

Risk of Drug-Induced Interstitial Lung Disease in Korean Patients With Lung Cancer: A Nested Case-Control Study

Il-Hyung Hwang^{1,2}, Seung Hyeun Lee³ and Hankil Lee^{*1,2}

¹Department of Biohealth Regulatory Science, Graduate School of Ajou University, Suwon, South Korea

²Ajou University College of Pharmacy, Suwon, South Korea

³Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, South Korea

(Presenting author: challyhwang@ajou.ac.kr, *Corresponding author: hankil@ajou.ac.kr)

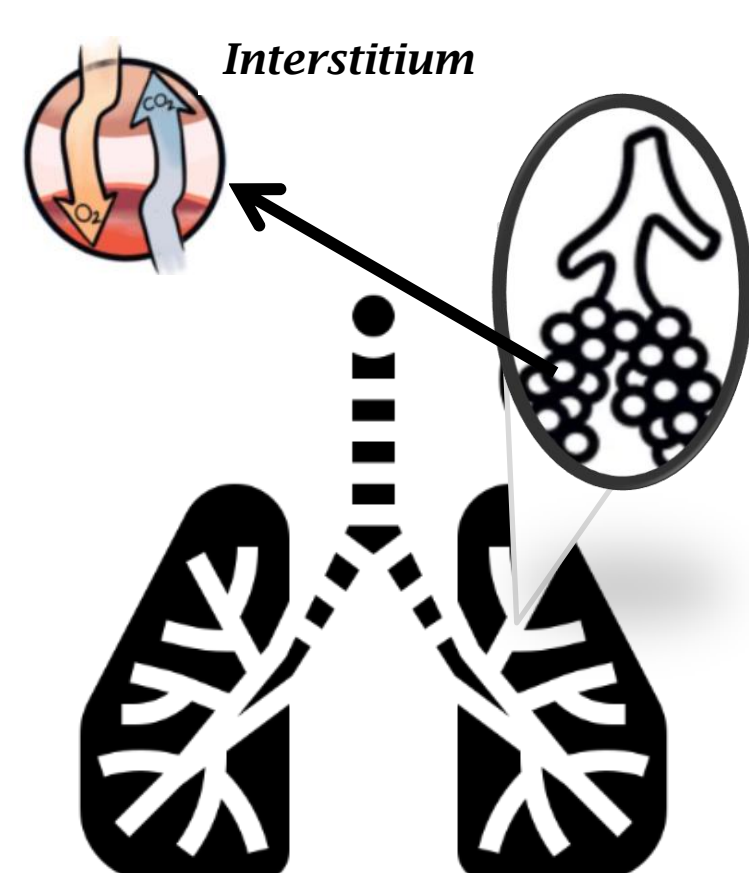
KEYWORDS

Drug-Induced Interstitial Lung Disease (DIILD); Lung Cancer; Anticancer drugs; Real-world data (RWD)

BACKGROUND

Drug-Induced Interstitial Lung Disease

- **Drug-induced interstitial lung disease (DIILD)** is a rare condition, but it can cause lung inflammation or lung fibrosis and, in severe cases, can lead to death.
- Hundreds of drugs are known to cause DIILD, and anticancer drugs account for half of the total cases. DIILD is difficult to identify because there are no accurate diagnostic and treatment methods.



RESULTS

Baseline Characteristics

After the matching by risk-set sampling, the baseline characteristics of the 934 cases and 9,136 matched control subjects were well balanced.

	Cases (n=934)	Matched Control (n=9,136)	P value
Age(years)			0.86
30-39	4	13	
40-49	20	169	
50-59	111	1,107	
60-69	366	3,615	
70-79	365	3,591	
80-89	68	641	
Sex			0.85
Male	754	7,399	
Female	180	1,737	
CCI scores			0.85
1-3	359	3,720	
4-6	286	2,363	
>6	221	2,374	
Missing	68	678	
Medical history			
Hypertension	354	3,645	0.22
Diabetes	294	2,839	0.56
Dyslipidemia	396	3,589	0.09
Cardiovascular disease	214	1,981	0.35
Cerebrovascular disease	128	1,125	0.26
Peripheral vascular disease	42	385	0.85
Chronic lung disease	529	4,596	0.00
(Mild) Liver disease	164	1,692	0.41

DIILD risks by drug categories

Drug category	Cases		Matched Controls		Odds Ratio ¹⁾		
	n	(%)	n	(%)	OR	95% CI	P value
ICIs	133	1.5%	840	9.2%	1.65	1.36 - 2.02	<0.0001
EGFR inhibitors	108	1.2%	1,477	16.2%	0.63	0.51 - 0.79	<0.0001
Multikinase inhibitors	38	0.4%	236	2.6%	1.59	1.12 - 2.26	0.01
Cytotoxic agents	644	7.0%	6,384	69.9%	0.96	0.83 - 1.12	0.61
Any combination	8	0.1%	128	1.4%	0.61	0.30 - 1.25	0.17

¹⁾ Mantel-Haenszel common odds ratios were calculated, stratified by sex and age. CI = Confidence Interval; EGFR = epidermal growth factor receptor; ICIs = Immune checkpoint inhibitors; OR = odds ratio

OBJECTIVES

This study aims to investigate the risk of DIILD according to the category of anticancer drugs in Korean patients with lung cancer.

METHODS

Study design

Database	Customized Claims data by the Korean Health Insurance Review and Assessment(HIRA)
Study type	Nested case-control study
Case	Patients diagnosed with lung cancer and developed DIILD
Control	Patients diagnosed with lung cancer and NOT developed DIILD
Matching	- Risk-set sampling, maximum 1:10 matching - Matching variable: same age, sex, and enrollment date (± 30 days)
Statistical Analysis	- Baseline characteristics were summarized descriptively. - To evaluate the risk of DIILD associated with anticancer drugs, Mantel-Haenszel common odds ratios were calculated, stratified by sex and age.
Exposures	Anticancer drugs categories (immune checkpoint inhibitors (ICIs), EGFR inhibitors, multikinase inhibitors, cytotoxic agents, and any combination with different categories)
Outcomes	- Patients' characteristics - The risk of DIILD associated with anticancer drug categories



Patients with anti-cancer drugs who were diagnosed with lung cancer, 2017-2021 (n=87,873)

Excluded:
History of anti-cancer drugs treatment (n=12,543)
History of ILD occurrence (n=3,769)
History of corticosteroid administration within 1 year (n=27,642)
Personal history of COVID-19 or Post COVID-19 condition (n=222)

Study Cohort: Patients with antineoplastic drugs who were newly diagnosed with lung cancer without ILD history (n=43,697)

Cases: Patients occurred with ILD (n=936)

Controls: Patients NOT occurred with ILD (n=42,761)

1:10 risk set matching
Excluded: Cases for whom no matched control patients (n=2)

Matched Cohort (n=10,070)

Cases (n=934)

Matched Controls (n=9,136)

EGFR = epidermal growth factor receptor

CONCLUSION

Incident DIILD differs significantly by the categories of anticancer agents. Our findings underscore the importance of careful consideration when selecting and administering specific antineoplastic agents. However, further long-term studies are required to identify the risk factors for DIILD.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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DISCUSSION

The 1st study to evaluate the characteristics of patients with DIILD, and the risks associated with various categories of anticancer drugs among all Korean patients with lung cancer using nationwide database.

- DIILD was more prevalent in males, older patients, and those with a history of chronic lung disease, which is consistent with previous findings. Notably, the proportion in men is 80%, which is higher than previously reported, and this increase is thought to be attributable to lung cancer.
- The smoking history that could not be included in this study may be associated with the higher risk observed in men.
- Among the mechanisms underlying the development of DIILD, immune-related responses are involved. In elderly individuals, immune suppression is thought to be a contributing factor.

What are the findings to be associated between DIILD and anti-neoplastic drugs?

- **Immune checkpoint inhibitors:** Immune checkpoint inhibitors, which activate the immune system, are associated with adverse events, including the development of DIILD, with reported incidence rates ranging from 0.9% to 22.7%. This study also indicates a high association with incident DIILD.
- **EGFR inhibitors:** Ethnic differences have been observed in the incidence of ILD. Despite both populations being Asian, DIILD is more prevalent in Japan, while the risk appears to be lower in South Korea. This suggests that a comprehensive evaluation considering multiple factors is essential.
- **Multikinase inhibitors:** The risk of DIILD associated with ingredients used in the treatment of non-small cell lung cancer has been established, and the findings of this study are consistent with previous findings.

EGFR = epidermal growth factor receptor, DIILD = drug induced-interstitial lung disease