein (CRP, mg/dl) and Krebs yon den lungen-6 (KL-6, U/ mL), pulmonary function test (%FVC, FEV1%, %DLCO), and arterial blood gas analyses [PaO, (mmHg), and PaCO₂ (mmHg)].

Data extraction

Titles and abstracts of all papers were read by XZ and LC, independently. Full-text articles were subsequently reviewed in duplicate and standard. Two authors, XZ and LC, independently, extracted information from all eligible full papers using a predefined extracted form. Extracted details included article characteristics (first author, year of publication, period of cases collection, research institute, region/ country, number of patients, study type), preoperative characteristics, and postoperative out-



Figure 1. Flow chart of study selection. IPF: Idiopathic pulmonary fibrosis; IPF-LC: patients comorbid with idiopathic pulmonary fibrosis and lung cancer.

comes. Data were checked by the third researcher (LZ) if any disagreements existed between the two researchers.

Statistical analysis

Differences are expressed as relative risks (RRs)/hazard ratios (HRs) with 95% confidence intervals (CIs) for dichotomous outcomes and weighted mean differences (WMDs) with 95% CIs for continuous outcomes. For time-to-event outcomes (OS and DFS), HRs were used as the effect size, while other dichotomous outcomes used RRs [18]. The effect measurement of HR/ RR/SMD was calculated by a random-effects model or a fixed-effects model. Heterogeneity was assessed between trials with Cochran's Q test and I² statistics. P-values and I² statistics are frequently quoted as the metric of the extent of between-study variability. P-values were easily influenced by the number of studies and I^2 was corrected by the degree of freedom. Thus, the l^2 should take precedence, with *P*-value playing a supporting role [19]. If the l^2 statistic was less than 50%, the assumption of heterogeneity was deemed invalid and a fixedeffect model was applied. Otherwise, a random-effects model was used.

The HR for time-to-event outcomes and variance were not obtained directly. These were calculated by Parmar and Tierney's techniques [18, 20]. Kaplan-Meier curves were read by Engauge Digitizer version 4.1 (http://sourceforge. net/projects/digitizer/). A funnel plot was used to investigate publication bias. All statistical analyses were performed with Stata SE 12.0. For all analyses, P-values were two tailed and the significance level was set at P<0.05.

Results

Study selection

A total of 4,379 relevant studies were searched, with 52 articles ultimately included

according to inclusion criteria. Of the 52 fulltext articles, 28 reported the incidence of lung cancer in IPF patients [12, 13, 17, 21-45], 21 described clinicopathological characteristics and postoperative outcome indicators between IPF-LC groups and LC-only groups [22, 29, 46-64], and 6 analyzed risk factors for postoperative AE of IPF-LC [46, 51, 65-68]. In all incorporated studies, 2 reported the first two contents simultaneously [22, 29], while another 2 articles showed the last two contents [46, 51]. The flow of literature search and study selection is shown in **Figure 1**.

Clinical characteristics and incidence of lung cancer in IPF

Of the 28 articles that reported incidence of lung cancer in IPF patients, 12 studies were conducted in Europe (nine in UK [12, 36-42], with one each in Italy [13], Germany [44], and Finland [43]), 3 in the United States [33-35], 4 in Korea [29-32], and 9 in Japan [17, 21-28]. Overall information was obtained from 9,152 IPF patients in all studies (7 autopsy cases [17, 22, 25, 27, 28, 33, 35], 18 case series [13, 21,

Study	Reference	Period of cases collection	Research institute	Region/Country	Cases of pulmonary fibrosis (n)	Cases of co- existent lung cancer (n)	Study type	Outcome of the research cases when diagnosed with lung cancer
Haddad 1968	[33]	-1960	Washington V.A. Hospital	US	8	3	Autopsy cases	Death
Stack 1972	[39]	1953-1970.1	Edinburgh Chest Units	UK	96	5	Case series	Uncertain
Fraire 1973	[34]	NO	Baylor College of Medicine, Houston	US	16	3	Case series	Uncertain
Turner-Warwick 1980	[38]	1955-1973	Brompton Hospital, London	UK	205	20	Case series	Uncertain
Wright 1981	[36]	1964-1976	London Chest and Brompton Hospitals	UK	31	7	Case series	Death
Tukiainen 1983	[43]	1967-1979	Helsinki University Central Hospital	Finland	44	2	Case series	Death
Kawai 1987	[27]	1970-1981	National Defense Medical College	Japan	47	8	Autopsy cases	Death
Nagai 1992	[24]	About 1980-1992	Tokyo Women's Medical College	Japan	99	31	Case series	Uncertain
Wells 1994	[37]	1979.1-1989.11	Royal Brompton National Heart and Lung Hospital	UK	127	6	Case series	Death
Matsushi 1995	[25]	1972-1992	Toranomon Hospital	Japan	83	40	Autopsy cases	Death
Harris 1998	[45]	1985-1986	Office for National Statistics (ONS)	England and Wales	1951	109	Case series	Death
Hironaka 1999	[17]	1974-1996	Jichi Medical School	Japan	70	32	Autopsy cases	Death
Hubbard 2000	[12]	-1998.4	General Practice Research Database	UK	890	39	Case control	Uncertain
Park 2001	[29]	1989.5-1998.8	Asan Medical Center in Seoul	Korea	281	63	Case control	Uncertain
Qunn 2002	[22]	1973-1996	Japanese Red Cross Medical Center	Japan	72	31	Autopsy cases	Death
Araki 2003	[28]	1978-1997	Tokyo Metropolitan Geriatric Medical Center	Japan	86	15	Autopsy cases	Death
Jeon 2006	[32]	1996.7-2002.6	Samsung Medical Center	Korea	50	4	Case series	Death
Jeune 2007	[41]	Up to 2004.11	The Health Improvement Network	UK	1064	29	Case control	Uncertain
Rudd 2007	[40]	1990.12.1-1992.11.30	British Thoracic Society Study	UK	398	47	Case series	Death
Daniels 2008	[35]	1996.1-2004.12	Mayo Clinic	US	42	0	Autopsy cases	Death
Harris 2010	[42]	1990.12.1-2001.12.31	Office for National Statistics(ONS)	UK	488	46	Case series	Death
Ozawa 2009	[23]	1986-2005	Hamamatsu University School of Medicine	Japan	103	21	Case series	Uncertain
Kurashima 2010	[26]	1997.1-2006.12	Saitama Cardiovascular and Respiratory Center	Japan	660	238	Case series	Uncertain
Kim 2012	[31]	2003.1.1-2007.12.31	The Korean Academy of Tuberculosis and Respiratory Diseases	Korea	1685	111	Case series	Uncertain
Kwaki 2014	[27]	2000.1-2011,12	Seoul National University Hospital	Korea	96	17	Case series	Uncertain
Sugino 2014	[21]	2003.4-2010.12	Toho University Omori Medical Center	Japan	108	32	Case series	Uncertain
Tomassetti 2015	[13]	2000.1.1-2012.3.31	Pulmonary Unit, G. B. Morgagni Hospital	Italy	181	23	Case series	Uncertain
Kreuter 2016	[44]	2004.1-2012.4	University of Heidelberg	Germany	171	13	Case series	Uncertain

Table 1. Main characteristics of articles which described the incidence of lung cancer in idiopathic pulmonary fibrosis (IPF) patients

subgroup	events	total	heterogeneity		ES (95% CI)
Total					
Overall	995	9152	96.7	+	0.15 (0.10, 0.20)
Outcome of the cases					
death cases	363	3668	95.1		0.15 (0.09, 0.24)
uncertain	632	5484	97.7		0.14 (0.07, 0.22)
Race humaine					
western country	352	5712	85.5	•	0.08 (0.06, 0.11)
eastern country	643	3440	96.6	→	0.24 (0.16, 0.35)
Country/Region					
US	6	66	66.6	→	0.15 (0.03, 0.49)
UK	308	5250	89	◆	0.07 (0.05, 0.10)
other western country	38	396	49	♦	0.09 (0.06, 0.15)
Japan	448	1328	80	→	0.32 (0.25, 0.39)
Korea	195	2112	95.8		0.12 (0.06, 0.26)
Decade of study compl	etion				
-1980	40	400	66.1	→	0.12 (0.07, 0.22)
1980-1990	140	2050	98.6	→	0.14 (0.02, 0.55)
1990-2000	122	1117	3.2	•	0.11 (0.09, 0.13)
2000-	196	2241	94.3	→	0.13 (0.07, 0.24)

Figure 2. Forest plots showing incidence of lung cancer in IPF patients. Heterogeneity=I² (%).

23, 24, 26, 30-32, 34, 36-40, 42-45), and 3 case controls [12, 29, 41]). Half of the articles reported mortality data of the patients (**Table 1**).

In all IPF patients, the real incidence of lung cancer was 15% (95% CI 0.10-0.20). There was, however, evidence of significant heterogeneity between the studies ($I^2=96.7\%$, P=0). To eliminate heterogeneity, subgroup analysis was conducted. When data from "Westernized countries" were combined, the incidence was 8% (95% CI 0.06-0.11). Studies from "Eastern countries" showed a higher incidence of 24% (95% CI 0.16-0.35). In view of the incidence of major differences between Eastern and Western countries, this study further analyzed incidence in different countries (US: 15%; UK: 7%; other western countries: 9%; Japan: 32%; Korea: 12%). In studies that reported incidence, some data were collected from "death cases". Thus, subgroup analysis was carried out based on patient outcomes when diagnosed with lung cancer. When studies were restricted to those from the "death cases" group, incidence was higher than other groups (15% versus 14%). Considering the lengthy timespan of cases collected, incidence in different time periods was observed. Compared with total incidence, there were no significant differences in each phase (total: 15%; before 1980: 12%; 1980-1990: 14%; 1990-2000: 11%; after 2000: 13%). Despite attempting subgroup analysis, heterogeneity between studies still existed (**Figure 2**).

Clinicopathological characteristics and outcome indicators of lung cancer patients with or without IPF

A total of 21 studies compared clinicopathological factors in lung cancer patients, with and without IPF. Of these, 16 studies were from Japan [22, 46-48, 50-60, 69], 3 from Korea [29, 61, 62], and 1 each from the United States

Study	Reference	Period of cases collection	Research institute	Region/ Country	IPF Pattern	Non-IPF Pattern	Extraction of indicators
Hashimoto 2016	[57]	2006.1-2011.12	Nagoya University Hospital	Japan	19	387	bdhklmop2457
0mori 2015	[50]	2004.1-2011.12	Kanagawa Cardiovascular and Respiratory Center	Japan	46	57	abdghjklmopstuvw1345
Fukui 2016	[59]	2008.1-2013.3	Juntendo University School of Medicine	Japan	84	950	abfjklmopstuw
Lee 2014	[61]	2003.5-2012.4	Seoul National University Bundang Hospital	Korea	33	66	abcdefklmopstuw 1567
Goto 2014	[58]	1995-2008	National Hospital Organization Tokyo Medical Center	Japan	65	322	abefghijklmnopq345
Kumagai 2014	[52]	2007.1-2012.12	Kitano Hospital	Japan	22	245	bcdeghjkImopst256
Usui 2011	[47]	2002.4-2009.9	NTT Medical Center	Japan	15	623	bdfopqr
Saito 2011	[48]	1994.9-2007.12	Saitama Cardiovascular and Respiratory Center	Japan	28	322	abfjopstuv(1)(3)(5)(7)
Kenmotsu 2011	[53]	2002.8-2010.4	Shizuoka Cancer Center	Japan	69	40	bopr ²
Jeon 2010	[62]	2003.3-2008.12	Sungkyunkwan University School of Medicine	Korea	42	168	abdghijop
Chida 2008	[69]	1996.11-2008.3	Ohta-Nishinouchi Hospital	Japan	91	743	3
Watanabe 2008	[46]	1994.1-2006.6	Sapporo Medical University School of Medicine	Japan	56	802	abeghijklmnopstw134567
Bando 2008	[60]	1991.1-2003.12	Jichi Medical University Hospital	Japan	22	142	abd
Kushibe 2007	[51]	1990.1-2005.12	Nara Medical University Hospital and Nara Prefectural Hospital	Japan	33	1030	abcdghjst①③
Kumar 2003	[64]	1991-2000	Royal Brompton Hospital	UK	24	964	bdghj③
Hayakawa 2003	[56]	1994-1997	Not mentioned	Japan	22	22	bopr
Qunn 2002	[22]	1973-1996	Japanese Red Cross Medical Center in Tokyo	Japan	31	226	abfopqr
kawasaki 2001	[55]	1992.8-1997.12	National Cancer Center Hospital East	Japan	53	658	dklmnopqrstuv
Aubry 2002	[63]	1990-1998	Rochester Mayo Clinic database	US	24	532	abf
kawasaki 2002	[54]	1992.8-1997.12	National Cancer Center Hospital East	Japan	53	658	befghj156
Park 2001	[29]	1989.5-1998.8	Asan Medical Center in Seoul	Korea	63	2660	abdopgr

Table 2. Report of clinicopathological characteristics and clinical outcome indicators of lung cancer patients with or without IPF

a=Age; b=Male; c=body mass index(BMI); d=Smoker; e=Left; f=Low; g=pneumonectomy; h=lobectomy; i=bilobectomy; j=limit resection; k=pathological stage I; l=pathological stage II; m=pathological stage II; n=pathological stage I; n=pathological stage I; n=pathological stage I; n=pathological stage II; n=pathological stage I

					Analysis			RR or			
Items	Total	cases number	Test for H	Test for Heterogeneity mode		Test for	r Overall Effect	WMD	95%CI		
	IPF	Non-IPF	I ²	Р		Z	Р			Invalid Line	
										1	
Age	527	7277	27.70%	0.173	fixed	7.4	<0.00001	0.35	(0.26,0.44)	•	
Male	751	10216	83.90%	<0.00001	random	6.48	<0.00001	1.27	(1.18,1.36)	•	
BMI	88	1341	0.00%	0.903	fixed	1.46	0.144	0.17	(-0.06,0.40)	•	
Smoker	372	7000	94.20%	<0.00001	random	4.38	<0.00001	1.32	(1.16,1.49)	•	
Primary site											
Left	229	2093	0.00%	0.817	fixed	1.02	0.306	1.09	(0.92,1.29)	+	
Low	333	3699	29.80%	0.19	fixed	7.94	<0.00001	1.61	(1.43,1.81)	+	
Operation performed	1										
Pne	340	4246	0.00%	0.621	fixed	1.06	0.287	0.75	(0.44,1.28)	· →	
Lob	360	4633	71.70%	< 0.00001	random	0.09	0.925	1.00	(0.91,1.08)	+	
Bilob	163	1292	0.00%	0.617	fixed	1.29	0.198	0.55	(0.22,1.36)	→	
Limit	453	5518	74.20%	< 0.00001	random	0.88	0.38	1.28	(0.74,2.24)	- +	
Pathological stage											
I	378	3487	0.00%	0.779	fixed	4.58	<0.00001	0.79	(0.71,0.81)	•	
п	378	3487	22.10%	0.254	fixed	3.13	0.002	1.46	(1.15,1.84)	→	
ш	378	3487	0.00%	0.713	fixed	1.44	0.15	1.17	(0.94,1.45)		
IV	174	1782	0.00%	0.5	fixed	1.85	0.064	1.75	(0.97,3.15)	r •	
Histological											
Ad	648	7549	63.10%	0.001	random	4.28	<0.00001	0.70	(0.59,0.82)	•	
Sq	648	7549	87.40%	<0.00001	random	3.82	<0.00001	1.86	(1.35,2.55)		
Large	227	4489	53.50%	0.072	random	0.49	0.622	1.35	(0.41,4.39)	+	
Small	253	4229	0.00%	0.607	fixed	1.02	0.308	1.18	(0.86,1.61)	+	
%FVC	355	4130	48.60%	0.059	fixed	4.72	< 0.00001	-0.27	(-0.38,-0.16)	•	
FEV1%	355	4130	49.60%	0.053	fixed	0.3	0.765	0.02	(-0.10.0.13)	+	
PaO2, mm Hg	244	2053	42.90%	0.136	fixed	2.87	0.004	-0.20	(-0.34,-0.06)	•	
PaCO2, mm Hg	127	1037	80.50%	0.006	random	1.15	0.25	-0.27	(-0.73,0.19)		
%DLCO	219	1875	86.90%	<0.00001	random	3.38	0.001	-0.76	(-1.200.32)	-	

Figure 3. Characteristics of lung cancer patients with or without IPF. Pne=pneumonectomy; Lob=lobectomy; Bilob=bilobectomy; Limit=limit resection; Ad=adenocarcinoma; Sq=squamous carcinoma; Large=large cell carcinoma; Small=small cell carcinoma; RR=relative risks; WMD=weighted mean differences; IPF=Idiopathic pulmonary fibrosis.

[63] and UK [64]. Demographics, clinicopathological features at presentation, preoperative pulmonary function tests, and arterial blood gas analyses of patients in IPF-LC groups and LC-only groups are summarized in Table 2. Compared to lung cancer patients without IPF, the distribution of IPF-LC cases was restricted to male (RR 1.27, 95% Cl 1.18-1.36; P<0.00001), smoking (RR 1.32, 95% CI 1.16-1.49; P<0.00001), and elderly age (SMD 0.35, 95% CI 0.26-0.44; P<0.00001) groups, with lesions usually located in the lower lobe (RR 1.61, 95% CI 1.43-1.81; P<0.00001). There were no significant differences in BMI, primary site (left), and operation performed (pneumonectomy or lobectomy or bilobectomy or limited resection) between the two groups. Based on pulmonary function and arterial blood gas analysis tests, %FVC (SMD -0.27, 95% CI -0.38--0.16; P<0.00001), PaO, (SMD -0.20, 95% CI -0.34--0.06; P=0.004), and %DLCO (SMD -0.74, 95% CI -0.89--0.58; P<0.00001) were significantly lower in the IPF-LC group than the LC-only group, while FEV1% and PaCO₂ were not statistically significant between the two groups. Adenocarcinoma, however, was significantly more frequent in the LC-only patients than in IPF-LC patients (RR 0.70, 95% CI 0.59-0.82; P<0.00001), whereas squamous cell carcinoma showed the opposite trend (RR 1.86, 95% CI 1.35-2.55; P<0.00001). There were no significant differences in other histological type (small or large cell lung cancer) between the two groups. In terms of pathological stages of lung cancer, the proportion of patients at stage I was significantly higher in the LC-only group (RR 0.79, 95% CI 0.71-0.81; P<0.00001), while patients in IPF-LC groups were mostly at stage II (RR 1.46, 95% CI 1.15-1.84; P=0.002). For stage III and IV patients, incidence in the IPF-LC group was slightly higher, but no statistical significance was observed (Figure 3).

Postoperative events in IPF patients with or without lung cancer

Postoperative events are listed in **Figure 4**. In patients undergoing surgical treatment, postoperative pulmonary complication was signifi-

						Test	for Overall			Invalid line
Items	Total cas	ses number	Test for H	leterogeneity	Analysis model		Effect	RR or HR	95%CI	
	IPF	Non-IPF	I^2	Р		Z	Р			
Postoperative pulmonary complication	249	2935	87.60%	<0.00001	random	3.35	0.001	3.01	(1.58,5.73)	• -
Recurrence	110	672	52.10%	0.124	random	1.51	0.132	1.65	(0.86,3.19)	•
AE	343	4240	35.90%	0.154	fixed	11.68	<0.00001	14.59	(9.30,22.88)	_
30day mortality	186	1568	0.00%	0.97	fixed	3.16	0.002	5.38	(1.90,15.27)	
Overall survival for all stage	294	2583	49.40%	0.054	fixed	11.2	<0.00001	1.17	(0.96,1.37)	•
Overall survival for stage I	91	1186	55.80%	0.079	random	5.09	<0.00001	1.76	(1.08,2.44)	•
Disease free survival	136	1495	71.70%	0.014	random	3.75	<0.00001	1.2	(0.57,1.83)	•

Figure 4. Postoperative morbidity and mortality in lung cancer patients with or without IPF. RR=relative risks; HR=hazard ratios; IPF=Idiopathic pulmonary fibrosis; AE=acute exacerbation.

cantly worse in the IPF-LC group than the LC-only group (RR 3.01, 95% CI 1.58-5.73; P=0.001). Patients in the IPF-group had a significantly higher incidence of postoperative AE (ALI/ARDS) than those in the other group (RR 14.95, 95% CI 9.30-22.88; P<0.00001). However, postoperative recurrence was similar between the two groups (RR 1.65, 95% CI 0.86-3.19; P=0.132). According to survival analysis, compared with the LC-only group, the IPF-LC group was significantly worse in short-term (30day) mortality (RR 5.38, 95% CI 1.90-15.27; P=0.002), OS for all stages (HR 1.17, 95% CI 0.96-1.37; P<0.00001), OS for stage I (HR 1.76, 95% CI 1.08-2.44; P<0.00001), and DFS (HR 1.2, 95% CI 0.57-1.83; P<0.00001). When analyzing OS for all stage patients, the IPF-LC group showed 17% of increased risk of death (HR 1.17), but it was much lower than that in stage I patients (17% vs 76%; HR 1.17 vs 1.76).

Postoperative events in IPF patients with concomitant lung cancer

Six studies from Japan analyzed perioperative risk factors of AE of IPF-LC. Preoperative profiles related to age, sex (male), surgery time, and blood loss were similar between AE and No-AE groups. Pulmonary function and arterial blood gas analysis tests showed significant differences in preoperative conditions in the presence of AE regarding %FVC (SMD -0.96, 95% CI -1.48--0.44; P<0.00001), whereas FEV1%, %DLCO, PaO₂, and PaCO₂ were not different between the two groups. This study collected all laboratory data from each study and carried out subgroup analysis. Although several reports have shown that serum LDH, CRP, and KL-6 can be used as preoperative risk factors of AE after surgical treatment for IPF-LC patients, no significant differences in laboratory tests were observed between AE and no-AE groups (**Figure 5**).

Discussion

The etiology of IPF and causal mechanisms of cancer remain unclear. However, it has been generally accepted that IPF increases the risk of lung cancer. The most likely explanation for this phenomenon is inflammation in lung tissues. Recently, evidence has suggested that inflammation plays a vital role in the development of lung cancer [70, 71]. Carcinogenic mechanisms suggesting that inflammation may increase the risk of cancer include three sections: increased genetic mutation [72], antiapoptotic signaling [73], and angiogenesis [74].

Based on merged data from all over the world, lung cancer occurs in 15% of IPF patients. Incidence varies in different countries, with the highest incidence in Japan. In this study, results that relied on "death cases" tended to produce higher estimates, compared with "uncertain cases". Current or ever smoking, sex (male), and age (aged) were more likely to show development of lung cancer [75, 76]. This kind of

	To	tal cases			Analysis	Test fo	or Overall	RR or		
Items	number		Test for H	Ieterogeneity	model	Effect		WMD	95%CI	Invalid Line
	EXA	Non-EXA	I^2	P		Z	P			
									(
Age	42	214	0.00%	0.567	fixed	0.43	0.668	-0.07	(-0.42,0.27)	
Male	42	214	0.00%	0.752	fixed	0.12	0.906	0.99	(0.89,1.11)	•
surgery time	27	156	0.00%	0.914	fixed	0.38	0.707	-0.08	(-0.50,0.34)	_ _
blood loss	14	85	0.00%	0.976	fixed	1.79	0.074	0.52	(-0.05,1.09)	⊢ •──
blood examization										
WBC(10/UL)	27	161	16.00%	0.311	fixed	1.52	0.129	0.32	(-0.09,0.74)	+⊷
CRP(mg/dl)	42	214	84.20%	<0.00001	random	1.33	0.185	0.60	(-0.29,1.50)	_ ↓ ◆
LDH(IU/L)	35	174	51.90%	0.08	random	1.25	0.21	0.35	(-0.20,0.90)	+
KL-6(u/ml)	23	134	76.10%	0.006	random	1.19	0.233	0.61	(-0.39,1.60)	_ _
SP-D(ng/ml)	11	92	0.00%	0.722	fixed	0.09	0.928	-0.03	(-0.66,0.60)	
Pulmonary function tests										1
%FVC	42	214	52.30%	0.063	random	3.63	<0.00001	-0.96	(-1.48,-0.44)	→
FEV1%	33	195	62.60%	0.03	random	0.54	0.588	0.17	(-0.45,0.80)	 •
PaO2, mm Hg	42	214	0.00%	0.919	fixed	0.63	0.53	-0.11	(-0.45,0.23)	_ • -
PaCO2, mm Hg	38	162	51.00%	0.086	random	0.25	0.801	0.07	(-0.45,0.59)	_ -
%DLCO	35	174	32.60%	0.204	fixed	0.54	0.589	-0.10	(-0.48,0.27)	_ _

Figure 5. Risk predictors of postoperative AE. RR=relative risks; WMD=weighted mean differences; EXA=exacerbation.

situation is even worse in IPF-LC patients. As for stages of lung cancer, it was found that IPFrelated lung cancer was more common in stage Il patients, but rare in stage I patients (Figure **3**). This can be explained by the difficulty of screening small tumors under the shadow of IPF through imagological examinations. This study did not find, however, significant higher incidence in pathologic stage III and IV in IPF-LC patients. Only surgically-resected cases were studied but lots of stage III/IV patients could not tolerate surgery. Thus, a definite conclusion on this issue could not be reached. Regarding histologic type of lung cancer, squamous cell carcinoma was significantly more frequent in the IPF-LC group (Figure 3). This is possibly because IPF-LC was more commonly found in heavy smoking patients and the risk of squamous cell carcinoma was increased rapidly with increased smoking duration [75, 77, 78]. It is also reported that small-cell lung cancer showed the strongest association with smoking [75, 77, 78], but this study did not observe high incidence of small cell lung cancer in heavy smoking patients (IPF-LC group). Patients with small-cell lung cancer did not conform to the indications of surgical removal, resulting in data deficiency. In this series, preoperative PaO, and %FVC levels were lower in the IPF-LC group, but incidence of postoperative pulmonary complications was significant higher in this group. These results may indicate that IPF-LC patients have less functional potential to tolerate pulmonary resections. When survival outcomes were compared between the two

groups, patients in the IPF-LC group showed significantly worse prognosis. Surprisingly, stage I patients in the IPF-LC group had a 76% increased risk of death, compared with same stage patients in the LC-only group (**Figure 4**). OS in stage I group was longer than all stage groups. IPF, as a fatal factor, resulted in a median survival of 3 to 5 years [79, 80]. Therefore, for stage I patients in IPF-LC group, risk of death may be mainly caused by IPF.

Postoperative AE was associated with high mortality rates after surgical treatment for primary lung cancer, mostly found in the IPF-LC group. Even though significant differences were not found, WBC, serum CRP, serum KL-6, and LDH were markedly increased in the AE group. Suzuki et al. [65] reported that cytokeratin fragments were higher in the AE group. Only one study reported this phenomenon, however, thus it was not merged into the present research. For pulmonary function tests, IPF patients with postoperative AE had significantly lower values of preoperative %FVC than the other group. The present study demonstrated that when IPF-LC patients suffer low preoperative %FVC and higher blood examinations (Shintani et al. [66] used preoperative %FVC (<80.6%) and LDH (≥241 IU/L) as predictive factors), they should be very carefully assessed prior to surgical removal. It has been reported that AE after thoracic surgery for lung cancer can be caused by excessive fluid infusion. Mizuno et al. [67] also found that patients that developed postoperative AE of IPF-LC also

received excessive fluid infusions. Presented intraoperative fluid balance should be restricted to within 5 mL/kg/h.

Several limitations to this meta-analysis are noteworthy. First, meta-analysis is commonly used in randomized-controlled trails (RCTs). Observational studies can be used in metaanalyses only if no RCTs are available. Present results were obtained from observational studies. Thus, present results may be controversial. Second, it is difficult to find a primary lung cancer shadow in IPF patients, therefore, incidence of lung cancer in IPF patients might be smaller than the real value. This may have resulted in selection bias. Third, all six studies that explored risk factors of AE in IPF-LC patients were from Japan. Present conclusions may only apply to Japanese patients. Although this is the largest study so far analyzing the risk factors of postoperative deterioration, these factors need to be further validated. Fourth, nearly all HRs and variances were not reported directly. These data were estimated from survival curves and may might differ from first-hand data. Fifth, confounding by a factor could also explain the worse prognosis in IPF-LC group patients. For example, IPF-LC patients showed higher tumor stage. This may have led to worse prognosis.

In conclusion, worldwide incidence of lung cancer in IPF patients is 15% but has reached up to 32% in Japan. Therefore, patients with IPF should be carefully checked to see if there is comorbid lung cancer. Compared with LC-only patients, IPF-LC is mostly found in older, male, and smoking patients. It is often located in the lower lobe, showing lower pulmonary function and less arterial blood gas, higher incidence of squamous cell carcinoma, and poorer prognosis. IPF-LC patients show more advanced pathological stages than LC-only patients. These clinical characteristics will help in the search for the pathogenesis of IPF-LC and make good nursing measures for these patients. It is necessary to take pulmonary function and blood tests for IPF-LC patients before surgery. If patients have low preoperative %FVC and high serum levels of LDH, CRP, and KL-6, they should be carefully assessed before surgical intervention. Moreover, attention should be paid to prevent excessive fluid infusion in patients undergoing pulmonary resections. More clinical studies are needed to assess risk factors of AE in IPF-LC patients, determining their critical value.

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Disclosure of conflict of interest

None.

Authors' contribution

XZ, CW, and YZ contributed to the conception of the study and drafted the manuscript. The search strategy was developed by all authors. XZ and LC participated in searching extracting data. LZ arbitrated in cases of disagreements and ensured the absence of errors. XX, HD, JM, PJ, and BL helped to assess risk of bias and complete data synthesis. All authors read and approved the final manuscript.

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