의학박사 학위논문

# Risk of Tuberculosis Following Immune Checkpoint Inhibitor Treatment in Cancer Patients: A Population-Based Study

# 심사평가원 빅데이터 자료 분석을 통한 종양 환자에서의 면역관문억제제 사용에 따른 결핵 위험 평가

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배 성 만

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이 논문을 의학박사 학위 논문으로 제출함

2021 년　2 월

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# Summary

**Background:** Development of tuberculosis (TB) during systemic chemotherapy in cancer patients is problematic due to uncontrolled TB infection and delayed cancer treatment, which leads to significant morbidity and mortality. However, there are limited data on whether the use of immune checkpoint inhibitors (ICIs), an emerging class of immunotherapy which stimulate lymphocytes against tumor cells, affects the development of tuberculosis (TB). We evaluated the risk of TB in cancer patients exposed to ICIs (ICI group) compared to the general population and patients receiving non-ICI chemotherapy (non-ICI group).

**Methods:** We performed a population-based retrospective cohort study using the National Health Insurance claims database in South Korea. All adult patients (aged 18 years or older) who were diagnosed with non-small cell lung cancer (NSCLC), urothelial cancer, or melanoma from August 2017 to June 2019 were selected, then those who received ICIs (nivolumab, pembrolizumab, or atezolizumab) or non-ICI chemotherapy were identified. Newly developed TB was defined by relevant International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes for TB and prescription records for anti-TB drugs. The incidence and the standardized incidence ratio (SIR) for TB in ICI users and non-ICI users were calculated. In addition, the risk of TB was compared between ICI users and non-ICI users.

**Results:** A total of 10,497 cancer patients were identified during the study period, including 5037 ICI users and 5460 non-ICI users. The incidence rates of TB were 675.8 and 797.5 per

100,000 person-years in the ICI group and non-ICI group, respectively. Compared with non-ICI users, interval between first ICI administration and development of TB was significantly shorter in ICI users (median [IQR], months, 2.1 [1.1-5.5] vs. 4.9 [2.1-9.4], p=0.049). The SIR of TB in ICI group was 8.06 (95%CI, 7.95–8.16). Compared with non-ICI users, a crude incidence rate ratio of risk for TB in ICI users was 0.74 (95% CI, 0.43–1.27). No differences in risk for TB between ICI users and non-ICI users were also observed in the multivariate analysis (hazard ratio [HR], 0.59; 95% CI, 0.34–1.05) and the inverse probability of treatment weighting analysis (HR, 0.73; 95% CI, 0.41–1.30).

**Conclusion:** Incidence for TB in the cancer patients receiving ICIs in South Korea was 8-fold higher relative to the general population. However, no significant difference was observed in the risk for developing TB among cancer patients according to ICI exposure.

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# INTRODUCTION

The use of immune checkpoint inhibitors (ICIs) has been increasing in the treatment for various types of advanced cancer.[1-3] ICIs exert an anti-cancer effects indirectly by restoring exhausted T cells and boosting T cell immunity through interference between immune checkpoint receptors such as PD1 and their ligands (PD-L1 and PD-L2). As with increasing use of ICIs, several adverse events, including immune-related adverse events, have been reported following its use.[4] In particular, concerns about the occurrence of active tuberculosis (TB) following the ICIs treatment have been continuously raised by various settings.[5] In addition, there were concerns that ICIs caused a more fulminant tuberculosis infection, as observed in several animal model studies.[6,7] However, the association between ICIs use and development of tuberculosis has not yet been established, as most studies describing the development of tuberculosis following the use of ICIs were case reports or case series.[8-15] The development of TB in cancer patients not only contributes to the morbidity and mortality, but also delays anti-cancer chemotherapy. Therefore, the risk of tuberculosis after ICI exposure in cancer patients should be elucidated. We evaluated whether the risk of TB in cancer patients was affected by ICI therapy using the National Healthcare Insurance claims data in South Korea.

# METHODS

## Study design, population, and database

This study is a population-based retrospective cohort study using the nationwide claims database. TB incidence was calculated in cancer patients who was exposed to ICIs (ICI group) and compared to the general population and cancer patients receiving chemotherapy other than ICIs (non-ICI group). In South Korea, the National Health Insurance (NHI) system provides healthcare coverage to entire population residing the country. Healthcare providers are required to claim medical services performed by those for reimbursement of payments by the NHI. All the reimbursing claims are collected and reviewed by the Health Insurance and Review Assessment (HIRA).[16] The HIRA data encompasses all claimed healthcare records, including medical visits, prescriptions, procedures, and surgeries. This database has become publically available for research purpose from 2009 after encryption and de-identification processing.

Using the repository of HIRA database, all the adult individuals (≥18 years) who had diagnostic codes for non-small cell lung cancer (NSCLC), urothelial cancer, or melanoma between January 1, 2010 and June 30, 2019, were identified. In South Korea, from August 21, 2017, the use of nivolumab and pembrolizumab has been covered by NHI for the palliative treatment in NSCLC patients who had failed platinum-based chemotherapy. Subsequently, the use of atezolizumab in patients with NSCLC or urothelial cancer who had failed platinum-based chemotherapy began to be covered by NHI on January 12, 2018. Lastly, the use of nivolumab and pembrolizumab in patients with advanced melanoma were eligible for NIH coverage on February 5, 2018. Considering that the HIRA data only includes claims data

for medical services covered by the NHI, we identified patients with NSCLC, urothelial cancer, or melanoma between August 1, 2017 and June 30, 2019, during which ICI uses were covered by the NHI. Before identifying ICI users and non-ICI users, several exclusion criteria were adopted. In order to minimize the difference of clinical setting between ICI users and non-ICI users, we excluded patients without receiving systemic chemotherapy. And we also excluded patients with NSCLC or urothelial carcinoma undergoing chemotherapy without prior treatment history of platinum-based regimens. Finally, we excluded following cases: i) patients with past history of tuberculosis, ii) patients who were diagnosed with human immunodeficiency virus infection (HIV), solid organ transplant (SOT), inflammatory bowel disease (IBD), or hematologic malignancy, iii) patients who previously received immunosuppressants other than corticosteroids, or iv) no available claims records after the first dose of ICI or comparator drugs.

In this study population, the TB incidences were calculated in ICI users and non-ICI users. Calculated TB incidence in ICI users was compared to the general population and non-ICI users (active comparators). For estimating standardized incidence ratio (SIR) for TB in ICI users compared with the general population, the annual reports for the notified tuberculosis cases in South Korea and an official statistical database for annual population census in South Korea were used.[17,18] This study was approved by the Institutional Review Board of the Asan Medical Center (Approval number. 2020-0088), which waived the requirement for written or verbal consent from the patients based on the observational nature of the study and the fact that the patient identifiers were fully encrypted prior to analysis.

**Outcome and definitions**

The outcome of interest in this study was development of active TB in cancer patients

requiring anti-TB therapy. Newly developed TB cases were identified by relevant diagnostic codes for active tuberculosis (International Classification of Diseases-10 [ICD-10] code A15, A16, A17, A18, or A19) with prescription records for anti-TB medications as described in our previous study.[19] Cancer patients with NSCLC, urothelial carcinoma, and melanoma were identified by the relevant diagnostic codes. ICI users were identified in cancer patients when the prescription records for ICIs was confirmed at least once during the study period. The non-ICI users (active comparators) were defined as cancer patients receiving systemic chemotherapy other than ICIs during the same time period. Comparator drugs of each type of cancer are summarized in Table 1. The length of observation period was from the first administration of the ICI or the comparator drug to the end of the follow-up data (lost to follow-up). At the date of development of TB or being lost to follow-up in patients during observation period were censored.

In addition, the following clinical characteristics that may act as potential confounders for development of TB were identified using the appropriate ICD-10 codes: age, sex, hypertension, diabetes, dyslipidemia, chronic lung disease, chronic kidney disease, chronic liver disease, rheumatic disease, prior treatment for latent TB infection (LTBI), concomitant corticosteroid use, and concomitant use of immunosuppressants such as tumor necrosis factor-alpha inhibitors. Corticosteroid use was defined by the prescription records for prednisone equivalents $\geq$ 15 mg/day for at least 14 days. Index for immunosuppressants is summarized in Table 2.

**Statistical analysis**

Categorical data were compared by chi-squared tests and continuous variables were analyzed by unpaired Student's *t*-tests. The incidence of TB was analyzed and presented as

**Table 1. Medication index for immunosuppressants used in this study.**

| Therapeutic class | Generic name |
|---|---|
| Biologics | abatacept |
| | adalimumab |
| | anakinra |
| | etanercept |
| | golimumab |
| | infliximab |
| | leflunomide |
| | rituximab |
| | tocilizumab |
| | tofacitinib |
| | baricitinib |
| Corticosteroids | prednisolone |
| | methylprednisolone |
| | hydrocortisone |
| | dexamethasone |
| | triamcinolone |
| Others | methotrexate |
| | leflunomide |
| | ciclosporin (cyclosporin A) |
| | cyclophosphamide |
| | tacrolimus |
| | sirolimus |
| | azathioprine |
| | sulfasalazine |
| | mycophenolate mofetil |
| | everolimus |
| | bucillamine |
| | mizoribine |

**Table 2. Medication index for chemotherapy agents prescribed in non-ICI users (active comparators).**

| Type of cancer | Generic name |
|---|---|
| non-small cell lung cancer | paclitaxel, docetaxel, gemcitabine, irinotecan, gefitinib, erlotinib, crizotinib, ceritinib, alectinib, osimertinib, brigatinib, pemetrexed |
| urothelial carcinoma | doxorubicin, ifosfamide, vinblastine, gemcitabine |
| melanoma | dacarbazine, high dose interferon alpha, vinblastine, cisplatin, vemurafenib, dabrafenib |

incidence rates per 100,000 person-years (PY). The confidence intervals (CI) of the incidence rates were estimated under the assumption that the number of cases followed a Poisson distribution. The incidence of TB in the ICI user group and that in the comparator group (non-ICI users) were calculated and compared. In addition, the incidence rate ratio (IRR) and standardized incidence ratio (SIR) with 95% CI were calculated to compare incidence of TB in ICI users to that in general population or non-ICI users. Adjusted hazard ratio was estimated using a multivariate Cox proportional model with controlling baseline covariates including age, sex, type of cancer, diabetes, hypertension, chronic lung disease, chronic kidney disease, chronic liver disease, rheumatic disease, prior platinum-based regimen, concomitant use of corticosteroid, and concomitant use of immunosuppressant. Inverse probability of treatment weighting (IPTW) based on the propensity score was applied to adjust for differences in baseline characteristics between two groups. Propensity scores were estimated using multiple logistic regression model in which baseline variables of clinical and demographic characteristics were included. Each patient was then weighted by the inverse of the probability of receiving the treatment that the patient received in reality. We utilized the standardized mean difference (SMD) to estimate the differences in baseline characteristics. Less than 10% SMD has been suggested to denote that the imbalance may be negligible.

We performed analyses in subgroups defined according to age (<50 years vs. ≥50 years), sex, and cancer type. Presence of interactions was evaluated in these subgroups. In addition, we conducted several sensitivity analyses to test the robustness of our results. These analyses were performed on following conditions: i) excluding TB cases within 30 days after first dose of ICI or comparator drug to rule out the influence of prior chemotherapy regimen, ii) restriction of observation period ends until 30 days after the last dose of ICI or comparator drug, and iii) restriction of observation period ends 90 days after the last dose of ICI or comparator drug.

In South Korea, the entire population residing within the country is a beneficiary of the National Healthcare System, which provides universal coverage. Healthcare providers are required to bill their medical services for reimbursement from the government, and the insurance claims data incorporate information such as diagnostic codes, procedures or prescription, and personal information. Considering the comprehensive nature of the claims data, we assumed that the database has minimal or no missing values. All reported *p* values are two-sided, and $p < 0.05$ were considered statistically significant. Data manipulation and statistical analyses were conducted using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA).

# RESULTS

During study period, a total of 160,078 adult patients (>18 years) with diagnostic codes for NSCLC, urothelial carcinoma, or melanoma was identified (Figure 1). Among these, 108,673 cancer patients receiving systemic chemotherapy were identified. After excluding patients according to exclusion criteria, 10,497 patients with NSCLC, urothelial carcinoma, or melanoma were analyzed. Of these, 5037 patients were ICI users, and remaining 5460 patients were non-ICI users. The number of patients who received nivolumab, pembrolizumab, and atezolizumab was used in 1972, 2593, and 472 patients, respectively.

The baseline characteristics of study population including ICI users and non-ICI users are shown in Table 3. We found that the majority of the patients in study cohort were male, elderly, and had lung cancer. ICI users had a high prevalence of NSCLC and urothelial cancer related to non-ICI users. The prevalence of diabetes, hypertension, chronic lung diseases were also higher in ICI users compared with non-ICI users. Proportion of latent TB treatment was similar between two groups. Prior use of platinum-containing chemotherapy, concomitant corticosteroid or immunosuppressant including TNF-alpha inhibitor were more common in the non-ICI users than ICI users.

**Newly developed TB cases in ICI users and non-ICI users**

A total of 20 TB cases were identified in ICI users. The detailed characteristics of TB cases following ICI use are summarized in Table 4. The majority of patients experiencing TB were male (80% [16/20]) and had NSCLC (95% [19/20]). Among 20 TB cases, 12 occurred

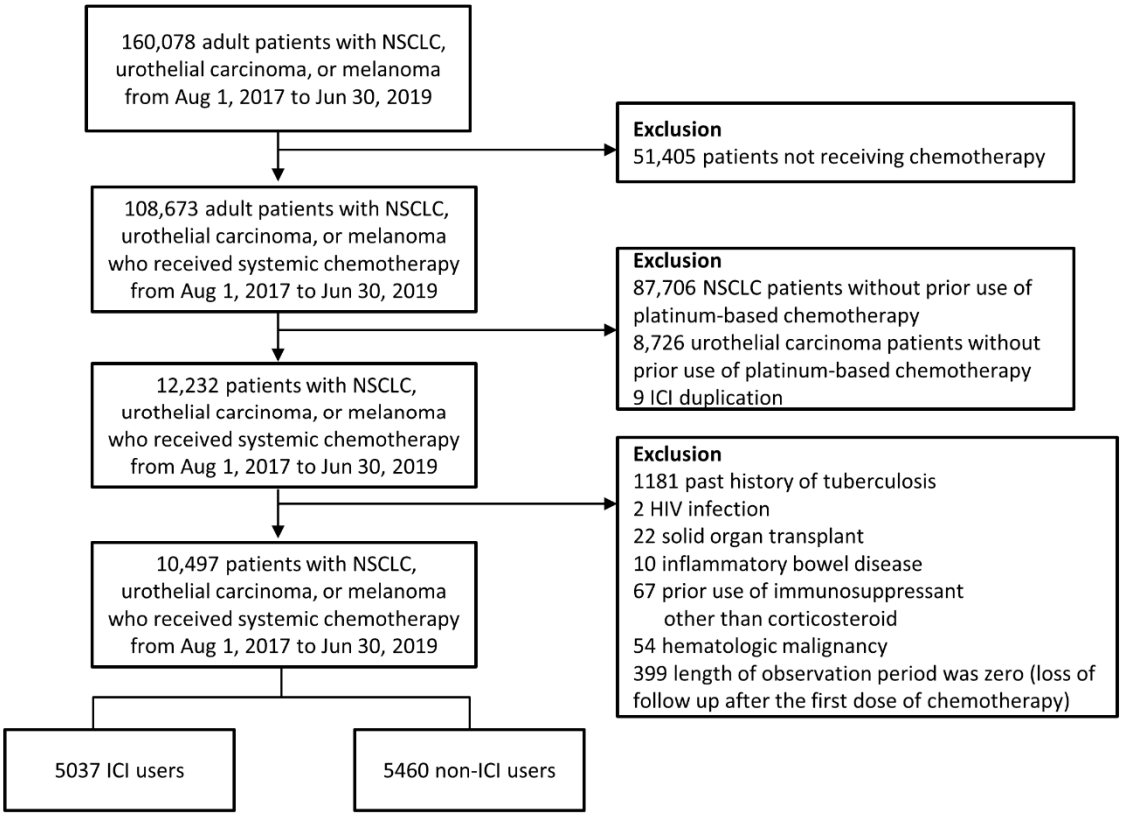


**Figure 1. Flow chart of study population selection**

**Table 3. Baseline characteristics of cancer patients with or without immune checkpoint inhibitor (ICI).**

| | ICI users | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Nivolumab (N=1972) | Pembrolizumab (N=2593) | Atezolizumab (N=472) | Total ICI user (N=5037) | Non-ICI users (N=5460) | p-value* | SMD* | IPTW-weighted SMD* |
| Age, year, mean±SD | 65.8±9.7 | 65.5±10.2 | 67.7±9.9 | 65.8±10 | 64.7±9.9 | <0.001 | 0.108 | 0.0187 |
| Gender | | | | | | <0.001 | 0.1342 | 0.0194 |
| Male | 1522 (77.2) | 1858 (71.7) | 372 (78.8) | 3752 (74.5) | 3737 (68.4) | | | |
| Female | 450 (22.8) | 735 (28.3) | 100 (21.2) | 1285 (25.5) | 1723 (31.6) | | | |
| Insurance | | | | | | <0.001 | 0.0652 | 0.0018 |
| Health insurance | 1779 (90.2) | 2380 (91.8) | 425 (90) | 4584 (91) | 5066 (92.8) | | | |
| Medical aids | 156 (7.9) | 193 (7.4) | 45 (9.5) | 394 (7.8) | 379 (6.9) | | | |
| Veterans | 37 (1.9) | 20 (0.8) | 2 (0.4) | 59 (1.2) | 15 (0.3) | | | |
| Type of cancer | | | | | | <0.001 | 0.4014 | 0.0514 |
| NSCLC | 1796 (91.1) | 2038 (78.6) | 154 (32.6) | 3988 (79.2) | 4712 (86.3) | | | |
| Urothelial carcinoma | 9 (0.5) | 10 (0.4) | 318 (67.4) | 337 (6.7) | 565 (10.3) | | | |
| Melanoma | 167 (8.5) | 545 (21) | 0 (0) | 712 (14.1) | 183 (3.4) | | | |
| Underlying diseases | | | | | | | | |
| Diabetes mellitus | 641 (32.5) | 804 (31) | 145 (30.7) | 1590 (31.6) | 1555 (28.5) | <0.001 | 0.067 | 0.008 |
| Hypertension | 968 (49.1) | 1220 (47) | 251 (53.2) | 2439 (48.4) | 2440 (44.7) | <0.001 | 0.075 | 0.003 |
| Chronic lung disease | 1163 (44.9) | 1392 (294.9) | 210 (10.6) | 2765 (54.9) | 2795 (51.2) | <0.001 | 0.074 | 0.005 |
| Chronic kidney disease | 72 (2.8) | 72 (15.3) | 55 (2.8) | 199 (4) | 192 (3.5) | 0.24 | 0.023 | 0.005 |
| Chronic liver disease | 37 (1.4) | 34 (7.2) | 6 (0.3) | 77 (1.5) | 54 (1) | 0.01 | 0.048 | 0.003 |
| Rheumatic disease | 49 (1.9) | 73 (15.5) | 17 (0.9) | 139 (2.8) | 109 (2) | 0.01 | 0.050 | 0.007 |
| Predisposing factors | | | | | | | | |
| History of LTBI treatment | 19 (0.7) | 28 (1.1) | 2 (0.1) | 49 (1.0) | 53 (1.0) | 0.99 | 0.000 | 0.004 |
| Prior use of platinum-based chemotherapy | 1734 (66.9) | 1983 (76.5) | 452 (22.9) | 4169 (82.8) | 5277 (96.6) | <0.001 | 0.469 | 0.015 |
| Concomitant use of corticosteroid | 459 (17.7) | 533 (20.6) | 71 (3.6) | 1063 (21.1) | 1807 (33.1) | <0.001 | 0.272 | 0.012 |
| Concomitant use of immunosuppressant | 14 (0.5) | 34 (1.3) | 26 (1.3) | 74 (1.5) | 338 (6.2) | <0.001 | 0.250 | 0.003 |

SD, standard deviation; NSCLC, non-small cell lung cancer; LTBI, latent tuberculosis infection; SMD, standardized mean difference; IPTW, inverse probability of treatment weighting.

* For comparison of total ICI users and non-ICI users.

**Table 4. Characteristics of the 20 patients with tuberculosis following ICI use.**

| Patient number | Age | Gender | Cancer type | Other comorbidities | Type of ICI | Interval* | Type of TB | concomitant corticosteroid | concomitant immunosuppressant |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 73 | male | lung cancer | | nivolumab | 5.7 | pulmonary | No | No |
| 2 | 80 | male | lung cancer | hypertension, chronic lung disease | nivolumab | 1.3 | pulmonary | No | No |
| 3 | 65 | male | lung cancer | chronic lung disease | nivolumab | 1.7 | miliary | No | No |
| 4 | 82 | male | lung cancer | chronic lung disease | pembrolizumab | 1.3 | pulmonary | No | No |
| 5 | 74 | female | lung cancer | hypertension, diabetes, chronic kidney disease | pembrolizumab | 0.4 | meningitis | Yes | No |
| 6 | 81 | female | melanoma | hypertension, chronic lung disease | pembrolizumab | 0.7 | pulmonary | No | No |
| 7 | 65 | male | lung cancer | | pembrolizumab | 2.8 | vertebra | Yes | No |
| 8 | 44 | female | lung cancer | hypertension | nivolumab | 1.5 | pulmonary | No | No |
| 9 | 61 | male | lung cancer | chronic lung disease | pembrolizumab | 4.7 | pericarditis | No | No |
| 10 | 64 | male | lung cancer | hypertension, diabetes | pembrolizumab | 5.3 | pulmonary | Yes | No |
| 11 | 58 | male | lung cancer | | pembrolizumab | 2.3 | pulmonary | No | No |
| 12 | 59 | male | lung cancer | hypertension, chronic lung disease | pembrolizumab | 0.9 | pulmonary | Yes | No |
| 13 | 71 | male | lung cancer | hypertension, chronic lung disease | nivolumab | 0.6 | pulmonary | No | No |
| 14 | 53 | male | lung cancer | chronic lung disease | nivolumab | 7.5 | pulmonary | Yes | No |
| 15 | 54 | male | lung cancer | diabetes, chronic lung disease | pembrolizumab | 2.8 | pulmonary | No | No |
| 16 | 79 | male | lung cancer | chronic lung disease | pembrolizumab | 2 | pulmonary | Yes | No |
| 17 | 67 | female | lung cancer | hypertension, diabetes | nivolumab | 16.5 | pulmonary | Yes | No |
| 18 | 78 | male | lung cancer | chronic lung disease | pembrolizumab | 13.6 | pulmonary | No | Yes |
| 19 | 61 | male | lung cancer | hypertension, diabetes, chronic lung disease | pembrolizumab | 0.6 | pulmonary | Yes | No |
| 20 | 83 | male | lung cancer | chronic lung disease | nivolumab | 9.1 | pulmonary | No | No |

* Time since ICI treatment, months

in patients received pembrolizumab, and 8 occurred in patients received nivolumab. No TB case was found in patients with urothelial carcinoma or patients receiving atezolizumab. TB developed at median 2.1 months (range, 0.4–16.5) after the first dose of ICI treatment.

In non-ICI users, 42 TB cases were identified during study period. The detailed characteristics of TB cases in non-ICI users are summarized in the Table 5. Compared with TB cases in non-ICI users, those in ICI users occurred significantly earlier in time after chemotherapy (median [IQR], months, 2.1 [1.1-5.5] vs. 4.9 [2.1-9.4], p=0.049). The comparison of TB cases that occurred in ICI users and non-ICI users are shown in Table 6.

**Incidence and standardized incidence ratio (SIR) of TB in ICI users and non-ICI users**

Incidences for newly-developed TB in ICI users and non-ICI users are summarized in Table 7. The crude TB incidence in the patients exposed to ICIs was 675.82 per100,000 PY, and that in the patients exposed to other chemotherapy agents was 797.48 per 100,000 PY. TB incidences were higher in the subgroup of male, elderly (≥50 year), and patients with NSCLC. In ICI users, the SIR estimates of total, male, and female population were 8.06 (95%CI, 7.95–8.16), 5.98 (95%CI, 5.88–6.09) and 10.89 (95%CI, 10.68–11.11), respectively (Table 8). The SIR estimates of total, male, and female population in non-ICI users were 6.55 (95%CI, 6.46–6.63), 9.43 (95%CI, 9.27–9.59) and 2.61 (95%CI, 2.55–2.67), respectively (Table 8).

**Comparison of risks for TB between ICI users and non-ICI users**

Compared with non-ICI users, the risk of TB was not significantly different in ICI users (crude IRR, 0.74; 95% CI, 0.43–1.27; Table 9). After multivariate Cox regression analysis,

**Table 5. Characteristics of the 42 patients with tuberculosis following non-ICI chemotherapy.**

| Patient number | Age | Gender | Cancer type | Other comorbidities | Interval* | Type of TB | concomitant corticosteroid | concomitant immunosuppressant |
|---|---|---|---|---|---|---|---|---|
| 1 | 69 | male | lung cancer | hypertension, chronic lung disease | 14.5 | pulmonary | No | No |
| 2 | 81 | male | lung cancer | | 2.5 | pulmonary | No | No |
| 3 | 60 | male | lung cancer | diabetes. Chronic lung disease | 9.4 | pulmonary | Yes | No |
| 4 | 55 | male | lung cancer | | 11.5 | pulmonary | Yes | No |
| 5 | 70 | male | lung cancer | hypertension, diabetes | 6.6 | pulmonary | No | No |
| 6 | 68 | male | lung cancer | hypertension, diabetes, chronic lung disease | 9.9 | pulmonary | No | No |
| 7 | 58 | male | lung cancer | | 1.4 | pulmonary | No | No |
| 8 | 80 | male | urothelial carcinoma | hypertension, diabetes, rheumatic disease | 0.9 | pulmonary | No | No |
| 9 | 78 | male | lung cancer | chronic lung disease | 5.9 | pulmonary | No | No |
| 10 | 78 | female | lung cancer | | 8.3 | pulmonary | Yes | No |
| 11 | 84 | male | lung cancer | hypertension, diabetes, chronic lung disease | 4.4 | pulmonary | No | No |
| 12 | 59 | male | lung cancer | chronic lung disease | 4 | pulmonary | Yes | No |
| 13 | 63 | female | lung cancer | chronic lung disease | 0.3 | bone | No | No |
| 14 | 74 | male | lung cancer | hypertension, chronic lung disease | 9.4 | pulmonary | No | No |
| 15 | 79 | male | lung cancer | chronic lung disease | 0.7 | pulmonary | No | No |
| 16 | 70 | male | lung cancer | hypertension, chronic lung disease | 6 | pulmonary | No | No |
| 17 | 50 | male | lung cancer | hypertension, diabetes, chronic lung disease | 0.7 | pulmonary | No | No |
| 18 | 57 | female | lung cancer | | 3 | pulmonary | Yes | No |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 19 | 59 | female | lung cancer | chronic lung disease | 8.1 | pulmonary | Yes | No |
| 20 | 61 | male | urothelial carcinoma | hypertension, diabetes, chronic kidney disease | 12.6 | pulmonary | No | No |
| 21 | 47 | male | lung cancer | chronic lung disease | 3.4 | pulmonary | No | No |
| 22 | 67 | male | lung cancer | hypertension, chronic lung disease | 3.8 | pulmonary | No | No |
| 23 | 61 | male | lung cancer | chronic lung disease | 9.5 | pulmonary | No | No |
| 24 | 67 | male | lung cancer | | 7.9 | pulmonary | No | No |
| 25 | 62 | male | lung cancer | chronic lung disease | 2.6 | pulmonary | No | No |
| 26 | 68 | male | lung cancer | hypertension, diabetes, chronic lung disease | 2.6 | pulmonary | No | No |
| 27 | 61 | male | lung cancer | hypertension, chronic lung disease | 1.1 | pulmonary | No | No |
| 28 | 69 | male | lung cancer | hypertension, diabetes, chronic lung disease | 1.8 | pulmonary | No | No |
| 29 | 49 | male | lung cancer | HTN | 18.1 | pulmonary | Yes | No |
| 30 | 64 | male | lung cancer | hypertension, diabetes | 2.6 | pulmonary | No | No |
| 31 | 72 | male | lung cancer | hypertension, chronic lung disease | 7.2 | pulmonary | No | No |
| 32 | 58 | female | melanoma | chronic lung disease | 5.4 | pulmonary | No | No |
| 33 | 64 | male | lung cancer | hypertension, chronic lung disease, chronic kidney disease | 11.9 | pulmonary | No | No |
| 34 | 62 | male | lung cancer | diabetes, chronic lung disease | 1.9 | pulmonary | No | No |
| 35 | 66 | male | lung cancer | chronic lung disease | 0.5 | pulmonary | No | No |
| 36 | 66 | male | lung cancer | hypertension, diabetes, chronic lung disease | 12.8 | pulmonary | No | No |
| 37 | 76 | male | urothelial carcinoma | hypertension, diabetes, chronic lung disease | 1.8 | pulmonary | No | No |
| 38 | 56 | male | lung cancer | HTN | 16.3 | pulmonary | Yes | No |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 39 | 61 | male | lung cancer | chronic lung disease, rhematic disease | 2.1 | pulmonary | No | No |
| 40 | 59 | male | lung cancer | | 22 | pulmonary | Yes | No |
| 41 | 63 | male | lung cancer | hypertension, chronic lung disease | 7.7 | pulmonary | Yes | No |
| 42 | 68 | male | lung cancer | hypertension, diabetes, chronic lung disease | 2.5 | pulmonary | No | No |

* Time since ICI treatment, months

**Table 6. Characteristics of newly developed TB cases in ICI users and non-ICI users.**

| Characteristics | ICI users (N=20) | Non-ICI users (N=42) | p |
|---|---|---|---|
| Age, yr, median (IQR) | 66 (60-78.5) | 64 (59-70) | 0.37 |
| Sex | | | 0.65 |
| Male | 16 (80.0) | 37 (88.1) | |
| Female | 4 (20.0) | 5 (11.9) | |
| Type of cancer | | | 0.42 |
| NSCLC | 19 (95.0) | 38 (90.5) | |
| Urothelial carcinoma | 0 (0.0) | 3 (7.1) | |
| Melanoma | 1 (5.0) | 1 (2.4) | |
| Time since initial ICI administration, months, median (IQR) | 2.1 (1.1-5.5) | 4.9 (2.1-9.4) | 0.049 |
| Type of TB | | | 0.13 |
| Pulmonary | 16 (80.0) | 41 (97.6) | |
| Bone | 1 (5.0) | 1 (2.4) | |
| CNS | 1 (5.0) | 0 (0.0) | |
| Miliary | 1 (5.0) | 0 (0.0) | |
| Heart | 1 (5.0) | 0 (0.0) | |
| Corticosteroid | 8 (40.0) | 10 (23.8) | 0.31 |
| Immunosuppressants | 1 (5.0) | 0 (0.0) | 0.70 |

TB, tuberculosis; ICI, immune checkpoint inhibitor; IQR, interquartile range.

**Table 7. The incidence rate of TB in cancer patients receiving immune checkpoint inhibitor.**

| | ICI users | | | | Non-ICI users | | | |
|---|---|---|---|---|---|---|---|---|
| | N (%) | TB events | person-years | Incidence* (95% CI) | N (%) | TB events | person-years | Incidence* (95% CI) |
| Total | 5037 (100) | 20 | 2959.37 | 675.82 (412.81-1043.75) | 5460 (100) | 42 | 5266.6 | 797.48 (574.75-1077.96) |
| Gender | | | | | | | | |
| Male | 3752 (74.5) | 16 | 2172.5 | 736.48 (420.96-1196) | 3737 (68.4) | 37 | 3311.2 | 1117.42 (786.77-1540.22) |
| Female | 1285 (25.5) | 4 | 786.87 | 508.34 (138.51-1301.56) | 1723 (31.6) | 5 | 1955.4 | 255.7 (83.03-596.72) |
| Age | | | | | | | | |
| 20-29 | 8 (0.2) | 0 | 4.86 | | 8 (0.1) | 0 | 10.8 | |
| 30-39 | 40 (0.8) | 0 | 26.25 | | 69 (1.3) | 0 | 86.5 | |
| 40-49 | 269 (5.3) | 1 | 183.7 | 544.37 (13.78-3033.01) | 318 (5.8) | 2 | 371.7 | 538.07 (65.16-1943.69) |
| 50-59 | 976 (19.4) | 4 | 607.25 | 658.71 (179.48-1686.55) | 1164 (21.3) | 9 | 1244 | 723.47 (330.82-1373.38) |
| 60-69 | 1793 (35.6) | 6 | 1057.73 | 567.25 (208.17-1234.67) | 2032 (37.2) | 20 | 1915.8 | 1043.95 (637.67-1612.3) |
| 70-79 | 1615 (32.1) | 5 | 914.45 | 546.78 (177.54-1275.99) | 1635 (29.9) | 8 | 1461.8 | 547.27 (236.27-1078.34) |
| ≥80 | 336 (6.7) | 4 | 165.13 | 2422.33 (660-6202.14) | 234 (4.3) | 3 | 176 | 1704.55 (351.52-4981.41) |
| Type of cancer | | | | | | | | |
| NSCLC | 3988 (79.2) | 19 | 2336.47 | 813.19 (489.6-1269.9) | 4712 (86.3) | 38 | 4459.7 | 852.08 (602.98-1169.54) |
| Urothelial carcinoma | 337 (6.7) | 0 | 172.5 | | 565 (10.3) | 3 | 617.9 | 485.52 (100.12-1418.88) |
| Melanoma | 712 (14.1) | 1 | 450.4 | 222.02 (5.62-1237.04) | 183 (3.4) | 1 | 189 | 529.1 (13.4-2947.96) |

TB, tuberculosis; ICI, immune checkpoint inhibitor; CI, confidence interval; NSCLC, non-small cell lung cancer.

*Number indicates incidence rate per 100,000 person-years.

**Table 8. The standardized incidence ratio (SIR) of TB in cancer patients treated with ICIs.**

| | standardized TB incidence rate in ICI users | 95% CI | TB incidence rate in general population | 95% CI | standardized incidence ratio (SIR) | 95%CI | p–value |
|---|---|---|---|---|---|---|---|
| ICI users | | | | | | | |
| Total | 494.38 | 492.25–496.52 | 61.35 | 60.60–62.11 | 8.06 | 7.95–8.16 | <.0001 |
| Male | 428.15 | 425.33–430.98 | 71.55 | 70.40–72.21 | 5.98 | 5.88–6.09 | <.0001 |
| Female | 559.30 | 556.11–562.50 | 51.35 | 50.39–52.33 | 10.89 | 10.68–11.11 | <.0001 |
| Non–ICI users | | | | | | | |
| Total | 401.58 | 399.65–403.50 | 61.35 | 60.6–62.11 | 6.55 | 6.46–6.63 | <.0001 |
| Male | 674.66 | 671.12–678.21 | 71.55 | 70.4–72.71 | 9.43 | 9.27–9.59 | <.0001 |
| Female | 133.89 | 132.33–135.46 | 51.35 | 50.39–52.33 | 2.61 | 2.55–2.67 | <.0001 |

TB, tuberculosis; ICI, immune checkpoint inhibitor; CI, confidence interval.

**Table 9. Risk of TB in cancer patients according to ICI treatment.**

| | no. of event | Hazard ratio | 95% CI | p-value |
|---|---|---|---|---|
| Primary analysis | | | | |
| Unadjusted analysis | 62 | 0.74 | 0.43–1.27 | 0.27 |
| Multivariate analysis* | 62 | 0.59 | 0.34–1.05 | 0.07 |
| IPTW analysis | 62 | 0.73 | 0.41–1.30 | 0.29 |
| Subgroup analysis | | | | |
| Age | | | | 0.84† |
| <50 year | 3 | 0.87 | 0.07–10.53 | 0.91 |
| ≥50 year | 59 | 0.58 | 0.33–1.05 | 0.07 |
| Gender | | | | 0.15† |
| Male | 53 | 0.51 | 0.27–0.94 | 0.03 |
| Female | 9 | 1.58 | 0.40–6.24 | 0.52 |
| Cancer subtype | | | | 0.83† |
| Patients with NSCLC | 57 | 0.65 | 0.36–1.18 | 0.16 |
| Urothelial carcinoma | 3 | 0.26 | 0.01–9.32 | 0.46 |
| Melanoma | 2 | 0.32 | 0.02–5.19 | 0.42 |
| Sensitivity analyses | | | | |
| Excluding TB cases within 30 days after first dose of ICI or comparator drug | 52 | 0.67 | 0.37–1.23 | 0.20 |
| Observation period ends 30 days after the last dose of ICI or comparator drug | 36 | 0.77 | 0.38–1.55 | 0.46 |
| Observation period ends 90 days after the last dose of ICI or comparator drug | 47 | 0.74 | 0.39–1.37 | 0.34 |

TB, tuberculosis; ICI, immune checkpoint inhibitor; IRR, incidence rate ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting.

* adjusted for age, sex, type of cancer, diabetes, hypertension, chronic lung disease, chronic kidney disease, chronic liver disease, rheumatic disease, prior platinum-based regimen, concomitant immunosuppressant use, concomitant use of corticosteroid (>15 mg/d), and past history of treatment for latent TB infection.

† These values denoted p for interaction.

the HR was 0.59 (95% CI, 0.34–1.05) after adjusting covariates including age, sex, type of cancer, diabetes, hypertension, chronic lung disease, chronic kidney disease, chronic liver disease, rheumatic disease, prior platinum-based regimen, concomitant immunosuppressant use, concomitant use of corticosteroids, and past history of treatment for latent TB infection. In IPTW cohort, all variables were adjusted and the SMD for each variable was less than 10% (Table 3). No differences in risk for TB between ICI users and non-ICI users were observed in the inverse probability of treatment weighting analysis (HR, 0.73; 95% CI, 0.41–1.30).

No significant risk was observed in subgroups according to age (<50 year vs. ≥50 year) or cancer type, except for male patients who received ICI showing a low risk for TB (Table 9). However, the incidence of TB was not different between ICI users and non-ICIs users regardless of age group, gender, and cancer type (p=0.84, p=0.15, p=0.83 for interaction, respectively). In the sensitivity analysis, excluding early TB cases that occurred within 30 days after chemotherapy, no significant difference in TB risk was observed between the ICI and non-ICI groups (Table 9). In addition, no significant difference in TB incidence was observed between two groups in the other sensitivity analyses in which the observation period was restricted to 30 and 90 days after the last chemotherapy.

# DISCUSSION

In this population-based, retrospective cohort study, incidence of TB in the patients exposed to ICIs was approximately 8-fold higher relative to that in the general population in South Korea. However, there was no significant differences of risk for TB in cancer patients between ICI users and non-ICI users. These results suggest a high risk of TB among the cancer patients receiving chemotherapy by the intrinsic immunocompromised status of solid cancer and the use of anticancer drugs, on the one hand, raising doubts about existing concerns that ICI will cause higher TB incidence than other anticancer drugs.

Resembling other chronic infections such as HIV, overexpression of PD-1 and PD-L1 in monocytes and NK cells collected from patients with active TB was observed.[20,21] Upregulated PD-1 and PD-L1 expressions caused dysfunction of effector immune cells. These findings indicated that TB exploited PD1/PD-L1 pathway to evade the host immune system and that blockage of this immune checkpoint can prevent overt TB infection. In the studies using experimental animal models, however, PD-1 deficient mice were more susceptible to TB than wild type, and a more fulminant TB infection process was observed.[6,7,22] Thus, the PD-1/PD-L1 pathway may contribute to controlling tissue damage by preventing excessive production of IFN-gamma from T cells activated by TB antigen.[23] However, it has been still unknown whether the TB susceptibility in cancer patients was clinically affected by the use of ICI.

In our study, a higher incidence of TB was observed in ICI users than in the general population. However, the study population of this study consisted mostly of patients with lung cancer in which the risk of TB was reported to be approximately 6 times higher than that

of the general population.[24,25] Therefore, the high TB incidence among ICI users may be due to an increased susceptibility to TB in lung cancer patients rather than effects of ICI itself. In addition, TB incidence in ICI users was not significantly higher compared to non-ICI users receiving other chemotherapy. Both in the multivariate analysis and IPTW analysis in which covariates including concomitant corticosteroid use were adjusted, the risk of TB in ICI users was not significantly different with that in non-ICI users. These findings contradicted previous studies using animal models in which the use of ICI might increase susceptibility to TB compared to other chemotherapy agents. Taken together, the development of TB following ICI therapy is more likely due to the suppressed immune system resulting from the cancer itself or the use of immunosuppressants for managing immune-related adverse events.[26]

The timing of TB occurrence was earlier in ICI users than in non-ICI users. It is possible that blocking PD1/PD-L1 pathway by ICIs can enhance or restore tuberculosis-specific T cell activity, resulting in unveiling the latent or subclinical TB infection. This phenomenon is reminiscent of the immune reconstitution inflammation syndrome (IRIS) in HIV-infected patients, in which pre-existing opportunistic infections are clinically exacerbated with restoration of host immune responses by antiretroviral therapy.[27] However, the total observation period of ICI users was shorter than that of non-ICI users, despite the comparable number of patients in both groups. Therefore, it should be interpreted with caution that the earlier occurrence of TB in ICI users may be due to the relatively limited observation time.

There are several strengths in this study. To the best of our knowledge, this is the first population-based study reporting the risk for TB following ICI exposure. By identifying nation-scale ICI users in a country with an intermediate TB burden, we were able to assess

the risk of TB occurrence following ICI treatment more easily compared to other countries with low TB burden. In addition, an accurate SIR could be calculated based on annual statistics on notified TB cases and population census of South Korea published by the government. Second, we controlled potential confounding factors in the development of TB by excluding patients with suppressed cellular immunity, such as HIV infection, hematologic malignancies, or users of immunosuppressants due to IBD or SOT. In addition, covariates including chronic kidney disease, chronic lung disease, concomitant corticosteroid use, concomitant immunosuppressant use were adjusted in the primary analysis. Finally, the robustness of our results was demonstrated through several sensitivity analyses. Since TB cases that occurred early after ICI use may have occurred due to the effects of previous chemotherapy regimen, we analyzed effect of ICI after excluding TB events that occurred during 30 days after the administration of first ICI dose. In addition, the observation period was restricted to 30 or 90 days after the last ICI exposure in these analyses since the exact duration of the effect by ICI on host immunity are unknown.

There are several limitations in our study. First, there is a possibility of misclassification in identifying TB cases or ICI users due to the observational nature of this study. However, reporting all the newly diagnosed TB cases to health authorities is mandatory for healthcare providers in South Korea, and annual statistics for notified TB based on this reporting system have been published by the government.[17,28] The completeness of the TB notification in South Korea by comparing the notification data from the National Tuberculosis Surveillance System with the reimbursement data from the National Health Insurance was reported to be over 90%.[29] Therefore, bias due to misclassification is rarely expected with data we used in this study. Second, we did not assess the severity of TB cases whether a fulminant or life-threatening TB occurred according to the ICI therapy. If blockade of the PD-1/PD-L1 pathway leads to a more severe TB infection with a prominent pathology

by hyperinflammatory reactions as shown in animal studies, strategies to prevent tuberculosis in ICI users may be needed, regardless of incidence. Further studies are warranted to assess whether TB infection after ICI therapy exhibits a more fulminant disease or not. Third, we only included PD1/PD-L1 inhibitors in this study, including nivolumab, pembrolizumab, and atezolizumab. Therefore, the risk of TB by the use of other types of ICIs, such as CTLA-4 inhibitors, cannot be assessed in this study. Fourth, information on cancer stage, performance status, and history of prior surgery or radiation therapy in cancer patients were not included in analysis. Therefore, these residual confounding factors were not controlled in this study. Finally, our study was conducted in an intermediate TB burden country, thus the impact of ICI on development of TB may differ in other countries with low or high TB incidence.

# CONCLUSION

In our study, the TB incidence in the cancer patients receiving ICIs was 8 times higher than that of the general population, but no significant difference was observed compared with in those receiving chemotherapy other than ICIs. These findings suggest that cancer patients undergoing anti-cancer chemotherapy are in a population at risk of development of TB regardless of ICI treatment. Further studies are needed for evaluating cost-effectiveness of testing and treatment for LTBI in cancer patients receiving systemic chemotherapy.

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# 국문요약

## 심사평가원 빅데이터 자료 분석을 통한종양 환자에서의 면역관문억제제사용에 따른 결핵 위험 평가

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**배경**: 면역관문억제제의 사용이 증가하면서 그에 따른 합병증 발생에 대한 우려도 증가하고 있다. 특히 심각한 감염성 합병증으로 면역관문억제제 사용에 뒤따른 결핵의 발생에 대한 보고들이 점차 증가하고 있으나 면역관문억제제 사용과 결핵 발생 간의 연관성에 대한 연구가 부재한 실정이다. 이에 저자는 한국의 국민건강보험 청구 자료를 이용하여 면역관문억제제 사용군에서의 결핵 발생 위험을 확인하고자 하였다.

**방법**: 저자는 한국의 건강보험 심사평가원 청구 자료를 이용하여 본 연구를 수행하였다. 2017년 8월부터 2019년 6월까지 면역관문억제제를 포함한 항암치료를 받은 비소세포성 폐암, 요로상피세포 암, 그리고 흑색종 환자를 포함하였다. 결핵의 발생은 결핵에 대한 진단 상병 코드와 더불어 항결핵치료제가 처방된 것으로 정의하였다. 면역관문억제제 사용군과 비사용군에서의 결핵의 발생률과 표준화 발생비를 계산하여 일반 인구에 대비한 결핵의 위험도를 추산하였고, 면역관문억제제 사용군과 비사용군 간의 결핵 발생 위험도를 비교하였다.

**결과**: 2017년 8월부터 2019년 6월까지 총 10,497명의 항암치료를 받은 비소세포성 폐암, 요로상피세포 암, 그리고 흑색종 환자가 확인되었다. 이 중 5037명은 면역관문억제제를 한번 이상 사용한 환자였고, 나머지 5460명은 면역관문억제제의 사용력은 없으며 이외의 항암치료를 받은 환자였다. 면역관문억제제 사용군에서는 총 20명의 결핵이 약제 사용 이후 중앙값 2.1개월에 발생하였다. 면역관문억제제 사용군에서의 결핵 발생률은 10만 인년 당 675.82명이었고, 표준화 발생비는 8.06 (95%신뢰구간, 7.95-8.16)였다. 같은 기간 면역관문억제제 비사용군에서의 결핵 발생률은 10만 인년 당 797.48명이었다. 면역관문억제제 비사용군과 비교 시에 면역관문억제제 사용군에서의 결핵 위험도는 발생률 비 0.74 (95% 신뢰구간, 0.43-1.27)이었고 다변량 콕스 회귀 분석으로 도출된 보정된 위험도 비는 0.59 (95% 신뢰구간, 0.34-1.05)이었다. 역확률가중치 기반의 분석에서도 보정된 위험도 비는 0.73 (95% 신뢰구간, 0.41-1.30)으로 면역관문억제제 사용군과 비사용군 간의 결핵 위험도의 유의한 차이는 관찰되지 않았다.

**결론**: 본 연구는 한국의 건강보험심사평가원의 의료 청구 자료를 이용하여 면역관문억제제 사용자에서의 결핵 발생 위험도를 조사하고 일반 인구 및 면역관문억제제 비사용자와의 위험도의 차이를 평가하였다. 일반인구군과 비교 시 면역관문억제제 사용자에서는 결핵 발생률이 8 배 높았다. 그러나 면역관문억제제가 아닌 다른 항암제를 투여 받는 대조군과 비교 시에는 유의한 차이가 확인되지 않았다. 본 연구결과는 면역관문억제제 치료를 받는 고형암환자에서의 잠복 결핵 검진과 치료 전략 수집의 토대로 활용될 수 있을 것으로 기대한다.