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Lung cancer in patients with pulmonary fibrosis: characteristics features and prognosis

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Abstract. *Background and aim:* Lung cancer is one of the significant comorbidities seen in patients with Idiopathic Pulmonary Fibrosis (IPF). However, there is limited data on non-IPF Pulmonary Fibrosis (PF) patients with lung cancer (LC). The present study aims to compare the characteristics and survival outcomes of patients diagnosed with LC in IPF and non-IPF PF. *Methods:* The multicenter data records of IPF and non-IPF PF patients diagnosed with lung cancer between 2010-2022 were analyzed in this descriptive, cross-sectional, and retrospective study. *Results:* Of the 251 patients involved in this study [164 IPF-LC, 87 non-IPF PF-LC], 89.6% were male, the mean age was 69±7.9 years and the smoking rate was 85.7%. Honeycomb pattern was more frequently observed in IPF-LC patients [62.8%,37.9%p<0.001], whereas ground-glass opacity [33.5%,59.8%p<0.001] and emphysema [37.8%,59.8%p<0.001] were more frequently seen in non-IPF PF-LC patients. The most commonly seen histological type was squamous cell carcinoma [42.7%,33.9%], followed by adenocarcinoma [28.2%; 32.2%]. [46.4%;47.2%] and their 5-year mortality rates were high [64.6%, 63.2%]. The median survival for both groups was 2±0.22 years [median 95% CI (1.55-2.44)]. The shortest survival time was observed in non-IPF PF-LC subgroup with unclassified PF [1±0.253 years median 95% CI (0.50-1.49) (p=0.030)]. *Conclusions:* The majority of IPF and non-IPF PF LC patients were male, elderly, and had a high smoking rate. Squamous cell carcinoma was the most frequently seen histological type and they had short survival periods and high mortality rates. The survival period of unclassified non-IPF PF-LC patients was found to be the shortest.

Key words: pulmonary fibrosis, idiopathic pulmonary fibrosis, lung cancer, radiology, histology, mortality

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrotic interstitial pneumonia characterized by an unknown cause, limited

to lungs, typically observed in elderly adults, presenting with the histopathological and/or radiological pattern of usual interstitial pneumonia (UIP) (1). The association between pulmonary fibrosis and lung cancer (LC) was suggested as early as 1965 (2), and multiple common genetic, molecular, and cellular processes predisposing individuals to both IPF and LC developments were reported to be responsible.

It was previously emphasized that pulmonary fibrosis is solely an independent risk factor for the development of lung carcinogenesis (3-6). The incidence of lung cancer in IPF patients is estimated to be between 4.4% and 48% (7-10). Moreover, it was reported that IPF patients who develop lung cancer have a shorter survival time (11,12). However, there is no consensus on the most common histological type in IPF-LC patients. Studies examining the characteristics of lung cancer in IPF patients were predominantly carried out several decades ago. Adenocarcinoma was the most common histological type in these patients, followed by squamous cell carcinoma (SCC) (13,14). A change in lung cancer epidemiology has been reported in recent years. Most studies indicate that SCC is now the most frequently observed type of LC in IPF patients, followed by adenocarcinoma (10-12,15-17).

Connective tissue disease (CTD) refers to a group of immunologically mediated inflammatory diseases affecting various organs. CTD includes rheumatoid arthritis (RA), systemic sclerosis (SS), polymyositis and dermatomyositis (PM/DM), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), and mixed CTD. Patients with CTD are highly susceptible to respiratory system disorders, particularly interstitial lung disease (ILD). As with IPF, CTD-associated ILD might be associated with an increased risk of LC. The incidence of LC development in CTD-ILD patients is estimated to range between 6.4% to 8.8%, with risk factors for cancer in these patients including heavy cigarette smoking and the presence of combined pulmonary fibrosis and emphysema (CPFE). However, these data are based on a limited number of cases, and little is known about lung cancer in patients with other ILDs (18,19).

In this context, the present study aims to reveal the characteristic features and progression of lung cancer in patients with IPF and non-IPF pulmonary fibrosis (PF).

Material and Method

Ethical approval for the present study was obtained from the Ethics Committee of Elazığ University (2022/06-04).

Patients and study design

This study was planned as a multicenter retrospective descriptive cross-sectional study. Patients diagnosed with idiopathic pulmonary fibrosis (IPF) and non-IPF pulmonary fibrosis, who also received a histopathological diagnosis of lung cancer between January 2010 and December 2022, were included in the study by evaluating institutional records. Patients with radiologically identified lung masses but without a pathological diagnosis were excluded from the study. Demographic characteristics of patients at the moment of cancer diagnosis (age, gender, smoking history), underlying disease treatment, radiological findings, functional assessments (pulmonary function tests (PFT): annual, forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO) variability, presence of pulmonary hypertension (PHT) (determined with echocardiography), histopathological diagnoses of lung cancer, primary localization, stage, diagnostic methods, lung and distant organ metastasis, administered treatment, and 5-year mortality information were obtained from institutional records.

High-resolution computed tomography (HRCT) findings of pulmonary fibrosis cases (UIP, Probable UIP, Indeterminate UIP, alternative pattern) (1,20) and CTD diagnoses (21-23) were reviewed and recorded by the participating researchers. Patients were divided into two groups: IPF and non-IPF pulmonary fibrosis. Non-IPF pulmonary fibrosis cases were categorized as sarcoidosis, chronic hypersensitivity pneumonitis (CHP), Systemic Lupus Erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SS), polymyositis/dermatomyositis, mixed CTD, combined pulmonary fibrosis and emphysema (CPFE), and unclassified pulmonary fibrosis. Lung cancer was classified by following the World Health Organization's classification (24), and staging was performed by using the 8th edition of the TNM classification for malignant tumors (25).

Statistical analyses

The IBM SPSS Statistics Version 22.0 package program was used in statistically analyzing the data

obtained. Categorical measurements were summarized as counts and percentages, whereas continuous measurements were summarized as means and standard deviations. The Chi-square test statistic was utilized for comparing the categorical measurements between groups. The Independent Samples t-test was used for comparing continuous measurements between groups in cases, where the assumptions were met for independent groups. Survival analysis for both groups was conducted by using the Log-Rank test within the Kaplan-Meier analysis. A statistical significance level was set at $p<0.05$ for all tests.

Results

Demographic characteristics of patients

A total of 251 patients (164 with IPF-LC and 87 with non-IPF PF-LC) were included in the study. The male-to-female ratio was significantly higher in both groups (93.3% and 82.8%, respectively ($p=0.015$)). The mean age of all patients was found to be 69±7.9 years. The rate of smoking was determined to be similar in both groups (91.3% and 89.6%, respectively). Among patients with non-IPF PF-LC, 51.7% were classified as having unclassified pulmonary fibrosis subtypes. No statistically significant differences were observed between the two groups in terms of key demographic characteristics, with the exception of gender (Table 1).

Given the results of high-resolution computed tomography (HRCT) patterns, definite usual interstitial pneumonia (UIP) pattern (70.7% vs. 18.4%, $p<0.001$) and probable UIP pattern (19.6% vs. 6.9%, $p<0.009$) were more frequent in patients with IPF-LC when compared to non-IPF PF-LC. However, alternative diagnosis was more commonly identified in non-IPF PF-LC patients (1.2% vs. 18.4%, respectively, $p<0.009$). The most common HRCT finding in both groups was traction bronchiectasis (70.1% and 60.9%, respectively). On the other hand, honeycombing was higher in IPF-LC patients (62.8% vs. 37.9%, $p<0.001$), whereas ground-glass opacity (33.5% vs. 59.8%, $p<0.001$) and emphysema (37.8% vs. 59.8%, $p<0.001$) were more frequently detected in non-IPF PF-LC patients. There were no statistically significant differences between the two groups in terms of PFT, annual FVC and DLCO variability, and the presence of PHT (Table 2). In patients with

Table 1. IPF-LC and non-IPF-LC Patients' General Demographic Characteristics.

	IPF-LC	**Non-IPF PF-LC**	
	n:164 (%)	**n:87 (%)**	**p-value**
Age	69.7±7.7	67.9±8.2	0.090
Sex			
Male	153 (93.3)	72 (82.8)	**0.015**
Female	11 (6.7)	15 (17.2)	
BMI	26.6±3.8	26.3±3.3	0.561
Smoking history			
Never	14 (8.8)	8 (10.4)	0.232
Former	122 (76.3)	51 (66.2)	
Current	24 (15)	18 (23.4)	0.222
Malignancy history in family	26 (16.3)	18 (22.8)	0.450
Environmental exposure	43 (26.9)	25 (31.6)	
Non-IPF Pulmonary Fibrosis			
Sarcoidosis		4 (4.6)	
Chronic HP		8 (9.2)	
CTD-Associated Interstitial Lung Disease (CTD-ILD)		16 (18.4)	
Rheumatoid arthritis		8 (9.2)	
Systemic sclerosis		3 (3.4)	
Polymyositis/Dermatomyositis		1 (1.1)	
SLE		1 (1.1)	
Mixed-type CTD		3 (3.4)	
CPFE		14 (16.1)	
Unclassified Pulmonary Fibrosis		45 (51.7)	

BMI: Body Mass Index, SLE: Systemic Lupus Erythematosus. HP: Hypersensitivity Pneumonia, KPFA: Combined Pulmonary Fibrosis and Emphysema

Table 2. Radiological and PFT results of all cases.

	IPF-LC	Non-IPF PF-LC	
	n:164 (%)	n:87 (%)	p-value
HRCT Patterns			
Definite UIP	116 (70.7)	16 (18.4)	<0.001
Probable UIP	32 (19.6)	6 (6.9)	<0.009
Indeterminate UIP	6 (3.7)	7 (8.0)	0.146
Alternative diagnosis	2 (1.2)	16 (18.4)	<0.001
HRCT Results			
Traction bronchiectasis	115 (70.1)	53 (60.9)	0.159
Honeycomb pattern	103 (62.8)	33 (37.9)	<0.001
Ground glass	55 (33.5)	52 (59.8)	<0.001
Mosaic attenuation	19 (11.6)	11 (12.6)	0.839
Emphysema	62 (37.8)	52 (59.8)	0.001
Mediastinal LAP	79 (48.2)	51 (58.6)	0.144
PFT			
FEV1 (%)	78.69±18.76	78.75±17.69	0.837
FVC (%)	74.06±16.69	78.67±19.52	0.298
FEV/FVC (%)	82.73±9.21	81.34±10.18	0.504
DLCO	48.20±16.63	46.14±17.20	0.930
TLC	64.24±16.57	63.43±22.97	0.139
Annual >10% decline in FVC			
No change	123 (75.0)	74 (85.1)	0.076
Decline	41 (25.0)	13 (14.9)	
Annual >15% decline in DLCO			
No change	128 (78.0)	15 (17.2)	
Decline	36 (22.0)	72 (82.8)	0.238
PHT	45 (27.4)	19 (21.8)	0.559

Abbreviations: UIP: Usual Interstitial Pneumonia, LAP: Lymphadenopathy, PFT: Pulmonary Function Test, FEV1: Forced Expiratory Volume per second, FVC: Forced Vital Capacity, DLCO: Diffusion Capacity for Carbon Monoxide, TLC: Total Lung Capacity, PHT: Pulmonary Hypertension *Descriptive statistic was presented as mean ± standard deviation.

IPF-LC and non-IPF PF-LC, the most common primary localization of lung cancer was predominantly peripheral (65.9% and 59.8%, respectively) and in the lower lobes (48.8% and 47.1%, respectively). The most frequently observed histological type in both groups was squamous cell carcinoma (42.7% and 33.9%, respectively), followed by adenocarcinoma (28.2% and 32.2%, respectively). A significant proportion of patients in both groups were diagnosed at stage IV (46.4% and 47.2%, respectively). In patients with IPF-LC, the most common localization of metastasis was the contralateral lung (19.1%), whereas metastasis was most frequently observed in bone and others (lymph nodes, pleura, chest wall) at an equal rate (17.6%). No statistically significant difference was found between the two groups in any of these parameters (Table 3).

The most commonly utilized diagnostic method in IPF-AC patients is Transthoracic Fine Needle Aspiration Biopsy (TTFNAB) (33.1%), whereas Fiberoptic Bronchoscopy/Endobronchial Ultrasound (FOB/EBUS) is more frequent (37.9%) in non-IPF PF-AC patients. The majority of patients in both groups had not received any treatment for their underlying diseases (40.2% and 70.1% respectively) and chemotherapy was the most common treatment for cancer, administered to only about one-third of the patients (31.7% and 33.3% respectively). Over a mean follow-up period of 5 years, more than half of all patients were lost (64.6% and 63.2%, respectively), and the most common cause of mortality was lung cancer and respiratory failure (40.6% and 47.3%, respectively). There was no statistically significant difference between the two groups in terms of these parameters (Table 4).

The median survival time for the IPF-LC and non-IPF PF-LC group was 2±0.289 and 2±0.364 years, respectively (Figure 1A). The median survival time for both groups was 2±0.22 years (median 95% CI (1.55-2.44), p=0.665), and there was no statistically significant difference in survival between the two groups. Subtypes of non-IPF PF-LC had a

Table 3. Cancer characteristics of all cases.

	IPF-LC	Non-IPF PF-LC	
	n:164 (%)	n:87 (%)	p-value
Localization of LC			
Left lung	60 (36.6)	36 (41.4)	0.496
Right lung	99 (60.4)	50 (57.5)	0.687
Bilateral	3 (1.8)	1 (1.1)	
Upper Lobe	75 (46.0)	34 (39.5)	0.894
Middle / Lingula	16 (9.8)	15 (17.2)	0.107
Lower Lobe	80 (48.8)	41 (47.1)	0.349
Periphery	108 (65.9)	52 (59.8)	0.408
Central	37 (22.6)	32 (36.8)	0.118
Histology			
Squamous-cell carcinoma	70 (42.7)	33 (37.9)	0.807
Adenocarcinoma	47 (28.7)	28 (32.2)	
Small-cell carcinoma	31 (18.5)	19 (21.8)	
Others	16 (9.8)	7 (8.0)	
Staging			
I	27 (16.4)	15 (17.3)	0.644
II	14 (8.6)	11 (12.6)	
III	47 (28.6)	20 (22.9)	
IV	76 (46.4)	41 (47.2)	
Metastasis			
Bone	24 (15.3)	15 (17.6)	0.714
Contralateral lung	30 (19.1)	14 (16.3)	0.842
Liver	15 (9.6)	9 (10.7)	0.912
Adrenal gland	8 (5.1)	3 (3.6)	0.235
Brain	5 (3.2)	2 (2.4)	0.717
Others (Lymph node, pleura, chest wall)	17 (10.9)	15 (17.6)	0.140

shorter survival time when compared to the IPF-LC group, with a median of 1±0.253 years (median 95% CI (0.50-1.49), p=0.030) (Figure 1B).

Discussion

In the present study, the majority of patients diagnosed with IPF and non-IPF pulmonary fibrosis were and elderly (mean age 69±7.9) and male gender was high [93.3% and 82.8%, respectively]. Moreover, it was observed that the median survival time for both groups was 2±0.22 years, with high 5-year mortality rates (64.6% and 63.2%, respectively).Even though the course of IPF varies, the time from the onset of symptoms after diagnosis to end-stage respiratory failure and mortality is, on average, 2-4 years (26). Pulmonary and extrapulmonary comorbid conditions such as lung cancer can influence the course and mortality of the disease. Advanced age, male gender, smoking history, and concomitant emphysema are strong risk factors contributing to the development of LC in IPF patients (9,10). In a study investigating CTD-associated lung cancer, smoking was shown to be a risk factor for emphysema (18, 19, 27). In the present study, male gender and advanced age were dominant in both groups and smoking rates were very high (91.3% and 89.6%, respectively).The HRCT pattern is very important in the IPF diagnosis algorithm (especially Definite UIP and Probable UIP) (1,28). These criteria are also used for non-IPF interstitial lung diseases presenting with similar features. In the present study, definite UIP and probable UIP patterns were more frequently seen in IPF-LC patients in comparison to non-IPF PF-LC patients, whereas alternative diagnosis was more common in the non-IPF PF-LC group. The most common radiological HRCT finding in both groups was traction bronchiectasis, with honeycombing more frequent in IPF-LC patients and ground-glass opacity and emphysema more frequently detected in non-IPF PF-LC patients. The high frequency of emphysema in the non-IPF PF-LC group in the present study was an interesting result. This result can be explained primarily by the high rates of smoking among patients (89.6%). However, on the other hand, the smoking rate was also considerably high in the IPF-LC group

Table 4. Diagnostic and treatment characteristics and mortality of all cases.

	IPF-LC	Non-IPF PF-LC	
	n:164 (%)	n:87 (%)	p-value
Modality of diagnosis			
FOB/EBUS	51 (31.3)	33 (37.9)	0.313
TTFNAB	54 (33.1)	27 (31.0)	
Mediastinoscopy	2 (1.2)	2 (2.3)	
Surgery	46 (28.2)	16 (18.4)	
Others	11 (6.7)	9 (10.3)	
Treatment of underlying diagnosis			
Steroid	21 (12.8)	13 (15.0)	-*
Nintedanib	42 (25.6)	4 (4.6)	
Pirfenidone	34 (20.8)	6 (6.9)	
Steroid + Nintedanib	-	2 (2.2)	
Steroid+ Pirfenidone	1 (0.6)	1 (1.2)	
Untreated	66 (40.2)	61 (70.1)	
Cancer treatment			
Untreated	29 (17.7)	17 (19.6)	0.528
Chemotherapy (CT)	52 (31.7)	29 (33.3)	
Radiotherapy (RT)	9 (5.5)	7 (8.0)	
CT/RT	37 (22.5)	12 (13.8)	
Surgery	22 (13.4)	16 (18.4)	
Palliative Treatment	15 (9.1)	6 (6.9)	
Death during follow-up			
Deceased	106 (64.6)	55 (63.2)	0.287
Living	37 (22.6)	15 (17.2)	
Unknown	21 (12.8)	17(19.5)	
Cause of mortality			
Respiratory failure + Lung cancer	43 (40.6)	26 (47.3)	
Primary respiratory failure	29 (27.4)	12 (21.8)	
Lung cancer	13 (12.3)	2 (3.6)	
Cardiac MI	4 (3.8)	1 (1.8)	
Pulmonary Thromboembolus	2 (1.9)	1 (1.8)	
Other	2 (1.9)	2 (3.6)	
Unknown	13 (12.3)	11 (20.0)	

Abbreviations: FOB: Fiberoptic Bronchoscopy, EBUS: Endobronchial Ultrasonography, TTFNAB: Transthoracic Fine Needle Aspiration Biopsy, MI: Myocardial Infarction -* p-value is not presented due to the loss of statistical significance.

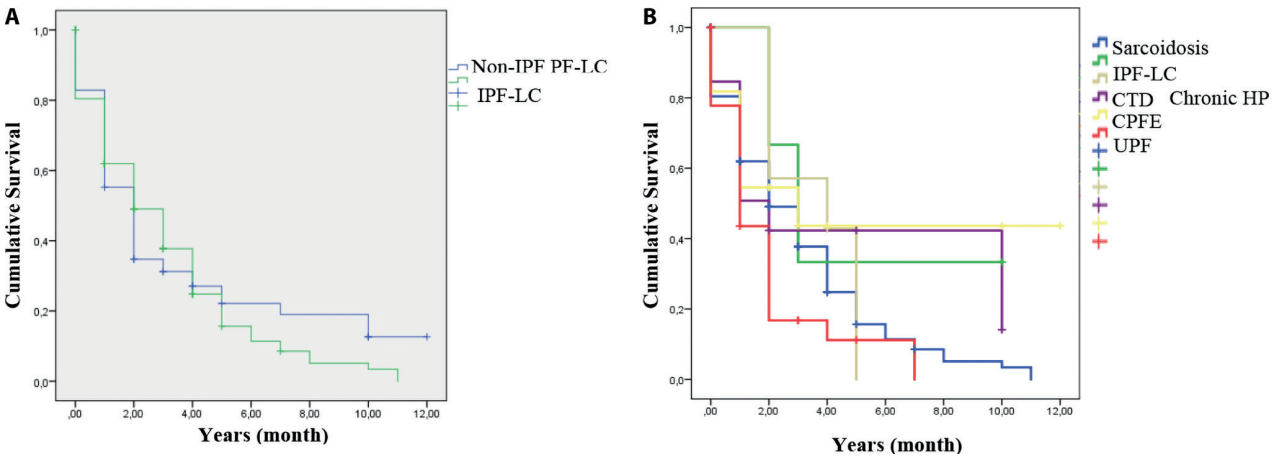

Figure 1. Kaplan-Meier survival curve. (A) Survival curve of IPF-LC and non-IPF PF-LC patients, (B) Survival curve of subgroups of IPF-LC and non-IPF PF-LC patients (sarcoidosis, chronic hypersensitivity pneumonitis (HP), connective tissue disease (CTD), Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Systemic Sclerosis (SS), polymyositis/dermatomyositis, Mixed Connective Tissue Disease, Combined Pulmonary Fibrosis and Emphysema (CPFE), Unclassified Pulmonary Fibrosis (UPF).

(91% and higher) Therefore, it is thought that this result might be primarily due to the lack of mention of emphysema in the radiological reports in the data records, and the second reason might be the lower number of non-IPF PF-LC patients when compared to the other group.In patients with IPF, lung carcinomas often appear in the peripheral areas of the lungs, particularly in the lower lobes and areas with honeycomb lesions (2,10,11). The border between honeycomb areas and non-fibrotic areas, where epithelial metaplasia develops, is more frequently observed in IPF-LC patients. It is hypothesized that this phenomenon may reflect a structural predisposition for lung carcinoma development in IPF patients (29). In the present study, the primary localization of lung cancer in both IPF-LC and non-IPF PF-LC patients was most commonly peripheral and in the lower lobes.

Another finding in this study was that a significant proportion of patients in both groups were in an advanced stage (stage IV) at the time of diagnosis. Furthermore, metastases were most commonly found in the contralateral lung in IPF-LC patients, whereas metastases were detected most frequently in various organs such as bones, lymph nodes, pleura, and chest wall, with equal frequency in non-IPF PF-LC patients. In another single-center study comparing the characteristic features of lung cancer in IPF and non-IPF interstitial lung diseases (30), and in other studies examining LC characteristics in both IPF (11) and non-IPF interstitial lung diseases (19), it was also found that the majority of patients were diagnosed at stage IV. In the general population, the predominant type of non-small cell lung cancer (NSCLC) is adenocarcinoma (LC). Similarly, NSCLC is also the dominant subtype of LC in patients with IPF- LC. Adenocarcinoma is the most common histological subtype of NSCLC in the general population (31). The most common histological subtype of LC in IPF has been controversial in recent years. Most recent studies indicate that squamous cell carcinoma (SCC) is the most frequently observed LC type in IPF patients, followed by adenocarcinoma (10-12,15-17). Similarly, in a study examining CTD-associated LC characteristics, SCC was found to be the most common histological type, but the number of studies on this topic is limited (27). In the present study, NSCLC was the most common histological type in both groups, with LC being the predominant histological type, followed by adenocarcinoma. The onset and progression of IPF lead to significant changes in the anatomical structure and biomechanical characteristics of the lungs, often resulting in respiratory failure due to impaired alveolar gas exchange and decreased lung function (32). IPF patients diagnosed with LC have a lower average survival time (1.6-1.7 years) when compared to IPF patients without LC (15,16). Kato et al. reported 1-, 3-, and 5-year all-cause mortality rates of 53.5%, 78.6%, and 92.9%, respectively, after the diagnosis of LC in IPF patients (10). Similarly, several studies showed that the development of lung cancer reduces survival in patients with connective tissue diseases and interstitial lung diseases. An observational study investigating CTD-associated LC revealed that LC is associated with a poor prognosis (19,27). Kreuter et al. determined the mean survival time among IPF patients with LC to be 20 months (33). In the present study, the median survival time for both groups were 2 ± 0.22 years, and there was no statistically significant difference in survival between the two groups (Figure 1A). Moreover, during an average 5-year follow-up in both groups, it was observed that more than half of the patients died and the most common cause of mortality was lung cancer accompanied by respiratory failure. Another important result documented in this study was that the majority of these patients did not receive any treatment for their underlying diseases. Furthermore, although chemotherapy was the most common treatment for cancer, it was only administered to approximately one-third of the patients. There is no consensus on lung cancer treatment in this group of patients. However, recent data showed that, even though two approved antifibrotic drugs, pirfenidone and nintedanib, may increase the survival time of IPF patients and reduce the incidence of LC, there is no effective therapeutic treatment that eliminates the progression of IPF and the associated risk of lung cancer initiation (34). An important result achieved in the present study is that, when separately comparing non-IPF PF-LC subtypes to IPF-LC, the survival time of patients with unclassified pulmonary fibrosis was 1±0.253, which was shorter than the others (p=0.030) (Figure 1B). This result is a new one that is not found in the literature, and it is difficult to interpret its causes. However, it is thought that there may be several possible causes. An important reason for the lower survival time may be the distribution of subtypes of non-IPF PF-LC, with more than half of the patients belonging to this group. Another

reason could be that, besides the CDT accompanied by pulmonary fibrosis, lung cancer itself might have contributed to mortality by laying the foundation for respiratory failure. Further studies are needed to investigate this group.

Limitations of this study include its retrospective nature and the use of hospital data records from multiple centers. Even though the institutional data records were carefully analyzed, there were records with insufficient information. Nevertheless, this study is the first multicenter study carried out in Türkiye.

Conclusion

In conclusion, the majority of patients diagnosed with LC in both IPF and non-IPF pulmonary fibrosis were male and elderly and had a significantly high smoking rate. Lung cancer was observed more frequently in the lower lobes and periphery. The most common radiological findings were traction bronchiectasis, honeycombing, emphysema, and ground-glass opacity. Squamous cell carcinoma was the most frequently observed histological type and they were at advanced stages when diagnosed, with short survival times and high mortality rates. The survival time of patients with unclassified non-IPF pulmonary fibrosis-associated lung cancer was the shortest.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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