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Original Article

Influenza and the risk of active tuberculosis occurrence among individuals with latent tuberculosis infection: A national cohort study in South Korea (2015—2020)

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Abstract *Background:* Influenza's potential impact on active tuberculosis (TB) development has been debated, with limited clinical evidence. To address this, we explored the association between influenza episodes and TB incidence in a national cohort of individuals with latent TB infection (LTBI).
Methods: We examined adults (≥20 years) diagnosed with LTBI between 2015 and 2020, using the Health Insurance Review and Assessment Service's national database in South Korea. We collected demographic data, comorbidities, and influenza episodes within 6 months before and after the initial LTBI diagnosis (prior vs. subsequent episode). We stratified the analysis into groups with and without TB preventive therapy (TPT).
Results: Among 220,483 LTBI subjects, 49% received TPT, while 51% did not. The average age was 48.4 years, with 52% having comorbidities. A prior and subsequent influenza episode was identified in 3221 and 4580 individuals, respectively. Of these, 1159 (0.53%) developed incident TB over an average follow-up of 1.86 years. The incidence rates of TB were comparable between individuals with and without prior and/or subsequent influenza episodes in the TPT group, but 1.4 times higher in the non-TPT group for those with such episodes. Cox proportional-hazards regression analysis indicated that influenza was not a risk factor for

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incident TB in the TPT group. However, a subsequent influenza episode significantly increased TB risk in the non-TPT group (hazard ratio: 1.648 [95% CI, 1.053—2.580]).
Conclusions: In individuals with LTBI not receiving TPT, experiencing an influenza episode may elevate the risk of developing active TB.

Introduction

According to the annual report on the notified cases of tuberculosis (TB) published by the Korea Disease Control and Prevention Agency in 2021, the overall notification rate of new TB cases was 38.8 per 100,000 population, indicating a 55% decrease from that in 2011.[1] Notwithstanding the general reduction in the occurrence rates of TB, it is noteworthy that the burden of TB in South Korea remains significantly high when taking into account its socioeconomic status.[2] The eradication of TB requires the implementation of measures to control latent tuberculosis infection (LTBI) along with improved case detection and effective management of active TB.[3] LTBI is a condition in which a competent human immune system effectively controls the infection caused by *Mycobacterium tuberculosis* (MTB) but can serve as a possible reservoir for the development of active TB in the future.[4] Particularly, as the burden of active TB declines, attention shifts to the prevention of future cases by identifying and treating individuals with LTBI.[3,5]

The factors that can increase the risk of progression of LTBI to active TB include weakened immune system such as human immunodeficiency virus infection, use of tumor necrosis factor-alpha inhibitors, old age, hemodialysis, or alcohol abuse.[4,6] The aforementioned conditions may lead to decreased cellular immunity, which plays a crucial role in controlling MTB infection.[4,7] Thus, individuals with LTBI who have compromised cellular immunity are considered a high-priority group for TB preventive therapy (TPT).[3,5] Additional preventive measures to reduce the risk of TB progression in individuals with LTBI, such as avoiding the use of harmful alcohol, should be implemented.[8]

Influenza virus, a common respiratory virus, can impair the immune system and increase bacterial infection susceptibility.[9] Previous animal and human epidemiologic studies suggested an association between influenza infection and an increased risk of developing active TB.[10—15] However, a retrospective cohort study conducted in an area with a high TB incidence failed to establish an association between the prevalence of antibodies against influenza A and the occurrence of active TB; this study suggested that influenza virus infections do not play a significant role in active TB development.[16] Thus far, evidence of the correlation between influenza virus infection and an increased risk of developing active TB in humans is limited.[17] In this study, we aimed to assess the potential influence of influenza on the progression to active TB in individuals with LTBI. We examined the incidence of TB concerning previous influenza episodes in two separate groups: one with TPT and one without, within a national cohort of individuals with LTBI.

Materials and methods

Data source and study population

This study was conducted using a retrospective population-based cohort from the database of the Health Insurance Review and Assessment Service (HIRA) in South Korea, a government agency that manages the national health insurance system for all citizens and collects their healthcare data. The customized HIRA data for all subjects with the International Classification of Disease (ICD)-10 codes (R768, R7680, R7688, and Z227) for LTBI between January 1, 2013, and December 31, 2021, were obtained. Those with any ICD-10 codes of active TB or LTBI within the past 2 years before the index date (the date of the first LTBI diagnosis) were excluded. Thus, the study population included all individuals with a newly diagnosed LTBI between January 1, 2015 and December 31, 2020. The analysis included subjects aged 20 years or older.

The Institutional Review Board of Kyungpook National University granted exemption approval to this study (approval no: 20220085). Because of the retrospective design of the study, the patients were not engaged in the entire research process, and their identities were anonymized in the claims data. To ensure the confidentiality of patient health information, the analysis was conducted *via* a remote-access program, and only summarized data were extracted.

Definition of TPT, TB, comorbidities, and influenza and study design

The individuals' demographic data, comorbidities, and TPT administration details were obtained, as well as data on influenza episodes, the main focus of this study. TPT was defined as the presence of a prescription for isoniazid alone, rifampicin alone, or both isoniazid and rifampin at least once during the study period. Those who had a prescription for any anti-TB drugs, except isoniazid or rifampin, were excluded (Fig. 1). The presence of recent close contact with and (suspected) exposure to active TB was defined using the ICD-10 code Z201.

The case of TB incidence within 3 months after the index date was considered as prevalent TB. Therefore, we defined incident TB as the presence of ICD-10 codes (A15-A19, U843) and anti-TB drug prescriptions (Supplemental Table 1) occurring more than 3 months but within 24 months after the index date (Fig. 1). Comorbidities including diabetes mellitus, chronic liver disease, chronic kidney disease, chronic lung disease, malignancy, rheumatoid arthritis, and human immunodeficiency virus infection

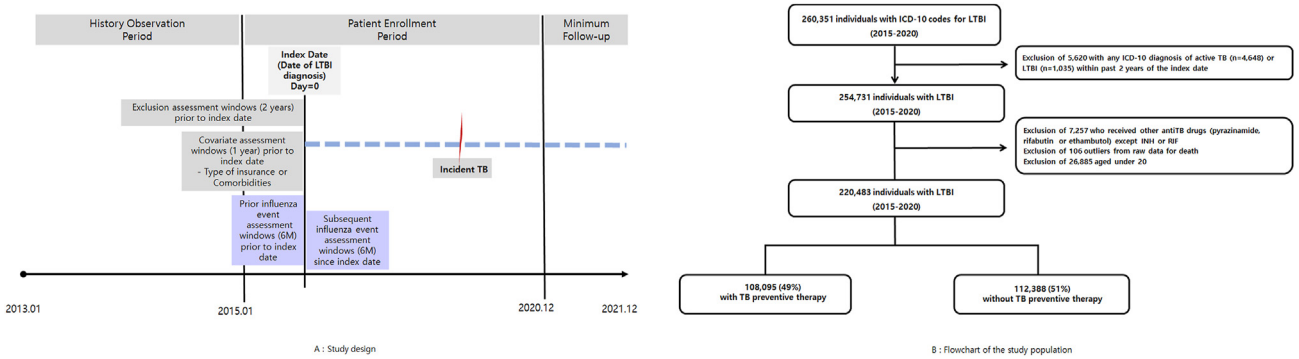

Figure 1. Study design (A) and flowchart of the study population (B). LTBI, latent tuberculosis infection; TB, tuberculosis; ICD10, International Classification of Disease; INH, isoniazid; RIF, rifampin.

in the preceding 12 months of the index date were identified as per the ICD-10 codes listed in Supplemental Table 2.

To assess the influence of previous influenza on the development of active TB, we gathered data on both influenza episodes occurring within a 6-month window before and after the index date (Fig. 1). We defined prior and subsequent influenza as the presence of either ICD-10 codes (J09-J11) or a prescription for oseltamivir within 6 months before and after the index date.[18] The association between influenza episodes and incident TB was examined separately in the TPT and non-TPT groups to mitigate the confounding influence of TPT. The follow-up period for each individual was determined based on their last recorded claim date within a 2-year period from the index date.

Statistical analysis

Statistical analyses were conducted using SAS Enterprise Guide V.7.1. To summarize the subjects' baseline characteristics, the categorical variables were expressed as frequency and percentage, whereas the continuous variables were expressed as mean and standard deviation. Comparison of the categorical and continuous variables was performed using the $\chi 2$ test and independent t-test, respectively.

To calculate the cumulative incidence of TB, the number of incident TB cases was divided by the number of the subjects. The incidence rate of TB was calculated as the number of incident TB cases per 100,000 person years (PY), along with 95% confidence interval (CI). Cox proportional-hazards regression analysis was employed to evaluate the impact of prior and subsequent influenza episode on TB incidence during the first 2 years after the index date. Several sensitivity analyses were conducted. We repeatedly analyzed the association between incident TB risk and influenza, defined either by diagnostic codes regardless of oseltamivir prescription, by oseltamivir prescription regardless of diagnostic codes, or by both diagnostic codes and oseltamivir prescription. Additionally, we conducted identical analyses in the population excluding immunosuppressive conditions.

Results

During the study period, 260,351 individuals with ICD-10 codes for LTBI were identified (Fig. 1). After implementing the exclusion criteria, 220,483 subjects were finally included in the analysis. Of the subjects, 49% received TPT, whereas 51% did not. The subjects' baseline characteristics are presented in Table 1. The mean age of the subjects was 48.4 years, and adults aged 40—59 years accounted for half of the total population. The number of women was twice that of men. Approximately one-tenth of the population consisted of recent close contact cases. A prior influenza episode before the index date was identified in 3221 individuals, making up 1.5% of the total population. A subsequent influenza episode after the index date was observed in 4580 individuals, accounting for 2.1% of the population. During the periods designated for assessing prior and subsequent influenza events, 114 (0.11%) individuals in the TPT group and 162 (0.14%) in the non-TPT group experienced reinfection with influenza. Among the observed comorbidities, chronic lung disease was the most frequent, followed by chronic liver disease and then diabetes mellitus, and 48% of the study population had no comorbidities. Additionally, there were no individuals infected with human immunodeficiency virus.

In both groups with and without TPT, individuals with subsequent influenza episodes were younger, more frequently female, and had more frequent prior influenza episodes occurring within 6 months before the index date, as well as a lower frequency of comorbidities (Table 1). The number of close contacts was significantly higher in the TPT group compared to the group without TPT ($P < 0.0001$). Within the TPT group, individuals with subsequent influenza episodes had a lower frequency of close contact.

Incidence rate of TB in LTBI subjects with and without prior or subsequent influenza episodes

Among 220,483 individuals, 915 patients developed active TB within three months since the index date, classifying them as prevalent TB cases. Out of the remaining 219,568 subjects, 1159 (0.53%) developed incident TB over an average follow-up period of 1.86 years. In the group with TPT, the incidence of TB was 1.6 times higher in those with a prior influenza episode compared to those without. Conversely, in the case of subsequent influenza episodes, the results were opposite. Overall, incidence rate of active TB was similar between the groups with and without prior and/or subsequent influenza episodes (Table 2).

Table 1 Baseline characteristics of latent tuberculosis infection individuals with and without tuberculosis preventive therapy according to the presence and absence of subsequent influenza episode for 6 months following the index date.

Variables	All (n = 220,483)	With TB preventive therapy (n = 108,095)			Without TB preventive therapy (n = 112,388)			*P*-value
		Subsequent influenza events for 6 months following the index date						
		Presence (n = 2385)	Absence (n = 105,710)	*P*-value	Presence (n = 2195)	Absence (n = 110,193)	*P*-value	
Age, mean (SD)	48.4 (14.2)	45.4 (11.6)	47.8 (12.4)	<0.0001	47.5 (15.8)	49.1 (15.8)	<0.0001	<0.0001
Age range, n (%)								
20 to 39	60,625 (27.5)	727 (30.5)	26,607 (25.2)	<0.0001	795 (36.2)	32,496 (29.5)	<0.0001	<0.0001
40 to 59	113,485 (51.5)	1411 (59.2)	61,421 (58.1)		928 (42.3)	49,725 (45.1)		
60 to 79	42,129 (19.1)	241 (10.1)	17,207 (16.3)		392 (17.9)	24,289 (22.0)		
≥80	4244 (1.9)	6 (0.3)	475 (0.4)		80 (3.6)	3683 (3.3)		
Sex, n (%)								
Male	66,884 (30.3)	493 (20.1)	29,242 (27.7)	<0.0001	612 (27.9)	36,537 (33.2)	<0.0001	<0.0001
Female	153,599 (69.7)	1892 (79.3)	76,468 (72.3)		1583 (72.1)	73,656 (66.8)		
Recent close contact, n (%)								
Yes	23,262 (10.6)	274 (11.5)	13,740 (13.0)	0.030	168 (7.7)	9080 (8.2)	0.322	<0.0001
No	197,221 (89.4)	2111 (88.5)	91,970 (87.0)		2027 (92.3)	101,113 (91.8)		
Type of insurance								
Health insurance	213,885 (97.0)	2325 (97.5)	102,777 (97.2)	0.446	2132 (97.1)	106,651 (96.8)	0.365	<0.0001
Medical aid	6598 (3.0)	60 (2.5)	2933 (2.8)		63 (2.9)	3542 (3.2)		
Prior influenza episodes for 6 months before the index date								
Presence	3221 (1.5)	114 (4.8)	1267 (1.2)	<0.0001	162 (7.4)	1678 (1.5)	<0.0001	<0.0001
Absence	217,262 (98.5)	2271 (95.2)	104,443 (98.8)		2033 (92.6)	108,515 (98.5)		
Comorbidity, n (%)								
No comorbidity	105,926 (48.0)	1132 (47.5)	53,439 (50.5)	<0.0001	883 (40.2)	50,472 (45.8)	<0.0001	<0.0001
Diabetes mellitus	8456 (3.8)	52 (2.2)	4121 (3.9)		59 (2.7)	4224 (3.8)		
Chronic liver disease	19,511 (8.9)	245 (10.3)	10,067 (9.5)		162 (7.4)	9037 (8.2)		
Chronic kidney disease	810 (0.4)	5 (0.2)	365 (0.4)		11 (0.5)	429 (0.4)		
Chronic lung disease	33,430 (15.2)	495 (20.3)	15,966 (15.1)		475 (21.6)	16,494 (15.0)		
Malignancy	3558 (1.6)	28 (1.2)	1522 (1.4)		34 (1.6)	1974 (1.8)		
Rheumatoid arthritis	3200 (1.5)	34 (1.4)	1501 (1.4)		22 (1.0)	1643 (1.5)		
Two comorbidities	30,405 (13.8)	291 (12.2)	13,329 (12.6)		310 (14.1)	16,475 (14.9)		
Three or more comorbidities	15,187 (6.9)	103 (4.3)	5400 (5.1)		239 (10.9)	9445 (8.6)		

Table 2 Incidence rate of active tuberculosis in latent tuberculosis infection individuals with and without tuberculosis preventive therapy according to prior and subsequent influenza episodes for 6 months before and following the index date.

	With TB preventive therapy				Without TB preventive therapy			
	N (%)	TB event, N (%)	Cumulative incidence/ 10^5 PY (95% CI)	Incidence rate/ 10^5 PY (95% CI)	N (%)	TB event, N (%)	Cumulative incidence/ 10^5 PY (95% CI)	Incidence rate/ 10^5 PY (95% CI)
Prior influenza episodes								
Presence	1379 (0.6)	11 (0.8)	797.7 (326.3—1269.1)	412.4 (168.7—656.1)	1832 (0.8)	10 (0.6)	545.9 (207.5—884.2)	283.2 (107.7—458.7)
Absence	106,443 (48.5)	524 (0.5)	492.3 (450.1—534.4)	262.6 (240.1—285.1)	109,914 (50.1)	614 (0.6)	558.6 (514.4—602.8)	301.5 (277.6—325.3)
Subsequent influenza episodes								
Presence	2380 (1.1)	6 (0.3)	252.1 (50.4—453.8)	126.9 (25.4—228.5)	2178 (1.0)	20 (0.9)	918.3 (515.8—1320.7)	469.3 (263.6—675.0)
Absence	105,442 (48.0)	529 (0.5)	501.7 (458.9—544.5)	267.9 (245.0—290.7)	109,568 (49.9)	604 (0.6)	551.3 (507.3—595.2)	297.7 (273.9—321.4)
Prior and/or subsequent influenza episodes								
Presence	3646 (1.7)	17 (0.5)	466.3 (244.6—687.9)	236.9 (124.3—349.6)	3849 (1.8)	30 (0.8)	779.4 (500.5—1058.3)	401.1 (257.6—544.6)
Absence	104,176 (47.5)	518 (0.5)	497.2 (454.4—540.1)	265.6 (242.7—288.4)	107,897 (49.1)	594 (0.6)	550.5 (506.3—594.8)	297.4 (273.5—321.4)

TB = tuberculosis; PY = person-years.; CI = confidence interval.

Within the group without TPT, the percentage of incident TB was similar between individuals with and without a prior influenza episode. However, individuals with a subsequent influenza episode presented a higher incidence of TB than those without a subsequent influenza episode (incidence rate per 100,000 PY; 469.3 [95% CI, 263.6—675.0] vs. 297.7 [95% CI, 273.9—321.4]). Overall, the incidence rates of TB per 100,000 PY were 401.1 (95% CI, 257.6—544.6) in the group with prior and/or subsequent influenza episodes and 297.4 (95% CI, 273.5—321.4) in the group without (Table 2). In the sensitivity analysis employing three distinct definitions of influenza, each subgroup exhibited consistent outcomes, demonstrating that individuals with subsequent influenza had approximately 1.6—1.8 times higher TB incidence compared to those without a subsequent influenza episode in the non-TPT group (Supplemental Table 3).

On the other hand, there were no cases of incident TB observed among individuals who experienced recurrent influenza infections (both prior and subsequent) in either the TPT or non-TPT groups during the follow-up period.

The Kaplan—Meier curve presented in Fig. 2A shows that among individuals who received TPT, those with a subsequent influenza episode developed active TB within approximately 6 months after the index date, with only a minor increase in cases with incident TB thereafter. Conversely, among individuals who did not receive TPT, those with a subsequent influenza episode exhibited a higher cumulative incidence of TB over the course of 2 years compared to those without a subsequent influenza episode (Fig. 2B).

Risk factors associated with incident TB in subjects with LTBI

To assess the impact of influenza episode on incident TB within the initial 2 years after the index date in individuals with LTBI, Cox proportional-hazards regression analyses were conducted for both the TPT and non-TPT groups. Within the TPT group, results from the multivariable Cox regression analysis indicated factors linked to an increased risk of TB, such as male gender, dependence on medical aid, diabetes mellitus, chronic kidney disease, chronic lung disease, rheumatoid arthritis, and multiple comorbidities (Table 3).

In the TPT group, there was no significant association between prior or subsequent influenza episodes and the risk of TB. In contrast, within the non-TPT group, advanced age, male gender, reliance on medical aid, subsequent influenza episodes, chronic kidney disease, rheumatoid arthritis, and multiple comorbidities were identified as factors associated with an increased risk of TB. Sensitivity analysis utilizing three distinct influenza definitions consistently revealed that individuals with subsequent influenza were associated with an increased TB risk in the non-TPT group (Supplemental Table 4). Additionally, upon excluding individuals with immunosuppressive conditions such as malignancy, transplantation, and rheumatoid arthritis from the study population, the analysis consistently demonstrated that subsequent influenza episodes were associated with an increased risk of incident TB (data not shown).

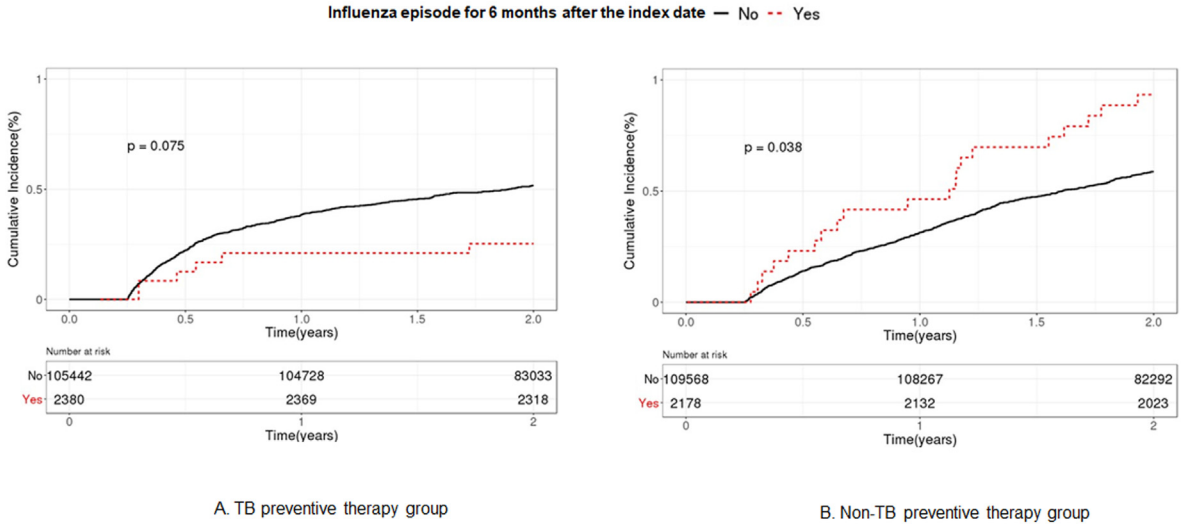

Figure 2. The Kaplan-Meier curve displaying the cumulative incidence of active tuberculosis among subjects with and without a subsequent influenza episode in the latent tuberculosis infection groups with (A) and without (B) tuberculosis preventive therapy. TB, tuberculosis.

Discussion

This nationwide population-based study aimed to determine whether individuals diagnosed with LTBI who had experienced previous influenza have an increased risk of TB in both the TPT and non-TPT groups. While no evidence was found to suggest that influenza played a contributory role among the adult LTBI population receiving TPT, influenza was significantly associated with an increased risk of TB in individuals without TPT. To the best of our knowledge, this is the first study to longitudinally examine the impact of influenza infection on the occurrence of TB among individuals with LTBI. Additionally, the study reaffirmed that advanced age, male gender, chronic kidney disease, chronic lung disease, rheumatoid arthritis, and reliance on medical aid, were associated with a heightened TB risk in a large LTBI population.

Previous studies conducted on mice has shown that the immune response triggered by influenza A virus, specifically the type 1 interferon response, impedes the production of Th1 cytokines, which are crucial for the control of MTB.[11,14,15,19] Contrarily, a previous retrospective cross-sectional study reported no correlation between the seroprevalence of influenza antibodies and the development of active TB.[16] Unlike animal studies, human studies are more complex and diverse, making it more difficult to control confounding factors. While it is possible that an influenza virus infection could contribute to the progression of LTBI to active TB, the extended time interval between TB reactivation and the emergence of TB-related clinical symptoms could lead to the underreporting of such events.[16] A cross-sectional study inherently has limitations in establishing a causal association with a slowly progressive infectious disease like TB. Therefore, this longitudinal nationwide population-based study aims to address this issue and provides an opportunity to assess the correlation between influenza and the reactivation of TB over an extended period.

This study found that influenza does not contribute to the development of active TB in the adult population with LTBI receiving TPT. However, influenza occurring within 6 months after the index date did impact the occurrence of TB in those without TPT. This suggests that influenza episodes may not carry the same level of risk for TB development as other major immunosuppressive conditions in individuals with LTBI. Consequently, in situations where TPT has effectively reduced TB risk, the additional increase in TB risk due to an influenza episode might be relatively minor. However, if TPT is not administered, it appears that events like influenza episodes could contribute to an elevated risk of TB. Moreover, in those not receiving TPT, subsequent influenza episodes affected TB incidence, while prior influenza episodes did not. It is plausible that a more recent infection episode compromised immunity, rendering individuals more susceptible to the progression to active TB. Therefore, it can be inferred that LTBI individuals not receiving TPT need to take precautions to avoid contracting influenza and to get vaccinated annually so as to reduce the risk of developing active TB. Additionally, it can be deduced that older individuals not undergoing TPT due to potential adverse effects are more likely to fall into this category.

This study also provides additional information regarding TB incidence and the risk factors for TB development in a sizable population with LTBI. Given that the annual incidence of TB among the general population in South Korea ranged from 38.8 to 63.2 per 100,000 persons between 2015 and 2020,[20] the TB incidence rate among individuals with LTBI was found to be four to ten times higher than that among the general population. The lower TB incidence in the TPT group, regardless of the presence of an influenza episode in this study, underscores the significance of TPT for individuals with LTBI. While there are numerous studies evaluating risk factors for TB reactivation in specific LTBI populations, such as individuals post-transplant or those with human immunodeficiency virus infections, there is a

Table 3 Cox proportional hazards regression analysis for incident active tuberculosis in individuals with latent tuberculosis infection.

Variables	With TB preventive therapy				Without TB preventive therapy			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age range								
20 to 39	Ref.		Ref.		Ref.		Ref.	
40 to 59	0.801 (0.650–0.988)	0.039	0.661 (0.533–0.820)	0.000	1.099 (0.896–1.347)	0.364	1.045 (0.850–1.286)	0.677
60 to 79	1.724 (1.364–2.179)	<0.0001	0.994 (0.770–1.283)	0.963	1.776 (1.432–2.201)	<0.0001	1.481 (1.172–1.871)	0.001
≥80	3.662 (1.795–7.473)	0.000	1.429 (0.688–2.965)	0.338	2.603 (1.829–3.703)	<0.0001	2.087 (1.438–3.030)	0.000
Sex								
Female	Ref.		Ref.		Ref.		Ref.	
Male	1.894 (1.594–2.249)	<0.0001	1.542 (1.290–1.842)	<0.0001	1.485 (1.267–1.741)	<0.0001	1.366 (1.162–1.605)	0.000
Recent close contact								
No	Ref.		Ref.		Ref.		Ref.	
Yes	1.043 (0.814–7.337)	0.741	0.973 (0.759–1.248)	0.829	1.215 (0.933–1.583)	0.148	1.299 (0.996–1.693)	0.054
Type of insurance								
Health insurance	Ref.		Ref.		Ref.		Ref.	
Medical aid	3.011 (2.189–4.140)	<0.0001	1.902 (1.369–2.642)	0.000	1.975 (1.417–2.753)	<0.0001	1.494 (1.064–2.099)	0.021
Prior influenza episodes								
Absence	Ref.		Ref.		Ref.		Ref.	
Presence	1.596 (0.879–2.901)	0.125	1.374 (0.755–2.502)	0.298	0.945 (0.506–1.765)	0.860	0.897 (0.479–1.682)	0.735
Subsequent influenza episodes								
Absence	Ref.		Ref.		Ref.		Ref.	
Presence	0.489 (0.219–1.903)	0.081	0.503 (0.225–1.126)	0.095	1.594 (1.021–2.489)	0.040	1.648 (1.053–2.580)	0.029
Comorbidity								
No comorbidity	Ref.		Ref.		Ref.		Ref.	
Diabetes mellitus	1.763 (1.130–2.751)	0.012	1.607 (1.022–2.525)	0.040	1.310 (0.874–1.963)	0.191	1.051 (0.695–1.588)	0.815
Chronic liver disease	1.119 (0.777–1.611)	0.547	1.139 (0.790–1.641)	0.487	1.009 (0.730–1.396)	0.955	0.920 (0.663–1.275)	0.615
Chronic kidney disease	4.546 (1.867–11.066)	0.001	3.614 (1.477–8.846)	0.005	2.966 (1.319–6.667)	0.009	2.269 (1.005–5.122)	0.049
Chronic lung disease	1.772 (1.370–2.292)	<0.0001	1.785 (1.379–2.311)	<0.0001	1.062 (0.829–1.359)	0.635	1.017 (0.793–1.304)	0.894
Malignancy	1.708 (0.840–3.472)	0.139	1.876 (0.921–3.822)	0.083	0.642 (0.285–1.442)	0.283	0.603 (0.268–1.359)	0.222
Rheumatoid arthritis	3.653 (2.218–6.018)	<0.0001	3.708 (2.246–6.123)	<0.0001	1.807 (1.054–3.097)	0.031	1.781 (1.038–3.057)	0.036
Two comorbidities	2.364 (1.840–3.037)	<0.0001	2.204 (1.701–2.856)	<0.0001	1.522 (1.220–1.898)	0.000	1.250 (0.989–1.580)	0.061
Three or more comorbidities	5.939 (4.619–7.635)	<0.0001	4.933 (3.759–6.474)	<0.0001	1.997 (1.561–2.555)	<0.0001	1.471 (1.124–1.925)	0.005

TB = tuberculosis; CI = confidence interval.

lack of nationwide studies focused on the general LTBI population.[5,21,22] It may be necessary to provide more proactive TPT in cases involving advanced age, male gender, chronic kidney disease, chronic lung disease, rheumatoid arthritis, and reliance on medical aid.

This study has some limitations. First, although the HIRA database includes a large number of patients, there may be missing or incomplete information. Influenza may have been underreported or misdiagnosed, which could lead to an underestimation of the true association between influenza and TB risk. Second, the duration of the impact of influenza episodes on the risk of TB development in the LTBI population remains uncertain. However, in this study, we assessed the TB risk within a two-year timeframe, and further research is needed to explore this issue. Moreover, we did not evaluate the association between influenza severity and TB reactivation within this cohort. Investigating this relationship would require a larger population with extensive clinical data. Additionally, this study did not account for other respiratory viral or bacterial infections. Lastly, we were unable to ascertain the specific diagnostic tests used for each individual or the types of viruses involved. These limitations could potentially impact the study's findings.

In conclusion, influenza did not appear to significantly contribute to TB reactivation in LTBI individuals receiving TPT. However, it is noteworthy that LTBI individuals not undergoing TPT may be at increased risk of developing active TB following an influenza episode. Therefore, it is advisable for individuals with LTBI who are not on TPT to receive influenza vaccination as a measure to reduce their risk of developing active TB.

Data availability

This study used Health Insurance Review and Assessment Service database (M20221026004). Requests to access these datasets should be directed to HIRA; Official website of HIRA: https://opendata.hira.or.kr; Contact information of data access committee: +82-33-739-1083.

Disclaimer

The authors of this report are responsible for its findings and conclusions, which may not reflect the official position or policy of the funding agencies. It should not be assumed that the funding agencies endorse the report. The funding agencies did not participate in the study's design, data collection, analysis, decision to publish, or manuscript preparation.

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CRediT authorship contribution statement

Jaehee Lee: Writing — review & editing, Writing — original draft, Conceptualization, Methodology. **Hyewon Seo:** Writing — review & editing, Conceptualization. **Dohyang Kim:** Formal analysis, Methodology, Writing — review & editing. **Jinseub Hwang:** Methodology, Formal analysis, Writing — review & editing. **Jin-Won Kwon:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing — review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2024.04.003.