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Pneumocystis jirovecii pneumonia in patients with lung cancer receiving immune checkpoint inhibitors: a retrospective nationwide population-based cohort study from South Korea

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Abstract

Background This study determined the incidence of *Pneumocystis jirovecii* pneumonia (PCP) in patients with lung cancer based on immune checkpoint inhibitor (ICI) exposure.

Methods National claims data were obtained from 68,174 patients with lung cancer treated with ICIs or comparator non-ICIs (cytotoxic chemotherapy, targeted therapy, or both) between August 2017 and December 2021 in South Korea. The ICI exposure group included patients who were treated with ICIs at least once during the study period. The incidence and standardized incidence ratios were computed according to sex, 10-year age, and calendar-specific cancer population, to estimate the effects of ICIs and non-ICIs on the incidence of PCP. A logistic regression analysis was performed that adjusted for sex, age, comorbidities, and concomitant immunosuppressive drugs use.

Results A total of 18,043 (26.4%) patients were in the ICI exposure group, and 50,131 (73.6%) were in the ICI non-exposure group. More than half of the patients in the ICI exposure group were men aged 60–79 years. Twenty-one PCP events occurred every 42,000.39 person-years in the ICI exposure group, and the incidence of PCP was lower than that in the ICI non-exposure group. Compared to the total cancer population, the incidence of PCP in patients with lung cancer was not significantly affected by ICI exposure, sex, or age. A 36% decreased risk of PCP with ICI exposure compared with non-exposure was estimated; however, this result was not statistically significant.

Conclusions The incidence of PCP in patients with lung cancer treated with ICIs did not differ significantly from that in patients not treated with ICIs.

Keywords Immune checkpoint inhibitors · Chemotherapy · *Pneumocystis jirovecii* Pneumonia · Immunomodulation

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1 Introduction

Recently, immune checkpoint inhibitors targeting programmed death receptor 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) have revolutionized oncology [1]. These monoclonal antibody immune checkpoint inhibitors (ICIs) are used to treat various cancers [2, 3] and as adjuvants to the direct cell-killing approach of conventional chemotherapy [4]. For example, PD-1, a transmembrane receptor expressed on activated lymphocytes that binds to PD-L1 and PD-L2 of other membrane proteins. PD-L1 is expressed in several neoplastic cells and plays a key role in immune evasion [5, 6]. T cells are inhibited when PD-L1 binds to PD-1 of a T cell. Consequently, anti-PD-1 antibodies act as immunostimulatory agents that reactivate tumor cell-induced anergic cytotoxic T cells.

Therefore, ICIs do not typically induce immunosuppression, and the potential risk of infectious diseases associated with ICIs has garnered limited attention from physicians. However, many immune-related adverse events arise because of off-target effects on healthy tissues caused by an excessively enhanced immune response, with incidences ranging from 54 to 76% [7]. The most common sites of involvement are the skin, gastrointestinal tract, liver, endocrine system, and lungs. ICI-induced pneumonitis is a complication associated with ICI therapy in approximately 4–6% of patients, most of whom have grades 2–3 [8, 9]. Pneumonitis is a leading cause of ICI-associated morbidity, despite a low fatality rate of approximately 1% [1] and is more prevalent in patients with non-small cell lung cancer (NSCLC) than in those with other cancer types [10, 11]. ICI-induced pneumonitis was defined as dyspnea, other respiratory symptoms, and new inflammatory lesions on chest computed tomography (CT) after ICI treatment, excluding pulmonary infection and tumor progression [12]. Patients with ICI-induced pneumonitis showed no specific clinical symptoms, characteristic CT manifestations, or serological markers. The differential diagnoses of ICI-induced pneumonitis are broad and include bacterial or viral pneumonia, active pulmonary tuberculosis, invasive fungal disease, and *Pneumocystis jirovecii* pneumonia (PCP). ICI-induced pneumonitis is typically treated using steroids. Therefore, it is crucial to rule out respiratory infections.

PCP, an infectious disease caused by *P. jirovecii* that must be differentiated from ICI-induced pneumonitis, is life threatening in immunocompromised patients [13] With the recent increase in the use of immunosuppressive therapy, the incidence of PCP has increased in immunosuppressed patients not infected with the human immunodeficiency virus (HIV) [14], including solid organ or hematopoietic stem cell transplant recipients and patients receiving chemotherapy for malignancies. Because *P. jirovecii* is extremely challenging to culture in vitro, PCP diagnosis relies on clinical symptoms, radiographic findings, and confirmation through staining and visualization of the organisms in lung specimens such as bronchoalveolar lavage fluid or induced sputum. However, these methods have low sensitivity in distinguishing ICI-induced pneumonitis from PCP in clinical settings [15]. Therefore, assessment of the incidence and risk of PCP in patients receiving ICIs is crucial.

However, few studies have investigated the association between ICIs and the risk of PCP, and these prior studies have primarily been sporadic case reports [16–18]. The incidence of PCP in patients receiving ICIs remains undetermined [19]; therefore, this study evaluated the incidence of PCP in patients with lung cancer who received ICIs such as PD-1 (nivolumab and pembrolizumab) or PD-L1 (atezolizumab and durvalumab) antibodies at least once (ICI exposure group). We also compared the incidence of PCP in patients treated with cytotoxic chemotherapeutic agents and targeted therapy (ICI non-exposure group) using real-world data. The incidence of PCP in the ICI exposure and non-exposure groups was estimated using the standardized incidence ratio (SIR). A Cox proportional hazards model was applied to all lung cancer patients and subgroups using a nationwide claims database in South Korea.

2 Methods

2.1 Study design, database, and population

National claims data were extracted from the Health Insurance Review and Assessment (HIRA) database, which covers the medical insurance fee-for-service for 97% of Koreans. The HIRA is a single healthcare insurance system that assesses the cost-effectiveness of submitted medical fees, determines the reimbursement of coverage, and provides de-identified individual medical information related to billing for insured health benefits.

National insurance coverage for ICIs in South Korea has been approved for patients with advanced NSCLC (stage IIIB or higher) treated with platinum-containing chemotherapy. The approved ICIs are PD-1 inhibitors, including

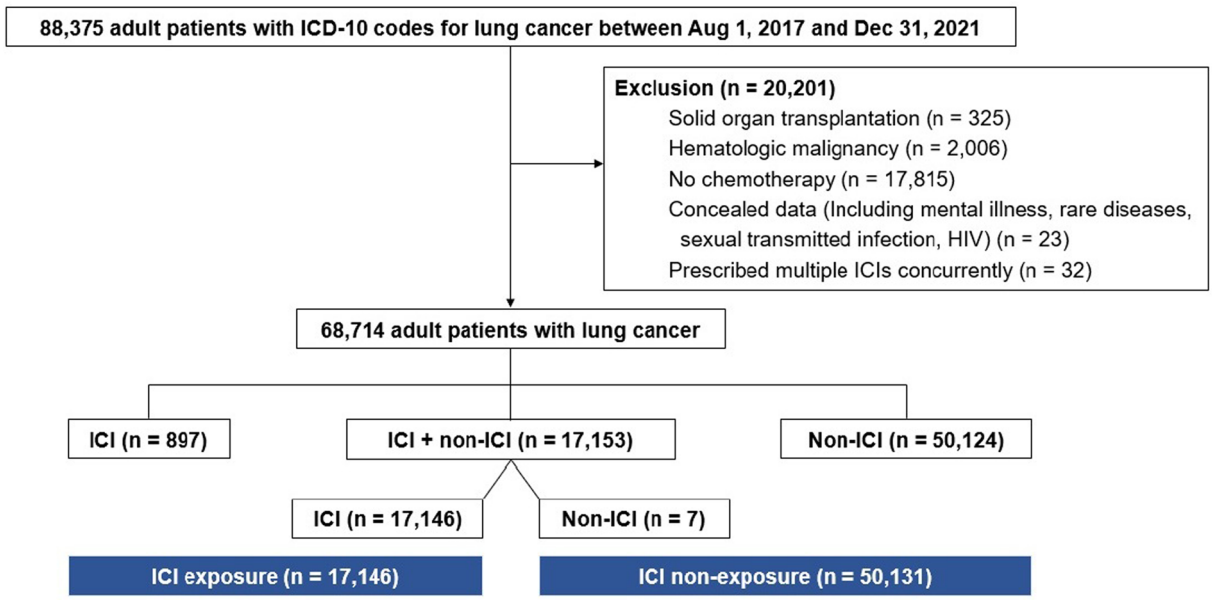

Fig. 1 Flowchart showing the details of the study population. Among 88,375 adult patients with ICD-10 codes for lung cancer between August 1, 2017, and December 31, 2021, a total of 20,201 were excluded based on predefined criteria, including history of solid organ transplantation, hematologic malignancy, absence of chemotherapy, concealed data (e.g., HIV, sexually transmitted infections, mental illness), or prescribed multiple ICIs concurrently. The final study population consisted of 68,714 patients, who were categorized into ICI exposure (n = 17,146) and ICI non-exposure (n = 50,131) groups based on their treatment history. ICD-10, International Classification of Diseases-10; HIV, human immunodeficiency virus; ICI, immune checkpoint inhibitor

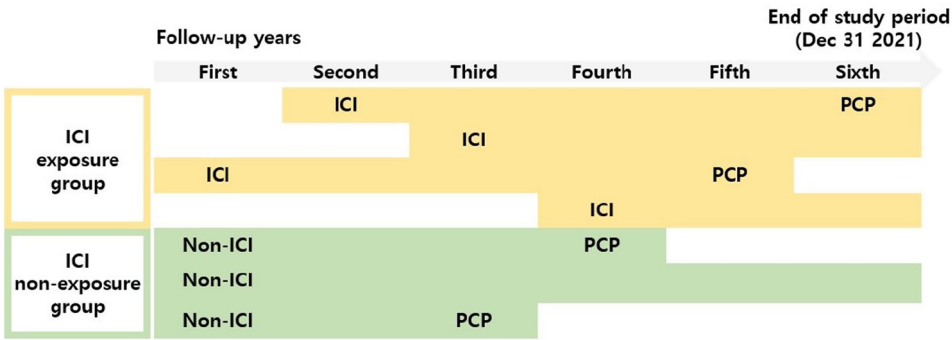

Fig. 2 Examples of study group classification and follow-up period. Each row represents a hypothetical patient scenario. Patients in the ICI exposure group (yellow) received immune checkpoint inhibitors during the follow-up period, whereas those in the non-exposure group (green) did not. Follow-up times are aligned by calendar year, and the timing of *Pneumocystis jirovecii* pneumonia (PCP) diagnosis is indicated within each timeline. ICI, immune checkpoint inhibitor; PCP, *Pneumocystis jirovecii* pneumonia

pembrolizumab and nivolumab, since August 2017; anti-PD-L1 inhibitors, such as atezolizumab, since January 2018; and durvalumab since April 2020. Based on the insurance coverage period, a customized claims dataset was obtained for general specifications and in-hospital treatment details of patients with lung cancer (International Classification of Disease-10 (ICD-10) code C34) older than 18 years between August 2017 and December 2021 (assigned number: HIRA Research Data [M20220920004]). A total of 88,375 patients with lung cancer were selected from the cohort; however, some patients were excluded according to the following criteria: (1) patients who underwent solid organ transplant (ICD-10 code, Z94; n = 325), (2) patients with hematologic malignancy (ICD-10 code, C81–96; n = 2,006), (3) patients that did not undergo chemotherapy (n = 17,815), (4) concealed diseases such as mental illness, rare diseases, sexually transmitted infections, and HIV (n = 23), and (5) patients who were concurrently prescribed multiple ICIs (n = 32). Therefore, 68,174 patients with lung cancer were included in this study (Fig. 1, 2).

3 Exposure, outcome, and confounding variable definitions

Exposure variables were classified as ICI exposure or non-exposure, depending on the treatment type received after lung cancer onset. Therefore, patients who were prescribed ICIs at least once after lung cancer diagnosis were included in the ICI exposure group and those who had never been prescribed ICIs were included in the non-exposure group. The baseline was designated as the first ICI prescription date for the ICI exposure or non-exposure groups and was followed up for outcome occurrence or the end of the study period (December 31, 2021) (Fig. 2). The dependent variable was new PCP cases identified using the main diagnostic code (ICD-10 code B59) after baseline.

Several confounding variables were considered while investigating the incidence of PCPs associated with ICI exposure. First, sex and age at baseline were obtained, and age was categorized into 10-year age groups. Second, several comorbidities were defined according to the ICD codes on the diagnostic statements between the onset of lung cancer and baseline: (1) diabetes; (2) cardiovascular diseases, including ischemic heart, cerebrovascular, arterial, arteriolar, and capillary diseases; (3) chronic lung diseases; (4) chronic kidney diseases; (5) chronic liver diseases; and (6) rheumatic diseases. Finally, concomitant immunosuppressive drug use was defined depending on prescription records for prednisone equivalent to ≥ 15 mg/day for at least 14 days during the study period or the preceding 12 months. The ICD codes for comorbidities and drug codes for ICIs, non-ICIs, corticosteroids, and immunosuppressants are presented in Supplementary Table 1.

4 Statistical analyses

Categorical characteristics such as 10-year age, sex, comorbidities, and concomitant immunosuppressive drug use were compared between the ICI- and non-exposure groups. The difference between groups was estimated using the χ^2 test. Incidence ratios per 100,000 person-years (PYs) were calculated based on the total and subgroup cancers (10-year age and sex) according to ICI exposure. To compare the incidence ratio of PCP in patients with lung cancer to the total number of patients with cancer, sex-, 5-year age-, and year-specific PCP incidences in patients with cancer were obtained from the Korean Statistical Information Service from 2018 to 2020. This was necessary because of the limited access to monthly data and national PCP statistics after 2021. Therefore, the SIR was evaluated using a 95% confidence interval (CI), assuming a Poisson distribution of PCP between 2018 and 2020. SIR was computed as the number of observed PCP events divided by the expected number of PCP events. The expected number was determined by multiplying the PYs in the cohort by the incidence rate of PCP in patients with cancer adjusted for sex, 10-year age, and calendar year.

Logistic regression analyses were conducted to investigate the effects of ICI exposure on PCP events using univariate and multivariate models adjusted for sex, age, comorbidities, and concomitant immunosuppressive drug use. Statistical significance was defined as a two-sided p-value < 0.05, and all analyses were conducted using R software version 4.0.3 (R Development Core Team).

5 Results

Table 1 presents the baseline characteristics of ICI exposure (26.4%, n = 18,043 patients) and non-exposure (73.6%, n = 50,131 patients) among 68,174 patients with lung cancer in South Korea between August 2017 and December 2021. Both groups showed common characteristics, with most patients being males aged 60–79 years old. Similar prevalence rates were observed for comorbidities such as diabetes ($p = 0.663$), chronic lung cancer ($p = 0.860$), and rheumatic disease ($p = 0.883$). However, patients who were not treated with ICIs had more cardiovascular ($p = 0.003$), chronic kidney ($p = 0.049$), and chronic liver disease ($p = 0.004$) comorbidities than those treated with ICIs. Immunosuppressants and steroids were administered more frequently in the ICI non-exposure group than in the ICI group. In the ICI exposure group, less than half of the patients (45.4%) were prescribed atezolizumab, followed by pembrolizumab (29.0%), nivolumab (18.7%), and durvalumab (0.07%). Similar characteristics in terms of age, sex, and comorbidities were observed regardless of the ICI type. However, the concomitant use of immunosuppressive drugs was slightly lower in patients treated with durvalumab than in those treated with the other medications.

Table 1 Baseline characteristics of 68,174 patients with lung cancer treated with immune checkpoint inhibitors or not between Aug 2017 and Dec 2021 in South Korea

		ICI exposure					ICI non-exposure (n = 50,131)	*P*-value
		Atezolizumab (n = 8,189)	Durvalumab (n = 1,266)	Nivolumab (n = 3,370)	Pembrolizumab (n = 5,218)	Total (n = 18,043)		
Age (year), n (%)								< 0.001
	< 40 (%)	54 (0.7)	7 (0.6)	23 (0.7)	46 (0.9)	130 (0.7)	475 (0.9)	
	40–49 (%)	327 (4.0)	37 (2.9)	145 (4.3)	261 (5.0)	770 (4.3)	2,019 (4.0)	
	50–59 (%)	1,291 (15.8)	208 (16.4)	644 (19.1)	991 (19.0)	3,134 (17.4)	8,040 (16.0)	
	60–69 (%)	3,033 (37.0)	522 (41.3)	1,299 (38.5)	1,953 (37.4)	6,804 (37.7)	1,8401 (36.7)	
	70–79 (%)	2,842 (34.7)	433 (34.2)	1,086 (32.2)	1,634 (31.3)	5,994 (33.2)	1,7556 (35.0)	
	≥ 80 (%)	643 (7.8)	59 (4.7)	176 (5.2)	333 (6.4)	1,211 (6.7)	3,640 (7.3)	
Sex, n (%)								< 0.001
	Male	6,430 (78.5)	1,087 (85.9)	2,681 (79.6)	4,081 (78.2)	1,4279 (79.1)	37,116 (74.0)	
	Female	1,759 (21.5)	179 (14.1)	689 (20.4)	1,137 (21.8)	3,764 (20.9)	1,3015 (26.0)	
Comorbidity, n (%)								
	Diabetes	3,798 (46.4)	632 (49.9)	1,268 (37.6)	2,082 (39.9)	7,780 (43.1)	21,712 (43.3)	0.663
	Cardiovascular disease*	3,731 (45.6)	589 (46.5)	1,092 (32.4)	1,841 (35.3)	7,253 (40.2)	20,793 (41.5)	0.003
	Chronic lung diseases	6,199 (75.7)	1,085 (85.7)	2,168 (64.3)	3,578 (68.6)	1,3030 (72.2)	36,239 (72.3)	0.860
	Chronic kidney diseases	499 (6.1)	63 (5.0)	134 (4.0)	224 (4.3)	920 (5.1)	2,751 (5.5)	0.049
	Chronic liver diseases	216 (2.6)	27 (2.1)	69 (2.0)	120 (2.3)	432 (2.4)	1,404 (2.8)	0.004
	Rheumatic diseases	641 (7.8)	100 (7.9)	139 (4.1)	286 (5.5)	1,166 (6.5)	3,221(6.4)	0.883
Concomitant use of immunosuppressive drugs, n (%)								
	Immunosuppressants	299 (3.6)	22 (1.7)	90 (2.7)	155 (3.0)	566 (3.1)	2,515 (5.0)	< 0.001
	Steroids**	507 (6.2)	16 (1.3)	199 (5.9)	334 (6.4)	1,056 (5.9)	3,332 (6.6)	< 0.001

*Includes ischemic heart diseases, cerebrovascular diseases, and arterial, arteriola, and capillary diseases

**Included the use of corticosteroids, which was prescription records for prednisone equivalents of ≥ 15 mg/day for at least 14 days

ICI, immune checkpoint inhibitor

Table 2 The incidence ratio of *Pneumocystis jirovecii* pneumonia according to immune checkpoint inhibitor exposure during the study period

		ICI exposure			ICI non-exposure		
		Event (n)	Person-years	Incidence (95% CI)	Event (n)	Person-years	Incidence (95% CI)
Total		21	42,000.39	50.00 (32.83–73.54)	86	123,671.77	69.54 (56.35–84.99)
Age, n (%)							
	< 40	0	307.53	0 (0–0)	1	1,194.78	83.70 (20.27–308.75)
	40–50	2	2,033.50	95.35 (30.42–273.99)	0	5,182.29	0 (0–0)
	50–60	5	8,047.01	62.13 (27.36–127.27)	13	20,900.75	62.20 (36.62–100.29)
	60–70	6	16,133.64	37.19 (17.44–72.32)	42	45,544.64	92.22 (68.33–122.12)
	70–80	7	13,205.14	53.01 (26.16–98.90)	26	42,569.03	61.08 (41.80–86.69)
	≥ 80	1	2,273.55	43.98 (10.65–162.25)	4	8,280.26	48.31 (19.61–105.88)
Sex, n (%)							
	Male	16	38,581.88	49.11 (30.39–75.93)	74	9,2234.49	80.23 (63.96–99.51)
	Female	5	9,418.51	53.09 (23.38–108.74)	12	31,437.27	38.17 (22.02–62.61)

Incidence per 100,000 people per year. ICI, immune checkpoint inhibitor

Table 2 shows the incidence of PCP in the total population and in subgroups (age and sex) according to ICI exposure. Twenty-one incidences of PCP occurred over 42,000.39 PYs in 18,043 patients treated with ICIs, compared to 86 PCPs observed over 123,671.77 PYs in the non-exposure group. The overall incidence rate of PCP was 50.00/100,000 PYs (95% CI, 32.83–73.54) in the ICI exposure group and 69.54/100,000 PYs (95% CI, 56.35–84.99) in the non-exposure group. In the age-specific subgroup, the incidence was highest in patients aged 40–49 years and 60–69 years in the ICI exposure and non-exposure groups, respectively. The incidence of PCP per 100,000 PYs in females was slightly higher than that in males in the ICI exposure group, whereas a decreased incidence of PCP was observed in women in the non-exposure group.

The incidence of PCP according to 5-year age groups was 0–1.36 and 0–0.98 in males and females, respectively, per 100,000 PYs, when comparing the incidence of the study cohort to the total number of patients with cancer between 2018 and 2020 (Table 3). The PCP incidence in male patients with lung cancer treated with ICIs was not significant compared to patients with cancer, whereas a decreased SIR was observed in those aged ≥ 80 years with non-exposure (SIR, 0.13; 95%, CI 0.03–0.51); however, the observed events were infrequent. The incidence of PCP in females with lung cancer was lower than that in female patients with other cancers, regardless of age or ICI exposure; however, the difference was not significant.

Table 4 presents the OR and 95% CI for PCP incidence associated with various risk factors in the univariate and multivariate models. ICI exposure was a protective factor for decreased PCP incidence risk compared to non-exposure in the unadjusted (odds ratio [OR], 0.68; 95%, CI 0.42–1.09) and adjusted (OR, 0.64; 95% CI 0.40–1.04) models, but not significant. Among the other risk factors, females had a significantly decreased PCP risk compared to males by 42% (95%, CI 0.34–0.97) in the unadjusted model and 44% (95% CI, 0.33–0.94) in the adjusted model.

6 Discussion

In this nationwide population-based study, ICI use did not significantly increase the risk of PCP in patients with lung cancer. Moreover, the PCP incidence in patients with lung cancer treated with ICIs did not significantly differ from that of the overall cohort of patients with cancer. ICI exposure was associated with a 36% reduced risk of PCP, compared with non-exposure in the adjusted model; however, these results were not statistically significant.

Although PCP has been documented in patients receiving ICIs, only a handful of studies on PCP associated with ICI have been reported. PCP occurred in three (0.4%) of the 740 patients with melanoma treated with nivolumab [19]. Furthermore, in Japan, PCP occurred two weeks after pembrolizumab administration without prior steroid or immunosuppressive drug administration [18]. A previous study that conducted a post-marketing pharmacovigilance analysis using US Food and Drug Administration Adverse Event Reporting System data reported that ICI showed a lower PCP signal than traditional chemotherapy [20]. Recently, Fan et al. [21] reported that patients with lung cancer receiving ICIs had a higher mortality rate after developing PCP than the non-ICI-treated cohort. However, the sample size was small

Table 3 Standardized incidence ratio of *Pneumocystis jirovecii* pneumonia for the total cancer population according to immune checkpoint inhibitor exposure, age, and sex between 2018 and 2020

		ICIs exposure					ICIs non-exposure				
		Person-years	Observed events (n)	Expected events (n)	SIR (95% CI)	*p*-value	Person-years	Observed events (n)	Expected events (n)	SIR (95% CI)	*p*-value
Male											
	< 40	118.71	0	0.63	0 (0–0)	1.00	330.37	1	1.76	0.57 (0.08–4.05)	0.57
	40–49	590.45	2	1.47	1.36 (0.34–5.42)	0.67	1,328.30	0	3.32	0 (0–0)	1.00
	50–59	3,003.55	2	3.98	0.50 (0.13–2.01)	0.33	6,969.55	7	9.24	0.76 (0.36–1.59)	0.46
	60–69	6,992.49	3	8.86	0.34 (0.11–1.05)	0.06	18,686.77	28	23.67	1.18 (0.82–1.71)	0.37
	70–79	6,135.11	5	6.12	0.82 (0.34–1.96)	0.65	18,773.66	11	18.71	0.59 (0.33–1.03)	0.08
	≥ 80	1,083.65	0	4.72	0 (0–0)	1.00	3,592.98	2	15.63	0.13 (0.03–0.51)	< 0.01
Female											
	< 40	71.18	0	0.08	0 (0–0)	1.00	318.81	0	0.38	0 (0–0)	1.00
	40–49	302.18	0	0.24	0 (0–0)	1.00	1,063.60	0	0.85	0 (0–0)	1.00
	50–59	839.57	0	0.57	0 (0–0)	1.00	3,120.36	2	2.12	0.94 (0.24–3.78)	0.94
	60–69	1,469.45	1	1.15	0.87 (0.12–6.16)	0.89	4,980.03	2	3.91	0.51 (0.13–2.05)	0.34
	70–79	1,172.96	1	1.12	0.80 (0.11–5.71)	0.83	4,290.00	2	4.55	0.44 (0.11–1.76)	0.24
	≥ 80	267.03	1	1.02	0.98 (0.14–6.98)	0.99	978.15	0	3.73	0 (0–0)	1.00

SIR, standardized incidence ratio

Table 4 The odds ratio of *Pneumocystis jirovecii* pneumonia associated with various risk factors

		PCP cases (n)	Unadjusted		Adjusted	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
ICIs						
	ICI exposure	86	1 (reference)		1 (reference)	
	ICI non-exposure	21	0.68 (0.42, 1.09)	0.11	0.64 (0.40, 1.04)	0.07
Age						
	< 40	1	1 (reference)		1 (reference)	
	40–49	2	0.43 (0.04, 4.79)	0.49	0.44 (0.04, 4.82)	0.49
	50–59	18	0.97 (0.13, 7.31)	0.97	0.93 (0.12, 7.03)	0.94
	60–69	48	1.15 (0.16, 8.36)	0.88	1.09 (0.15, 7.95)	0.93
	70–79	33	0.85 (0.12, 6.21)	0.87	0.82 (0.11, 6.05)	0.84
	≥ 80	5	0.62 (0.07, 5.34)	0.66	0.62 (0.07, 5.41)	0.66
Sex						
	Male	90	1 (reference)		1 (reference)	
	Female	17	0.58 (0.34, 0.97)	0.03	0.56 (0.33, 0.94)	0.02
Comorbidity						
	Diabetes	46	0.99 (0.67, 1.45)	0.99	1.06 (0.71, 1.59)	0.76
	Cardiovascular disease*	36	0.73 (0.49, 1.08)	0.11	0.70 (0.45, 1.07)	0.09
	Chronic lung diseases	78	1.03 (0.67, 1.58)	0.88	1.06 (0.69, 1.65)	0.78
	Chronic kidney diseases	3	0.51 (0.16, 1.60)	0.24	0.55 (0.17, 1.75)	0.30
	Chronic liver diseases	1	0.34 (0.05, 2.44)	0.28	0.33 (0.05, 2.36)	0.27
	Rheumatic diseases	9	1.34 (0.67, 2.65)	0.40	1.67 (0.83, 3.35)	0.15
Concomitant use of immunosuppressive drugs						
	Immunosuppressants	2	0.40 (0.10, 1.63)	0.20	0.36 (0.09, 1.47)	0.15
	Steroids**	0	–	–	–	–

*Includes ischemic heart diseases, cerebrovascular diseases, and arterial, arteriola, and capillary diseases

**Included the use of corticosteroids, which was prescription records for prednisone equivalents of ≥ 15 mg/day for at least 14 days

ICI, immune checkpoint inhibitors; OR, odds ratio; PCP, *Pneumocystis jirovecii* pneumonia

(n = 20), with only nine patients in the ICI group, which limited the statistical power and generalizability of the results. Considering the limited evidence, the strength of this study lies in its use of nationwide population data from the HIRA Health Insurance Claims Database. A multivariate analysis was used to control for potential confounders, by adjusting for various variables in the risk factor analysis. Moreover, the SIR was accurately calculated using reported PCP and census data from the overall cancer cohort published by the Korean government.

Distinguishing ICI-induced pneumonitis from other infections is crucial because its diagnosis relies on clinical symptoms, imaging findings, and ICI treatment history. PCP is a particularly notable respiratory infection owing to its high mortality rate in non-HIV patients [22], and its differential diagnosis can be challenging, with ground-glass shadows on images that are similar to those of ICI-induced pneumonitis [22]. Therefore, evaluating the prevalence of and susceptibility to PCP among patients treated with ICIs is crucial. Despite concerns regarding potential immune dysregulation with ICI therapy, the incidence of PCP did not increase in the ICI group in the present study. This finding is clinically significant, as it suggests that ICI exposure may not predispose patients to a higher risk of PCP. Furthermore, this finding may aid in prioritizing differential diagnoses when evaluating patients receiving ICIs who present with chest imaging abnormalities in clinical practice.

Current research is being conducted on the immunological mechanisms underlying PCP, with a focus on lymphocytes, which are the determinant immune cells in PCP. Administering IL-12 stimulates T helper cell type 1 (Th1) differentiation, accelerates fungal clearance, reduces mortality, and increases immune cell infiltration into the lungs [23]. Furthermore, PD-1 inhibition promotes Th1 and Th17 responses and inhibits Th2 responses [24]. Another murine model revealed that PD-1 deficiency enhanced the pulmonary Th1/Th17 response and the phagocytic function of macrophages. This was accompanied by macrophage polarization toward a protective M1 phenotype, which may contribute to pulmonary

Pneumocystis clearance [25]. M1-polarization is beneficial for antifungal immunity and associated with increased natural killer cell activation, phagocytic capacity, and interferon-gamma (IFN-γ) secretion in response to other classes of pathogenic fungi [26, 27]. Moreover, the phagocytic activity of alveolar macrophages is impaired by increased PD-L1 production in myeloid-derived suppressor cells (MDSCs) during PCP, which can be partially reversed by pretreating *ex-vivo* MDSCs with anti-PD-L1 [28]. In *Candida* sepsis, CTLA-4 and PD-1 inhibitors attained therapeutic benefits by reversing immune suppression and improving survival. Another study proposed that ICI-induced immune enhancement accelerated fungal clearance and reduced PCP-related symptom duration and severity [29]. These findings align with the results of our study and suggest that ICI exposure may not increase the risk of PCP and, in some cases, may lead to a less severe disease course.

The immune response triggered by ICIs can be a double-edged sword, potentially leading to immune-mediated lung damage. Th1 predominance shifts macrophage polarization from M2 to M1, which, while beneficial for fungal clearance, may also contribute to lung injury and increased inflammation [30]. Pro- and anti-inflammatory cytokines are upregulated in PD-1-deficient mice, and increased inflammatory cell proliferation has been observed in the lungs [25]. Furthermore, ICIs induce hyperinflammatory toxicity and may cause immune reconstitution inflammatory syndrome (IRIS). IRIS induces abrupt restoration of immune activity and latent or chronic infectious disease reactivation, leading to profound systemic inflammation, exaggerated immune responses to primary infections, and tissue damage [31, 32]. PCP clinical symptoms are often observed in HIV-negative immunosuppressed patients during immunosuppression reversal upon steroid dose reduction [33]. The paradoxical exacerbation of clinical PCP symptoms has been observed in patients with HIV infection after initiating antiretroviral treatment [34–36]. Further research is required to elucidate the detailed mechanisms underlying ICI-mediated changes in the immune environment at the infection site. Analysis of B and T cell subsets and associated inflammatory cytokines at baseline and upon PCP onset in patients receiving ICI treatment may be helpful for understanding the differential mechanisms underlying PCP incidence.

This study had several limitations that must be considered when interpreting the results. First, few PCP events were observed, and the PCP incidence may have been underestimated or misclassified because of the observational nature of the claims database. Second, only a few ICIs (atezolizumab, durvalumab, nivolumab, and pembrolizumab) were evaluated and most patients received pembrolizumab; consequently, the differential effects of each ICI on the PCP risk could not be determined. Further investigations should explore the risk of PCP in patients with different cancers and those receiving other ICIs, such as anti-CTLA-4, anti-LAG-3, and anti-TIM-3 inhibitors. Third, despite being a crucial risk factor for PCP, the OR values were not calculated for steroid usage variables in the statistical model. No patient with PCP received steroids, resulting in the inability of the model to calculate the OR for this particular subgroup. Future studies should include a more extensive and diverse patient population, including patients treated with steroids, to comprehensively analyze this potential risk factor. Fourth, potential confounding variables, including socioeconomic status, NSCLC subtype, and the impact of prior cytotoxic agents before ICI treatment, were not adjusted for because of limitations in claims data availability. Moreover, clinical and laboratory data could not be adjusted because the HIRA database does not provide this information for individual claims. Fifth, while heterogeneity according to sex, age, and drugs between the ICIs and non-ICI groups was identified, matching was difficult because of the representativeness of the national data and the number of PCP occurrences. Finally, the HIV infection status, which is the most significant risk factor for PCP, could not be determined because the HIRA database conceals the individual identification of patients with HIV. However, because the concealed data was limited to the overall patient population, it did not significantly affect our research findings.

In conclusion, this study reveals that ICI exposure does not increase the risk of PCP in patients with lung cancer. Moreover, the incidence of PCP in patients treated with ICIs did not differ significantly from that in patients not treated with ICIs. Although the 36% reduction in PCP risk in the ICI exposure group compared with the non-exposure group was not significant, the clinical implications of this finding highlight the need for further research to elucidate the complexity of ICI immunological interventions for infectious complications in the cancer population. The use of a real-world dataset strengthened this study; however, limitations such as its observational nature and potential underreporting must be considered when interpreting our findings.

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Author contributions Jiyun Jung and Sungim Choi wrote the manuscript, performed data curation and evaluation, statistical evaluation, prepared all figures, tables and supplementary materials. Seong Yeon Park, Hee Bum Jo, Jae Yoon Park, Dalyong Kim and Kyoungmin Lee participated in study supervision and review and edit for manyscript. All authors have read and agreed to the published version of the manuscript.

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Data availability In terms of further use of our data, we asked the researchers to cite our paper in the Methods section. Data presented in this study are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate All methods were carried out in accordance with the relevant ethical guidelines and regulations, including the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Dongguk University Ilsan Medical Center (approval no. 2022–09-005). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study and the use of anonymized data.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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