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Risk of tuberculosis in patients with cancer treated with immune checkpoint inhibitors: a nationwide observational study

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ABSTRACT

Background While some recent studies have reported the development of tuberculosis (TB) in patients exposed to immune checkpoint inhibitors (ICIs), there is limited evidence to date. Therefore, we evaluated the risk of TB in patients with cancer exposed to ICIs using the National Health Insurance claims data in South Korea.

Methods Patients with diagnostic codes for non-small cell lung cancer, urothelial carcinoma or melanoma between August 2017 and June 2019 were identified. The incidence rate and standardized incidence ratio (SIR) of TB were calculated for both the ICI exposure and non-exposure groups. The risk of TB according to ICI exposure was assessed using a multivariable Cox regression model.

Results During the study period, 141 550 patients with cancer and 916 new TB cases were identified. Among the 5037 patients exposed to ICIs, 20 were diagnosed with TB at a median of 2.2 months after the ICI was initiated. The crude incidence rate of TB per 100,000 person-years was 675.8 (95% CI 412.8 to 1043.8) for the ICI exposure group and 599.1 (95% CI 560.5 to 639.6) for the non-exposure group. The SIR for TB was 8.1 (95% CI 8.0 to 8.2) in the ICI exposure group. After adjusting for potential confounding factors, ICI treatment was not significantly associated with an increased risk of TB (HR: 0.73; 95% CI 0.47 to 1.14).

Conclusions While the incidence of TB in cancer patients exposed to ICIs was eightfold higher than in the general population, the risk of patients with cancer developing TB did not significantly differ according to ICI exposure.

BACKGROUND

Inhibiting the immune checkpoint pathway has been shown to be effective in treating patients with advanced solid cancers.[1–3] Since immune checkpoint inhibitors (ICIs) were introduced, the use of these drugs to treat various types of cancer has increased, and a better understanding of adverse events, such as immune-related adverse events, is increasingly necessary.[4] Recently, several studies have reported the development of tuberculosis (TB) in patients during or after ICI therapy.[5–12] The development of active TB in patients with advanced cancer entails significant risks, including delayed antineoplastic therapy and death. The risk of developing active TB is two to three times higher in patients with solid cancer than in the general population.[13–16] In addition, antineoplastic therapy was reported as an independent risk factor for active TB in patients with cancer.[17] However, there are no specific guidelines for screening or treating latent tuberculosis infection (LTBI) in patients with cancer.[18 19] Notably, the Society for Immunotherapy of Cancer (SITC) guideline recommends LTBI screening prior to initiating ICI[20]; however, this recommendation was made considering the potential use of corticosteroids or tumor necrosis factor (TNF) inhibitors for the treatment of immune-related adverse events during ICI use, rather than the direct association between ICI and the development of active TB. Therefore, it is necessary to evaluate the burden of active TB in patients with cancer receiving ICI as well as the association between ICI exposure and the subsequent development of active TB.

Estimating the incidence of active TB in patients with cancer poses significant challenges in terms of the need for longitudinal studies with large sample sizes and long observation periods, especially in high-income countries where the burden of active TB is low (<30 cases/100,000 persons per year).[21] South Korea is a high-income country with an intermediate TB burden (55/100,000 persons in 2017) and thus has a considerably higher incidence of TB than other developed countries.[22] In this respect, South Korea provides a unique and promising study setting including: (1) accessibility to the database of the National Health Insurance (NHI) program covering 50 million people, (2)

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nationwide TB notification system, and (3) an intermediate TB burden; therefore, we presumed that the analysis of the NHI claims data of South Korea could provide an important answer to the clinicoepidemiologic question about the risk of TB in patient with cancer receiving ICIs.

METHODS

Study design, population, and database

This population-based retrospective cohort study was conducted using the nationwide claims database in South Korea. The NHI system in South Korea provides universal healthcare coverage to the entire population residing in the country. The healthcare providers are required to claim their medical services for reimbursement, and all these claims are collected and reviewed by the Health Insurance and Review Assessment Service (HIRA).[23] The data collected by the HIRA encompasses all the claimed healthcare records, including medical visits, prescriptions, procedures and surgeries. The HIRA database is available for research purposes after the encryption and deidentification process is complete. Using the HIRA data repository, the burden of TB was estimated in patients with cancer according to ICI exposure. To determine the incidence of TB in patients receiving ICIs compared with the general population, annual statements regarding reported cases of TB and the official statistical database of the annual population census in South Korea were used.[22 24]

In South Korea, NHI coverage for ICIs have been approved for the following: nivolumab and pembrolizumab for advanced non-small cell lung cancer (NSCLC) since August 2017; atezolizumab for advanced NSCLC or urothelial carcinoma since January 2018; and nivolumab and pembrolizumab for advanced melanoma since February 2018. Insurance coverage for ICIs in patients with NSCLC and urothelial carcinoma are approved for patients who were previously treated with platinum-containing chemotherapy. We conducted an analysis on adult patients with cancer (aged ≥18 years) with diagnostic codes for NSCLC, urothelial carcinoma, or melanoma from August 2017 to June 2019. The exclusion criteria were as follows: (1) history of active TB, (2) HIV infection, (3) solid organ transplant, (4) inflammatory bowel disease, (5) hematologic malignancy, (6) past medication history of immunosuppressants, or (7) no available records after the first visit (lost to follow-up). The need for written or verbal consent was waived by the review board due to the observational nature of the study and the fact that the patient identifiers were fully encrypted prior to analysis.

Definitions and outcomes

Cancer patients with NSCLC, urothelial carcinoma, and melanoma were identified using International Classification of Diseases-10 (ICD-10) codes (C34, C66, C67, and C43) as primary or secondary diagnoses. ICI exposure was defined as the presence of a prescription for ICIs at least once during the study period. The remaining patients were categorized into the non-exposure group. The index date was defined as the date of the first administration of the ICI for the exposure group and the date of the first visit with diagnostic codes for cancer during the study period for the non-exposure group. The date of the last follow-up was determined by the last documented claim record for each individual during the study period. The main outcome of interest was the development of active TB requiring treatment. New cases of TB were identified by the presence of relevant diagnostic codes for active TB (ICD-10 code A15, A16, A17, A18, or A19) and prescription records for anti-TB medications as described in our previous study.[25]

In addition, the following potential confounding factors in the development of TB were identified based on claims records present during the study period or in the preceding 12 months: age, sex, hypertension, diabetes, dyslipidemia, chronic lung disease, chronic kidney disease, chronic liver disease, rheumatic disease, previous history of latent TB infection (LTBI) treatment, active chemotherapy, and concomitant use of corticosteroids or immunosuppressants. The use of corticosteroids was defined as the presence of prescription records for prednisone equivalents ≥15 mg/day for at least 14 days. The diagnostic and drug codes used in this study are summarized in online supplemental table 1.

Statistical analysis

Categorical data were compared using the χ^2 test, and continuous variables were analyzed using the independent t-test. Incidence rates were presented as the number of TB episodes per 100,000 person-years (PYs) of follow-up. The CIs for the incidence rates were estimated under the assumption that the number of TB cases followed a Poisson distribution. To estimate the burden of TB in patients with cancer relative to the general population, standardized incidence ratios (SIRs) and 95% CIs were calculated. The risk factors for TB were identified using the Cox proportional hazard model. In the multivariable Cox regression model, baseline covariates including age, sex, health insurance type, type of cancer, diabetes, hypertension, chronic lung disease, chronic kidney disease, chronic liver disease, rheumatic disease, history of treatment for latent TB infection, active chemotherapy, concomitant use of corticosteroids, and concomitant use of immunosuppressants were included. A number of sensitivity analyses were performed to test the robustness of our findings. First, we repeatedly measured the outcome of TB as defined by diagnostic codes regardless of receiving anti-TB agents. In addition, we reanalyzed the study cohort after excluding TB cases diagnosed within 30 days after cancer diagnosis. We performed analyses in subgroups defined according to age (<50 years vs ≥50 years), sex, and cancer type. The presence of interactions in these subgroups was evaluated. Considering the comprehensive nature of the claims data, we assumed that the database has minimal or no missing
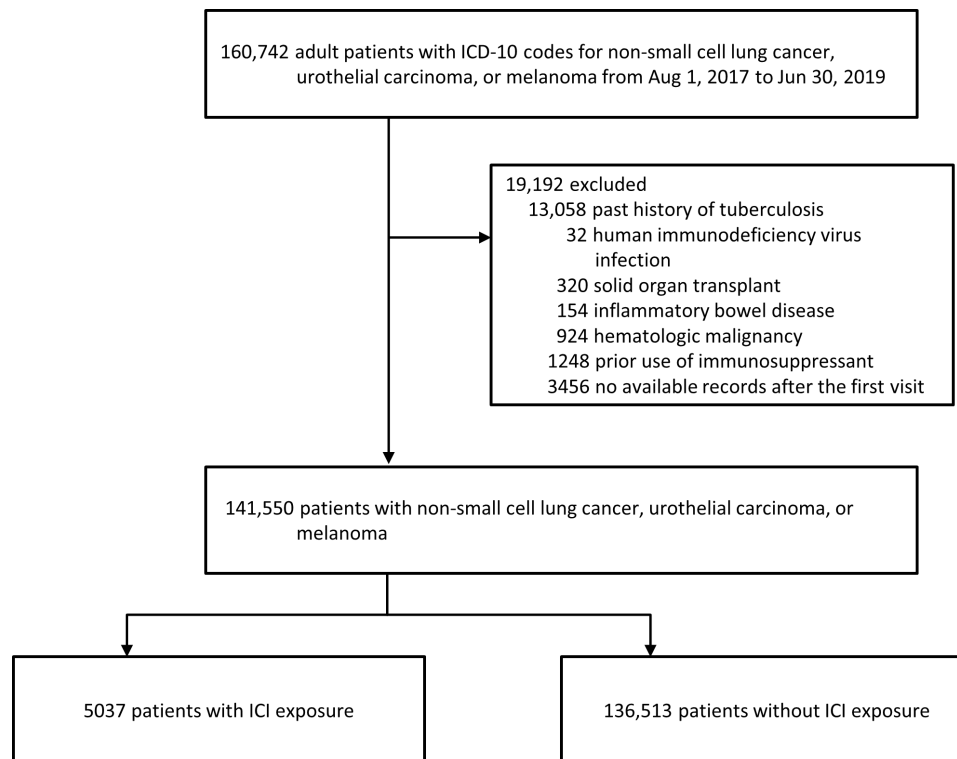
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┌──────────────────────────────────────────────────────────────┐
│ 160,742 adult patients with ICD-10 codes for non-small cell    │
│ lung cancer, urothelial carcinoma, or melanoma from            │
│ Aug 1, 2017 to Jun 30, 2019                                    │
└──────────────────────────────────────────────────────────────┘
                          ┌──────────────────────────────────────┐
                          │ 19,192 excluded                       │
                          │  13,058 past history of tuberculosis   │
                          │     32 human immunodeficiency virus    │
                          │        infection                       │
                          │    320 solid organ transplant          │
                          │    154 inflammatory bowel disease      │
                          │    924 hematologic malignancy          │
                          │   1248 prior use of immunosuppressant  │
                          │   3456 no available records after the  │
                          │        first visit                     │
                          └──────────────────────────────────────┘
┌──────────────────────────────────────────────────────────────┐
│ 141,550 patients with non-small cell lung cancer, urothelial   │
│ carcinoma, or melanoma                                         │
└──────────────────────────────────────────────────────────────┘
┌────────────────────────────┐    ┌────────────────────────────┐
│ 5037 patients with ICI     │    │ 136,513 patients without   │
│ exposure                   │    │ ICI exposure               │
└────────────────────────────┘    └────────────────────────────┘
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Figure 1 Flow chart of study population. ICD-10, International Classification of Diseases-10; ICI, immune checkpoint inhibitor.

values. All reported p values are two sided, and a p value less than 0.05 was considered statistically significant. Data processing and statistical analyses were conducted using SAS Enterprise Guide V.7.1 (SAS Institute).

RESULTS
During the study period, a total of 160,742 adult patients (aged >18 years) with diagnostic codes for NSCLC, urothelial carcinoma, or melanoma were identified (figure 1). After excluding patients according to the exclusion criteria, 141,550 patients with NSCLC, urothelial carcinoma, or melanoma were included in the analysis. Of these, 5037 (3.6%) were in the ICI exposure group, and the remaining 136,513 (96.4%) patients were in the ICI non-exposure group. Among the 5037 patients in the exposure group, 1972 (39.2%), 2593 (51.5%) and 472 (9.4%) received nivolumab, pembrolizumab, and atezolizumab, respectively. The baseline characteristics of the study population are shown in table 1. We found that most of the cancer patients included in this study were male, were elderly, and had lung cancer. Patients in the ICI exposure group differed significantly from those in the ICI non-exposure group in terms of age, sex, type of cancer, comorbidities, active chemotherapy, and concomitant use of corticosteroids. No differences concerning a previous history of LTBI treatment were found between the ICI exposure and non-exposure groups.

There were 916 cases of TB infections in the 141,550 patients included in this study, 20 of which occurred in the ICI exposure group. Detailed characteristics of these 20 cases of TB are summarized in table 2. Most of the patients were male (80% (16/20)) and most had NSCLC (95% (19/20)). Of the 20 cases of TB, 12 occurred in patients who had received pembrolizumab, and eight occurred in patients who had received nivolumab. No cases of TB occurred in patients who received atezolizumab or patients with urothelial carcinoma. TB developed a median of 2.2 months (range: 0.4–16.5) after ICI treatment was initiated, and most of the cases of TB (80% (16/20)) were pulmonary infections. Eight (40%) patients were taking corticosteroids concomitantly.

Incidence rate and standardized incidence ratio of TB in the ICI exposure and non-exposure groups
The total observation time was 152,521 PY for all the patients with cancer included in this study. Of this, 2959 PY was attributed to the ICI exposure group, and 149,562 PY to the ICI non-exposure group, with average follow-up periods of 0.59 and 1.10 years, respectively. The crude TB incidence per 100,000 PY was 675.8 in the ICI exposure group and 599.1 in the ICI non-exposure group (table 3). The SIR of TB in the ICI exposure group was 8.1 (95% CI 8.0 to 8.2), 6.0 (95% CI 5.9 to 6.1), and 10.9 (95% CI 10.7 to 11.1) for the total, male, and female participants, respectively (table 4). The SIR estimates of TB for the total, male, and female participants in the non-exposure group were 8.2 (95% CI 8.1 to 8.3), 8.4 (95% CI 8.2 to 8.4), and 7.9 (95% CI 7.8 to 8.1), respectively.

Risk factors for TB in patients with cancer
The univariable Cox analysis (table 5) revealed that the following risk factors were significantly associated with TB: increasing age (HR 1.02; 95% CI 1.02 to 1.03), male sex (HR

Table 1 Baseline characteristics of patients with cancer in the immune checkpoint inhibitor (ICI) exposure and non-exposure groups

	ICI exposure			Total ICI exposure (n=5037)	ICI non-exposure (n=136,513)	P value*
	Nivolumab (n=1972)	Pembrolizumab (n=2593)	Atezolizumab (n=472)			
Age, year, mean (SD)	65.8 (9.7)	65.5 (10.2)	67.7 (9.9)	65.8 (10.0)	68.5 (11.1)	<0.001
Sex						<0.001
Male	1522 (77.2)	1858 (71.7)	372 (78.8)	3752 (74.5)	92 050 (67.4)	
Female	450 (22.8)	735 (28.3)	100 (21.2)	1285 (25.5)	44 463 (32.6)	
Type of insurance						<0.001
National Health Insurance	1779 (90.2)	2380 (91.8)	425 (90.0)	4584 (91.0)	127 201 (93.2)	
Medical aids†	156 (7.9)	193 (7.4)	45 (9.5)	394 (7.8)	8495 (6.2)	
Veterans	37 (1.9)	20 (0.8)	2 (0.4)	59 (1.2)	817 (0.6)	
Type of cancer						<0.001
NSCLC	1796 (91.1)	2038 (78.6)	154 (32.6)	3988 (79.2)	94 208 (69.0)	
Urothelial carcinoma	9 (0.5)	10 (0.4)	318 (67.4)	337 (6.7)	39 268 (28.8)	
Melanoma	167 (8.5)	545 (21.0)	0 (0)	712 (14.1)	4086 (3.0)	
Underlying diseases						
Diabetes mellitus	641 (32.5)	804 (31.0)	145 (30.7)	1590 (31.6)	39 015 (28.6)	<0.001
Hypertension	968 (49.1)	1220 (47.0)	251 (53.2)	2439 (48.4)	71 349 (52.3)	<0.001
Chronic lung disease	1163 (59.0)	1392 (294.9)	210 (44.5)	2765 (54.9)	55 289 (40.5)	<0.001
Chronic kidney disease	72 (3.7)	72 (15.3)	55 (11.7)	199 (4.0)	6346 (4.6)	0.02
Chronic liver disease	37 (1.9)	34 (7.2)	6 (1.3)	77 (1.5)	1506 (1.1)	0.01
Rheumatic disease	49 (2.5)	73 (15.5)	17 (3.6)	139 (2.8)	2873 (2.1)	0.002
Predisposing factors						
History of LTBI treatment	19 (1.0)	28 (1.1)	2 (0.4)	49 (1.0)	1686 (1.2)	0.10
Active chemotherapy	569 (28.9)	675 (26.0)	70 (14.8)	1314 (26.1)	31 870 (23.3)	<0.001
Concomitant use of corticosteroid	459 (23.3)	533 (20.6)	71 (15.0)	1063 (21.1)	12 603 (9.2)	<0.001
Concomitant use of immunosuppressant	14 (0.7)	34 (1.3)	26 (5.5)	74 (1.5)	1889 (1.4)	0.69

Data are n (%).
*Comparison of total ICI exposure group to non-exposure group.
†Medical aid is a public assistance program that targets impoverished people in need of medical assistance as part of the South Korean social welfare program.
LTBI, latent tuberculosis infection; NSCLC, non-small cell lung cancer.

1.54; 95% CI 1.33 to 1.79), medical aids (HR 1.40; 95% CI 1.10 to 1.78), lung malignancy (HR 3.35; 95% CI 1.80 to 6.25), diabetes (HR 1.22; 95% CI 1.07 to 1.41), hypertension (HR 1.18; 95% CI 1.04 to 1.34), chronic lung disease (HR 1.77; 95% CI 1.55 to 2.01), active chemotherapy (HR 1.72; 95% CI 1.50 to 1.98), and the concomitant use of corticosteroids (HR 1.56; 95% CI 1.29 to 1.88). As a risk factor, ICI treatment was not found to be significantly associated with the development of TB in the univariable analysis (HR 0.85; 95% CI 0.55 to 1.33) and in the multivariable Cox regression analysis (HR 0.73; 95% CI 0.47 to 1.14).

Subgroup and sensitivity analyses
In the subgroup analyses, no significant difference in incidence for TB was observed between the ICI exposure and ICI non-exposure groups, regardless of age group, sex, and type of cancer (all p values for interaction >0.05) (table 6). The results were robust in sensitivity analyses in which the definition of TB was made by diagnostic codes regardless of anti-TB medication. In the sensitivity analysis conducted in the study cohort, excluding TB cases diagnosed within 30 days of cancer diagnosis, no significant difference in TB incidence was observed between the ICI exposure and ICI non-exposure groups (table 6).

DISCUSSION
In this nationwide population-based study, the incidence of TB in the patients exposed to ICIs was approximately

Table 2 Characteristics of the 20 patients with tuberculosis following ICI exposure

Patient number	Age, years	Sex	Cancer type	Other comorbidities	Type of ICI	Total ICI cycles received	Interval* (months)	Type of TB	Concomitant corticosteroid	Concomitant immunosuppressant
1	73	Male	Lung cancer	None	Nivolumab	5	5.7	Pulmonary	No	No
2	80	Male	Lung cancer	Hypertension and chronic lung disease	Nivolumab	1	1.3	Pulmonary	No	No
3	65	Male	Lung cancer	Chronic lung disease	Nivolumab	8	1.7	Miliary	No	No
4	82	Male	Lung cancer	Chronic lung disease	Pembrolizumab	6	1.3	Pulmonary	No	No
5	74	Female	Lung cancer	Hypertension, diabetes and chronic kidney disease	Pembrolizumab	2	0.4	Meningitis	Yes	No
6	81	Female	Melanoma	Hypertension and chronic lung disease	Pembrolizumab	2	0.7	Pulmonary	No	No
7	65	Male	Lung cancer	None	Pembrolizumab	3	2.8	Vertebra	Yes	No
8	44	Female	Lung cancer	Hypertension	Nivolumab	2	1.5	Pulmonary	No	No
9	61	Male	Lung cancer	Chronic lung disease	Pembrolizumab	7	4.7	Pericarditis	No	No
10	64	Male	Lung cancer	Hypertension and diabetes	Pembrolizumab	7	5.3	Pulmonary	Yes	No
11	58	Male	Lung cancer	None	Pembrolizumab	2	2.3	Pulmonary	No	No
12	59	Male	Lung cancer	Hypertension and chronic lung disease	Pembrolizumab	1	0.9	Pulmonary	Yes	No
13	71	Male	Lung cancer	Hypertension and chronic lung disease	Nivolumab	2	0.6	Pulmonary	No	No
14	53	Male	Lung cancer	Chronic lung disease	Nivolumab	10	7.5	Pulmonary	Yes	No
15	54	Male	Lung cancer	Diabetes and chronic lung disease	Pembrolizumab	2	2.8	Pulmonary	No	No
16	79	Male	Lung cancer	Chronic lung disease	Pembrolizumab	3	2.0	Pulmonary	Yes	No
17	67	Female	Lung cancer	Hypertension and diabetes	Nivolumab	10	16.5	Pulmonary	Yes	No
18	78	Male	Lung cancer	Chronic lung disease	Pembrolizumab	10	13.6	Pulmonary	No	Yes
19	61	Male	Lung cancer	Hypertension, diabetes and chronic lung disease	Pembrolizumab	2	0.6	Pulmonary	Yes	No
20	83	Male	Lung cancer	Chronic lung disease	Nivolumab	10	9.1	Pulmonary	No	No

*Interval from the first administration of the ICI to the development of TB
ICI, immune checkpoint inhibitor; TB, tuberculosis.

Table 3 The incidence rate of TB in patients with cancer exposed to ICIs

	ICI exposure				ICI non-exposure			
	n (%)	TB events	Person-years	Incidence* (95% CI)	n (%)	TB events	Person-years	Incidence* (95% CI)
Total	5037 (100.0)	20	2959	675.8 (412.8 to 1043.8)	136 513 (100.0)	896	149 562	599.1 (560.5 to 639.6)
Sex								
Male	3752 (74.5)	16	2173	736.5 (421.0 to 1196.0)	92 050 (67.4)	676	98 733	684.7 (634.0 to 738.3)
Female	1285 (25.5)	4	787	508.3 (138.5 to 1301.6)	44 463 (32.6)	220	50 829	432.8 (377.5 to 494.0)
Age (years)								
20–29	8 (0.2)	0	5		288 (0.2)	3	319	939.7 (193.8 to 2746.1)
30–39	40 (0.8)	0	26		1278 (0.9)	6	1464	409.9 (150.4 to 892.2)
40–49	269 (5.3)	1	184	544.4 (13.8 to 3033.0)	5805 (4.3)	28	6992	400.5 (266.1 to 578.8)
50–59	976 (19.4)	4	607	658.7 (179.5 to 1686.6)	20 749 (15.2)	86	25 013	343.8 (275.0 to 424.6)
60–69	1793 (35.6)	6	1058	567.3 (208.2 to 1234.7)	40 364 (29.6)	258	47 363	544.7 (480.3 to 615.4)
70–79	1615 (32.1)	5	914	546.8 (177.5 to 1276.0)	46 003 (33.7)	335	49 406	678.1 (607.4 to 754.7)
≥80	336 (6.7)	4	165	2422.3 (660.0 to 6202.1)	22 026 (16.1)	180	19 006	947.1 (813.8 to 1096.1)
Type of cancer								
NSCLC	3988 (79.2)	19	2336	813.2 (489.6 to 1269.9)	94 208 (69.0)	752	96 624	778.3 (723.6 to 836.0)
Urothelial carcinoma	337 (6.7)	0	173		38 931 (28.5)	135	49 047	275.3 (230.8 to 325.8)
Melanoma	712 (14.1)	1	450	222.0 (5.6 to 1237.0)	3374 (2.5)	9	3891	231.3 (105.8 to 439.0)

*Indicates incidence rate per 100,000 person-years.
ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; TB, tuberculosis.

eightfold higher relative to the general population. However, there were no significant differences in risk for TB in patients with cancer according to ICI exposure. These findings suggest that the development of TB in patients with cancer receiving ICIs was associated with the underlying malignancy rather than the exposure to ICIs. To the best of our knowledge, this is the first study illustrating the burden of TB in cancer patients with or without ICI exposure.

Similar to findings in several chronic infections, including HIV, immune checkpoint proteins (programmed death-1 [PD-1] and programmed death-ligand 1 [PD-L1]) were overexpressed in the monocytes or natural killer cells collected from patients with active TB.[26 27] An enhanced PD1/PD-L1 pathway can contribute to chronic and persistent infections through the dysfunction of immune effector cells. Inhibiting the immune checkpoint pathway may therefore prevent TB reactivation by interfering with the ability of mycobacterium to exploit the PD1/PD-L1 pathway for immune evasion. In animal models, however, PD-1 deficient mice were more susceptible to mycobacterium than wild-type mice, and they showed more evidence of

Table 4 The standardized incidence ratio of TB in patients with cancer exposed to ICIs

	Standardized TB incidence rate*	95% CI	TB incidence rate in general population*	95% CI	Standardized incidence ratio	95% CI	P value
ICI exposure							
Total	494.4	492.3 to 496.5	61.4	60.6 to 62.1	8.1	8.0 to 8.2	<0.001
Male	428.2	425.3 to 431.0	71.6	70.4 to 72.2	6.0	5.9 to 6.1	<0.001
Female	559.3	556.1 to 562.5	51.4	50.4 to 52.3	10.9	10.7 to 11.1	<0.001
ICI non-exposure							
Total	502.6	500.5 to 504.8	61.4	60.6 to 62.1	8.2	8.1 to 8.3	<0.001
Male	600.0	596.7 to 603.4	71.6	70.4 to 72.2	8.4	8.2 to 8.5	<0.001
Female	407.1	404.4 to 409.9	51.4	50.4 to 52.3	7.9	7.8 to 8.1	<0.001

*Indicates incidence rate per 100,000 person-years.
ICI, immune checkpoint inhibitor; TB, tuberculosis.

Table 5 Risk of tuberculosis in patients with cancer

	Total, (n)	TB cases, (n)	Person-years	Unadjusted		Adjusted	
				HR (95% CI)	P value	HR (95% CI)	P value
Age, year				1.02 (1.02 to 1.03)	<0.001	1.03 (1.02 to 1.03)	<0.001
Sex							
Male	95,802	692	100 905	1.54 (1.33 to 1.79)	<0.001	1.61 (1.39 to 1.89)	<0.001
Female	45,748	224	51,616	1 (reference)		1 (reference)	
Health insurance type							
National health insurance	127,201	837	142,716	1 (reference)	0.02	1 (reference)	
Medical aids*	8495	73	8544	1.40 (1.10 to 1.78)	0.01	1.28 (1.01 to 1.63)	0.04
Veterans	8147	6	1262	0.90 (0.40 to 2.01)	0.80	0.77 (0.34 to 1.72)	0.52
Type of cancer							
NSCLC	98,196	771	98,960	3.35 (1.80 to 6.25)	<0.001	2.43 (1.30 to 4.54)	0.01
Urothelial carcinoma	39,268	135	49,220	1.27 (0.67 to 2.41)	0.47	0.91 (0.48 to 1.73)	0.76
Melanoma	4086	10	4342	1 (reference)	<0.001	1 (reference)	
Underlying diseases							
Diabetes mellitus	40,605	295	42,149	1.22 (1.07 to 1.41)	0.004	1.07 (0.93 to 1.24)	0.34
Hypertension	73,788	509	78,074	1.18 (1.04 to 1.34)	0.01	0.99 (0.86 to 1.14)	0.86
Chronic lung disease	58,054	491	59,344	1.77 (1.55 to 2.01)	<0.001	1.32 (1.15 to 1.51)	<0.001
Chronic kidney disease	6545	53	6988	1.28 (0.97 to 1.69)	0.08	1.29 (0.97 to 1.72)	0.08
Chronic liver disease	1583	15	1560	1.56 (0.94 to 2.60)	0.88	1.38 (0.83 to 2.31)	0.22
Rheumatic disease	3012	27	3159	1.42 (0.97 to 2.09)	0.07	1.31 (0.89 to 1.93)	0.17
Predisposing factors							
History of LTBI treatment	1735	11	1903	0.97 (0.54 to 1.76)	0.93	0.97 (0.54 to 1.76)	0.92
Active chemotherapy	33,184	306	32,353	1.72 (1.50 to 1.98)	<0.001	1.45 (1.24 to 1.69)	<0.001
Concomitant use of corticosteroid	13,666	125	13,196	1.56 (1.29 to 1.88)	<0.001	1.09 (0.89 to 1.34)	0.4
Concomitant use of immunosuppressant	1963	14	2273	1.03 (0.61 to 1.75)	0.90	0.98 (0.58 to 1.68)	0.95
ICI treatment	5037	20	2959	0.85 (0.55 to 1.33)	0.48	0.73 (0.47 to 1.14)	0.17

*Medical aid is a public assistance program that targets impoverished people in need of medical assistance as part of the South Korean social welfare program.
ICI, immune checkpoint inhibitor; ; LTBI, latent tuberculosis infection; NSCLC, non-small cell lung cancer; TB, tuberculosis.

fulminant infectious processes.[28–30] Thus, the PD-1/PD-L1 pathway may aid in controlling tissue damage by preventing the excessive production of IFN-gamma in effector T cells activated by TB antigens.[31] However, whether TB susceptibility in patients with cancer could be clinically affected by the use of ICIs has not yet been clarified.

We found that there was no significant difference in the TB incidence among cancer patients according to ICI exposure. This finding was consistently observed before and after adjusting for multiple variables including age, sex, cancer type, underlying comorbidities, previous treatment of LTBI, active chemotherapy, and concomitant use of corticosteroids. Therefore, the high rate of TB in the ICI exposure group in our study was likely due to the underlying malignancy rather than exposure to ICIs, given that 19 out of 20 TB cases previously exposed to ICI were

patients with lung cancer. In addition, the use of immunosuppressive medications such as corticosteroids to manage immune-related adverse events following ICI administration may also have contributed to the development of TB in this patient population.[32] Considering the increased risk for TB with corticosteroid use, there may be an additive risk of developing TB in patients with cancer receiving concomitant corticosteroids.[33] Therefore, prescreening for LTBI should be considered in patients with cancer using ICI as recommended by the SITC guideline regarding the possibility of immune-related adverse events requiring the use of corticosteroids or TNF inhibitors.[20 32]

It has been reported that patients with solid cancers have a risk of developing active TB that is two to three times greater that of the general population.[13–15] In particular, the incidence of TB in patients with lung cancer was

Table 6 Subgroup and sensitivity analyses

	TB events in non-exposure group, (n)	TB events in ICI exposure group, (n)	HR (95% CI)	P value
Subgroup analyses*				
Age				0.98†
<50	37	1	0.62 (0.09 to 4.55)	0.64
≥50	859	19	0.69 (0.44 to 1.09)	0.11
Sex				0.56†
Male	676	16	0.71 (0.43 to 1.16)	0.17
Female	220	4	0.89 (0.33 to 2.42)	0.83
Cancer subtype				0.98†
NSCLC	752	19	0.76 (0.48 to 1.19)	0.23
Urothelial carcinoma	135	0	0.93 (0.06 to 15.15)	0.96
Melanoma	9	1	0.84 (0.14 to 5.15)	0.85
Sensitivity analyses*				
Defining TB by ICD-10 codes only	1765	44	0.83 (0.61 to 1.12)	0.21
Excluding TB cases within 30days following cancer diagnosis	637	15	0.89 (0.53 to 1.50)	0.67

*All subgroup and sensitivity analyses were adjusted for age, sex, health insurance type, type of cancer, diabetes, hypertension, chronic lung disease, chronic kidney disease, chronic liver disease, rheumatic disease, active chemotherapy, concomitant immunosuppressant use, concomitant use of corticosteroid, and history of treatment for latent TB infection.
†P value for interaction.
ICD-10, International Classification of Diseases code version 10; ICI, immune checkpoint inhibitor; ; NSCLC, non-small cell lung cancer; PS, propensity matching; TB, tuberculosis.

reported to be six to nine times that of the general population.[15 16] Consistent with these findings, our study showed that patients with cancer (including those with lung, urothelial, and skin cancers) had about an eightfold higher rate of developing active TB compared with the general population in South Korea. Given the greater risk of TB in patients with lung cancer compared with those with other types of cancer, the high TB incidence observed in our study was likely due to the large proportion of patients with lung cancer in the study population. Considering the high risk for TB in patients with cancer regardless of ICI exposure, further targeted study is needed to evaluate the cost-effectiveness of prescreening and treatment for LTBI in patients with cancer.

There were several strengths to this study. To the best of our knowledge, this is the first population-based study reporting the risk of TB following ICI exposure. By identifying those exposed to ICIs in a nationwide sample from a country with an intermediate burden of TB, we were able to effectively determine the incidence of the disease in those exposed to ICIs and thus assess whether ICIs were associated with TB occurrence. In addition, an SIR was accurately calculated based on annual statistics of reported TB cases and population census data published by the Korean government. We also excluded individuals with suppressed cellular immunity, which is a known risk factor for the development of TB. In the risk factor analysis, a multivariable analysis was conducted to control for potential confounders after adjusting for a range of variables. In addition, we performed several subgroup and sensitivity analyses to confirm the robustness of our results.

There were several limitations to our study. First, due to the observational nature of the claims database, it cannot be ruled out that TB cases may have been misclassified. The methods used to identify cases of TB in the national claims data and the national reported data were not the same. However, healthcare providers are required to report new cases of TB through a web-based notification system in South Korea,[22 34] and the completeness of the TB reporting data has been found to be over 90% in comparison with the reimbursement data from the NHI.[35] Therefore, misclassification bias is expected to be low in this study. Second, data on TB severity were not assessed. Since concerns have been raised about the more fulminant course of TB after ICI treatment, as seen in animal studies, further studies are needed to address the severity of TB following ICI exposure. Third, only a limited number of ICIs (nivolumab, atezolizumab, and pembrolizumab) and types of cancer (lung cancer, urothelial carcinoma, and skin cancer) were assessed in this study. Therefore, the risk of TB in patients with other types of cancers, as well as in those receiving other types of ICIs, such as CTLA-4 inhibitors, were not evaluated in this study. Fourth, detailed information on PD-1 expression, cancer stage, performance status, surgical history, and prior radiation therapy in patients with cancer were not collected as raw data and therefore not included in the analysis. Fifth, the observation period in the ICI exposure group was relatively short compared with the ICI non-exposure group. Due to the nature of the slow-growing mycobacteria and the shorter observation period in the ICI exposure group, the number of TB events may have been underestimated in current study. Further studies with a longer follow-up

periods may provide better answers in the future. Sixth, because the claims data did not contain the information on exposure history to the index TB patient, it was not possible to distinguish between recently transmitted TB and reactivation of remote infection among the cases of active TB. Therefore, the results of this study should be interpreted with caution, especially in areas with low TB burden where remote infection rather than recent transmission substantially contributes to the burden of active TB.[36]

In our study, the incidence of TB in patients with cancer receiving ICIs was eight times higher than in the general population. However, no significant differences were observed among patients with cancer according to ICI exposure. These findings suggest that patients with cancer undergoing chemotherapy are at risk for developing TB regardless of the type of treatment they are receiving. Further studies are needed to evaluate the cost-effectiveness of testing for and treating LTBI in patients with cancer receiving systemic chemotherapy.

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