

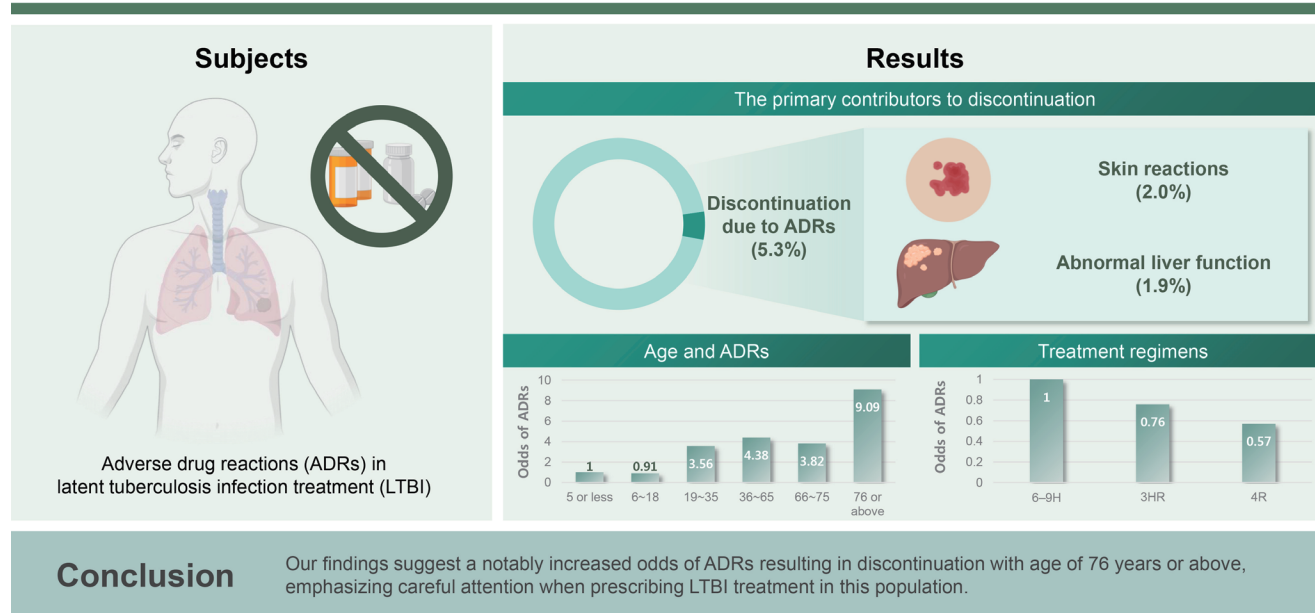


Adverse drug reactions following treatment of latent tuberculosis infection: a linked national tuberculosis surveillance with claims database

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Background/Aims: Few real-world studies explored factors associated with latent tuberculosis infection (LTBI) treatment-related adverse drug reactions (ADRs). This study evaluate ADRs that lead to the discontinuation of LTBI treatment and identify the associated factors, including age groups and drug regimens.

Methods: Using the Korean national tuberculosis registry and HHC investigation database linked to the National Health Insurance Service claims database, we examined treatment discontinuation due to ADRs among HHCs on LTBI treatment from January 2015 to December 2018. Multivariable logistic regression analysis was conducted to examine factors associated with ADRs, including demographics, LTBI treatment, comorbidities, and steroid use.

Results: Among 11,913 participants initiated LTBI treatment, 633 participants (5.3%) discontinued treatment due to ADRs.

The primary contributors to discontinuation were adverse skin reactions (2.0%) and abnormal liver function (1.9%). Risk associated with ADRs and abnormal liver function showed age-related increase, except for the age group 66–75 (adjusted odds ratio [AOR] 3.82, 95% confidence interval [CI] 2.31–6.31) which reported lower OR to that of age group 36–65 (AOR 4.38, 95% CI 3.09–6.21). Three months isoniazid/rifampin and 4 months rifampin exhibited a lower odds of ADRs and abnormal liver function when compared to 6–9 months isoniazid.

Conclusions: We discovered the real-world prevalence of LTBI treatment discontinuation due to ADRs among HHCs. Our findings suggest a notably increased odds of ADRs resulting in discontinuation with age of 76 years or above, emphasizing careful attention when prescribing LTBI treatment in this population. Further studies are warranted to validate these results.

Keywords: Latent tuberculosis; Antitubercular agents; Drug-related side effects and adverse reactions

INTRODUCTION

The prevalence of latent tuberculosis infection (LTBI) is estimated to be approximately 25 percent (95% confidence interval [CI] 19.7–30.0%) globally, and 5 to 15 percent of infected persons develop active tuberculosis (TB) during their lifetime [1–3]. Hence, proper management of LTBI is crucial for eradicating TB, using a strategic prioritization of risk population groups and emphasizing targeted interventions of LTBI testing and treatment [4].

South Korea initiated an LTBI program with HIV-infected persons and household contacts (HHCs) younger than six years in 2004 and expanded its contact investigations to congregate settings in 2013 [5]. The examination rates for TB and LTBI in HHCs increased from 74.5% in 2013 to 99.1% in 2016, contributing to a decrease in new TB notification cases from 36,089 to 30,892 [6]. Despite the successful reduction of TB incidence with LTBI examination, South Korea still has the second-highest incidence of TB among the 34 member countries in the Organization for Economic Cooperation and Development [7].

To further reduce the incidence of new TB cases in Korea, it is imperative to enhance the completion rate of LTBI treatment, which varied from 83 percent among persons with LTBI under 36 years in 2013–2014 to 20.3 percent for HHCs in 2015 [6,8]. Adverse drug reactions (ADRs) are the primary reported reasons for discontinuation and non-completion of LTBI treatment and pose concerns when prescribing LTBI treatment for older adults [4,9]. Given that 51.3% of new TB cases involve older adults, it becomes crucial to provide safety evidence for this population. This evidence could pave the way for potentially expanding the age limit (< 65 yr) of LTBI treatment in Korean guidelines and ultimately reducing

the incidence of new TB cases [7,10].

Limited studies with real-world data on the safety evidence for adults 65 years or older on LTBI treatment have investigated factors associated with ADRs. This study addresses these gaps by examining ADRs that lead to the discontinuation of LTBI treatment and identifying the associated factors, including age groups and drug regimens.

METHODS

Study design and data source

The retrospective cohort study investigated treatment discontinuation due to ADRs among HHCs on LTBI treatment using the linked dataset of the three national databases: the national TB registry, the HHC investigation database, and the National Health Insurance Service (NHIS) database in Korea. We obtained the TB registry and HHC investigation database from January 2015 to December 2018 from the Korean National Tuberculosis Surveillance System (KNTSS). The NHIS claims database between January 2014 and December 2019 was linked to the KNTSS database.

The KNTSS, a web-based TB case notification system of the Korea Disease Control and Prevention Agency, provides a TB registry database for active TB and HHC investigation, including demographic information, LTBI test results, treatment information, treatment discontinuation, and ADR reports of HHCs [6]. TB registry data were linked to the HHC investigation data to examine the incidence of active TB after HHC investigations. We supplemented missing or unknown information from the HHC investigation database by linking it with the NHIS claims database. The NHIS database provided information on participants' comorbidities, treatment of

LTBI course (completion/incompletion), or ADRs [11].

The National Health Insurance Sharing Service (NHIS) provided the data linkage process between KNTSS and NHIS datasets. The data linkage was processed with a deterministic approach and paired with the national identification number. We manually checked matches by comparing the registry and national claims data. The national identification number was deidentified and assigned with an alternative personal identification number after linkage. The linked datasets were provided in a closed environment under the supervision of the NHIS for privacy protection. Data with missing national identification numbers were eliminated from the datasets. This study was approved by the Institutional Review Board (IRB) of Chung-Ang University (IRB number: 1041078-201801-HR-012-01). Informed consent was waived by the IRB. This study was reported under the guidance of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

Study population

The HHCs with positive LTBI tests from January 2015 to December 2018 were investigated for LTBI treatment, completion, and ADRs that resulted in discontinuation (Fig. 1). HHC is the person who has lived in the same house as the participants with active TB for three months of treatment initiation. We excluded HHCs with the incidence of active TB within 30 days of contact investigations. LTBI was determined by positive test results of the tuberculin skin test or interferon-gamma releasing assay administered at the discretion of a physician following national tuberculosis guidelines in Korea. The study cohort received follow-ups until the end of LTBI completion, discontinuation, or up to the NHIS database availability (December 31, 2019). For cases without information on treatment completion in the HHC investigations, we defined treatment discontinuation in the claims database when the treatment duration was below 80% of the defined regimen period (Supplementary Table 1). Participants who discontinued treatment for active TB occurrence and for reasons other than ADRs were excluded from the analysis to identify associated risk factors.

ADRs

The HHC investigation database comprises information on the completion of treatment, including the underlying reason for treatment discontinuation, which is surveyed and recorded by a trained nurse. ADRs were defined using the

aforementioned reported data of main ADRs contributing to treatment discontinuation or identified using the claims database by the International Classification of Disease, Tenth Revision (ICD-10) codes: abnormal liver function (K71, K72, R945), adverse skin reaction (L25–29, L50–54, T784), and platelet abnormality (D473). These codes were assessed after reports of treatment discontinuation for unknown reasons to mitigate the misclassification bias resulting from unreported cases.

Covariates

Demographic variables (i.e., age, sex, level of income) of the study cohort were examined as categorical variables. Age groups were categorized as 0–5, 6–18, 19–35, 36–65, 66–75, 76 years and above. This classification was based on tuberculosis contact screening and treatment guidelines, separating groups under 5 years, 6–18 years, and individu-

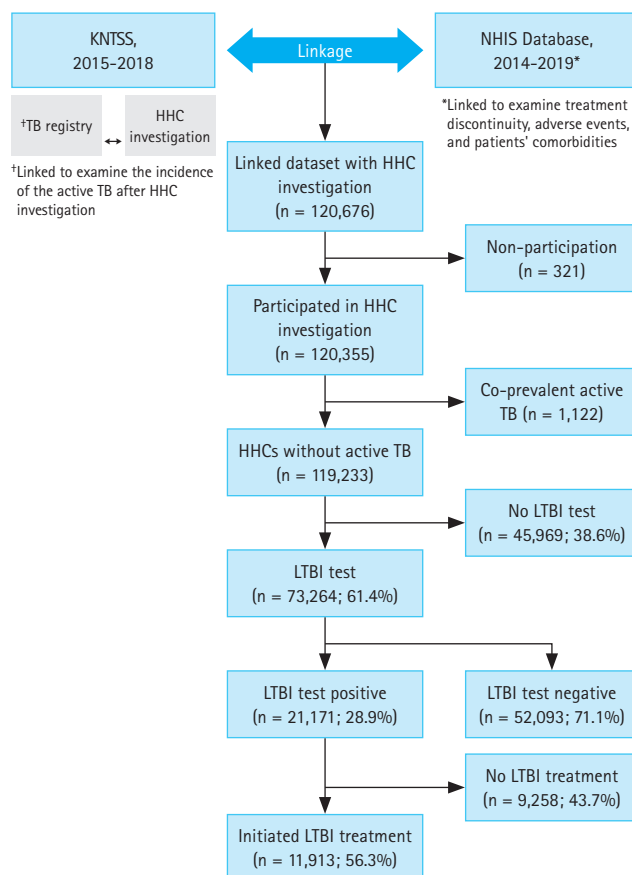


Figure 1. Data sources and flowchart of HHCs who initiated the treatment of LTBI. KNTSS, Korean National Tuberculosis Surveillance System; TB, tuberculosis; HHC, household contact; NHIS, National Health Insurance Service; LTBI, latent tuberculosis infection.

als aged 65 and older for different screening or treatment approaches. The older population was further subdivided to assess the risks associated with advanced age. Insurance level was assessed in quintiles. LTBI treatment comprised either three months of isoniazid/rifampin (3HR), four months of rifampicin (4R), or six to nine months of isoniazid (6–9H), as recommended by Korean tuberculosis guidelines [10]. Comorbidities considered as study variables included chronic obstructive pulmonary disease, diabetes mellitus, renal failure, liver disease, acquired immune deficiency syndrome, malignancy, rheumatic disease/collagen vascular disease, and alcohol abuse [12]. Steroid use was also examined and defined based on records of systemic (oral or injection) steroid prescriptions. Comorbidities and steroid use were assessed within one year before the HHC investigation using the ICD-10 codes of the NHIS database (Supplementary Table 2).

Statistical analysis

Descriptive statistics were used to present the demographics and clinical characteristics of the cases with and without treatment discontinuation due to ADRs. Categorical variables were compared between cases with treatment discontinuation due to ADRs and non-cases using the chi-square test. Continuous variables were summarized by mean and standard deviation, and a t-test was conducted to compare cases and non-cases. The prevalence of treatment discontinuation due to ADRs was reported in numbers and percentages. To identify the risk factors associated with ADRs resulting in discontinuation, we conducted multivariable logistic regression analyses with demographics (sex, age, insurance level), LTBI treatment (3HR, 4R, 6–9H), comorbidities, and steroid use. The results were reported in odds ratios (ORs) and a corresponding 95% CI. Only statistically significant ($p < 0.05$) study variables were included in the final model. The same analysis was also conducted for abnormal liver function and adverse skin reactions.

RESULTS

The linked dataset included 120,676 HHCs from 2015 to 2018, and 119,233 HHCs participated in HHC investigations without active TB (Fig. 1). Among HHCs without active TB, 61.4% underwent an LTBI test ($n = 73,624$), and 28.9% had a positive LTBI test ($n = 21,171$). Approximately half of

the HHCs with LTBI test-positive results initiated the treatment ($n = 11,913$; 56.3%) with 6–9H ($n = 4,545$; 38.1%), 3HR ($n = 5,330$; 53.1%), and 4R ($n = 1,038$; 8.7%). A study cohort of 11,913 HHCs on LTBI treatment was followed up for treatment completion and adverse event reports at discontinuation. Participants who initiated LTBI treatment achieved an overall completion rate of 80.4%, with completion rates for 6–9H at 79.5%, 3HR at 80.9%, and 4R at 81.9% (Table 1). Throughout the follow-up period, 5.3% (633 of 11,913) of the study population discontinued the treatment due to ADRs. Most ADRs ($n = 377$; 59.6%) resulting in discontinuation were detected through the HHC investigation database, while an additional 40.4% ($n = 256$)

Table 1. Prevalence of the adverse drug reactions resulting in treatment of LTBI discontinuation

Treatment course of participants initiated treatment of LTBI	Total ($n = 11,913$)
Treatment completion	9,584 (80.4)
6–9H	3,613 (79.5)
3HR	5,121 (80.9)
4R	850 (81.9)
Discontinued by other reasons ^{a)}	1,696 (14.2)
6–9H	763 (16.8)
3HR	802 (12.7)
4R	131 (12.6)
Discontinued by adverse drug reactions	633 (5.3)
6–9H	169 (3.7)
3HR	407 (6.4)
4R	57 (5.5)
Adverse drug reactions	
Abnormal liver function	230 (1.9)
Adverse skin reaction	233 (2.0)
Platelet abnormality	38 (0.3)
Gastrointestinal disorder	50 (0.4)
Pain	39 (0.3)
Others	43 (0.4)

Values are presented as number (%).

LTBI, latent tuberculosis infection; 6–9H, six to nine months of isoniazid; 3HR, three months of isoniazid/rifampin; 4R, four months of rifampicin.

^{a)}Other reasons include unknown causes ($n = 1,224$; 10.27%), confirmed treatment resistance ($n = 45$; 0.4%), and others ($n = 427$; 3.6%), including uncooperative behavior, self-discontinuation, misclassification of LTBI, etc.

were identified through the claims database.

Table 1 shows the prevalence of treatment discontinuations due to ADRs. The most common ADR resulting in treatment discontinuation was adverse skin reactions, with 233 cases (2.0%), followed by abnormal liver function with

230 cases (1.9%), and gastrointestinal disorders with 50 cases (0.4%). Participants who discontinued LTBI treatment for reasons unrelated to ADRs ($n = 1,696$; 14.2%) were excluded from the analysis, which included unknown reasons, self-discontinuation, death, pregnancy and lactations, TB

Table 2. Demographics, LTBI treatment, and comorbidities of participants with treatment discontinuation due to adverse drug reactions after LTBI treatment compared to participants without discontinuation due to adverse reactions

Variable	Total ($n = 10,217$)	Discontinuation due to adverse drug reaction ($n = 633$)	Without discontinuation due to adverse drug reaction ($n = 9,584$)	<i>p</i> value
Sex				
Male	4,523 (44.3)	225 (35.5)	4,298 (44.8)	< 0.0001
Female	5,694 (55.7)	408 (64.5)	5,286 (55.2)	
Age (yr)				
Less than 5	31.61 ± 23.13	43.49 ± 20.45	30.82 ± 23.26	< 0.0001
5–18	1,883 (18.4)	48 (7.6)	1,835 (19.1)	< 0.0001
19–35	2,304 (22.6)	50 (7.9)	2,254 (23.5)	
36–65	1,347 (13.2)	100 (15.8)	1,247 (13.0)	
66–75	4,191 (41.0)	380 (60.0)	3,811 (39.8)	
76 or above	369 (3.6)	32 (5.1)	337 (3.5)	
Insurance level (quintile)				
0–5th	123 (1.2)	23 (3.6)	100 (1.0)	
6–10th	2,171 (21.2)	157 (24.8)	2,014 (21.0)	0.0027
11–15th	2,076 (20.3)	143 (22.6)	1,933 (20.2)	
16–20th	2,900 (28.4)	179 (28.3)	2,721 (28.4)	
Missing	2,998 (29.3)	154 (24.3)	2,844 (29.7)	
LTBI treatment				
6–9H	72 (0.7)	0 (0.0)	72 (0.8)	
3HR	3,782 (37.0)	169 (26.7)	3,613 (37.7)	< 0.0001
4R	5,528 (54.1)	407 (64.3)	5,121 (53.4)	
Comorbidities				
Chronic obstructive pulmonary disease	907 (8.9)	57 (9.0)	850 (8.9)	
Diabetes mellitus	2,973 (29.1)	175 (27.6)	2,798 (29.2)	0.4062
Renal failure	887 (8.7)	98 (15.5)	789 (8.2)	< 0.0001
Liver disease	51 (0.5)	5 (0.8)	46 (0.5)	0.2839
AIDS	417 (4.1)	41 (6.5)	376 (3.9)	0.0017
Malignancy	4 (0.0)	1 (0.2)	3 (0.0)	0.1187
Rheumatic disease/collagen-vascular disease	287 (2.8)	23 (3.6)	264 (2.8)	0.1949
Alcohol abuse	186 (1.8)	24 (3.8)	162 (1.7)	0.0001
Steroid use	64 (0.6)	8 (1.3)	56 (0.6)	0.0358
	3,965 (38.8)	297 (46.9)	3,668 (38.3)	< 0.0001

Values are presented as number (%) or mean $\pm$ standard deviation.

LTBI, latent tuberculosis infection; 6–9H, six to nine months of isoniazid; 3HR, three months of isoniazid/rifampin; 4R, four months of rifampin; AIDS, acquired immune deficiency syndrome.

resistance, and other conditions.

Table 2 compares the baseline characteristics of cases with and without treatment discontinuation due to ADRs. Participants discontinuing treatment due to ADRs had a higher average age (ADRs: 43.5 yr vs. without ADRs: 30.8 yr) with a significantly higher proportion of females (64.5% vs. 55.2%) compared to those without ADRs ($p < 0.0001$; $p < 0.0001$, respectively). Participants with treatment discontinuation due to ADRs mostly received 3HR (64.3% vs. 53.4%) and less 6–9H (26.7% vs. 37.7%) ($p < 0.0001$). A higher prevalence of the lower quintile of insurance level was observed in participants with treatment discontinuation due to ADRs ($p = 0.0027$). The prevalence of comorbidities, including diabetes mellitus (15.5% vs. 8.2%), liver disease (6.5% vs. 3.9%), rheumatic disease/collagen vascular disease (3.8% vs. 1.7%), alcohol abuse (1.3% vs. 0.6%), and steroid use (46.9% vs. 38.3%), was significantly higher among participants with treatment discontinuation due to ADRs compared to those without discontinuation.

The multivariable logistic regression model revealed that female sex, age above 19 years, an insurance quintile of

16–20th, LTBI treatment, and steroid use were associated with treatment discontinuation due to ADRs (Fig. 2). The odds for treatment discontinuation due to ADRs were significantly increased by 1.27 times in female participants (adjusted OR [AOR] 1.27, 95% CI 1.07–1.51), and participants in the group 76 years or above had the highest odds compared to those aged 5 years or below (AOR 9.09, 95% CI 5.12–16.15). Participants who used steroids had 1.31 times higher odds of treatment discontinuation due to ADRs (AOR 1.31, 95% CI 1.11–1.54). Participants in the 16–20th insurance quintile had lower odds than participants in the 0–5th quintile (AOR 0.78, 95% CI 0.61–0.98). Also, participants prescribed with 3HR or 4R had reduced odds of treatment discontinuation due to ADRs by 24% and 43%, respectively, compared to participants prescribed with 6–9H (3HR: AOR 0.76, 95% CI 0.61–0.94; 4R: AOR 0.57, 95% CI 0.41–0.79).

The odds of treatment discontinuation due to ADRs were increased by 3.6, 4.4, 3.8, and 9.1 times in the age group of 19–35, 36–65, 66–75, and 76 years or above, respectively, compared to the age group of 5 years or below (Table 3).

Adverse reactions (n = 633)

Adjusted OR (95% CI)

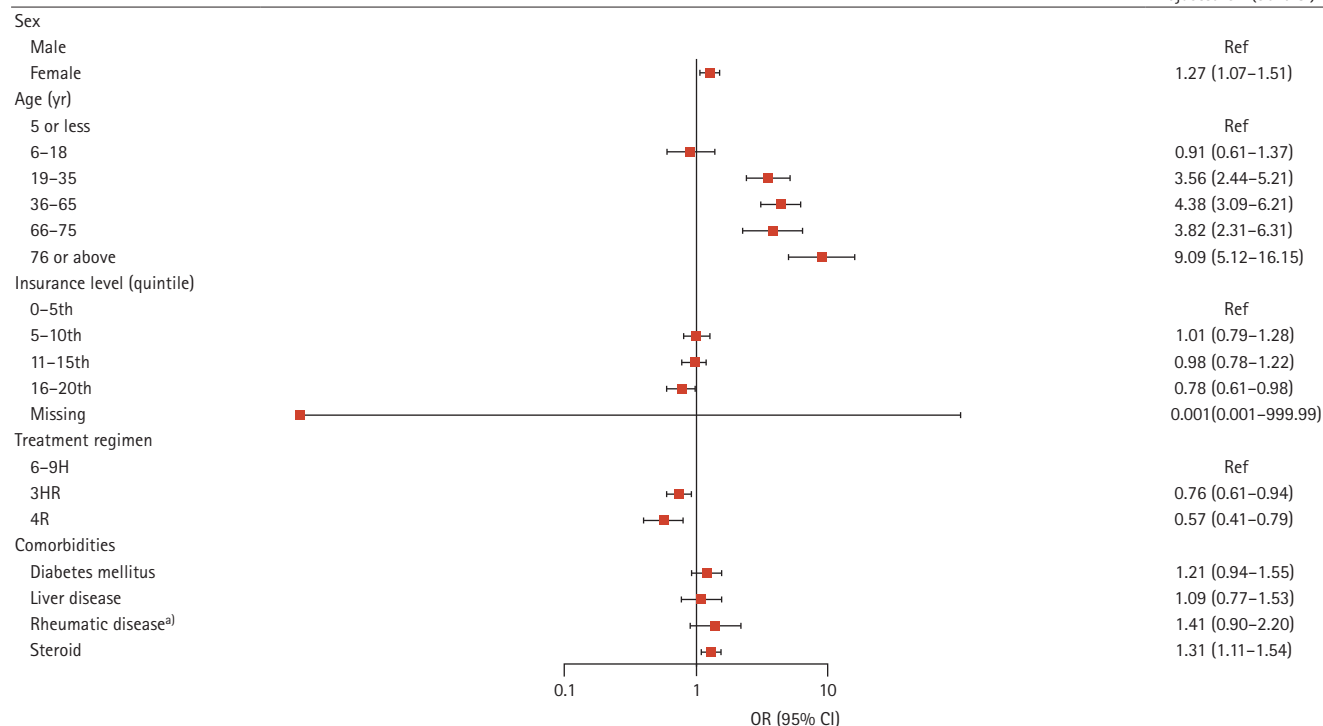


Figure 2. Associated factors for adverse drug reactions by adjusted OR. OR, odds ratio; CI, confidence interval; 6–9H, six to nine months of isoniazid; 3HR, three months of isoniazid/rifampin; 4R, four months of rifampicin. ^{a)}Rheumatic disease/collagen-vascular disease.

Table 3. Association of age and LTBI treatment with adverse drug reactions, abnormal liver function, and adverse skin reactions

Variable	Adverse drug reactions ^{a)}	Abnormal liver function ^{b)}	Adverse skin reactions ^{c)}
Age (yr)			
Less than 5	1.00	1.00	1.00
5–18	0.91 (0.61–1.37)	1.19 (1.18–1.20)	0.70 (0.44–1.13)
19–35	3.56 (2.44–5.21)	4.65 (4.61–4.68)	1.69 (1.08–2.65)
36–65	4.38 (3.09–6.21)	7.92 (7.89–7.95)	1.12 (0.76–1.64)
66–75	3.82 (2.31–6.31)	5.50 (5.43–5.57)	1.70 (0.91–3.17)
76 or above	9.09 (5.12–16.15)	8.20 (8.04–8.36)	1.68 (0.64–4.40)
LTBI treatment			
6–9H	1.00	1.00	NA
3HR	0.76 (0.61–0.94)	0.56 (0.55–0.56)	NA
4R	0.57 (0.41–0.79)	0.37 (0.36–0.37)	NA

LTBI, latent tuberculosis infection; 6–9H, six to nine months of isoniazid; 3HR, three months of isoniazid/rifampin; 4R, four months of rifampicin; AIDS, acquired immune deficiency syndrome; NA, not available.

^{a)}The model was adjusted by sex, age group, insurance level, treatment, and comorbidities including diabetes mellitus, liver disease, rheumatic/collagen-vascular disease, and steroid use.

^{b)}The model was adjusted by sex, age group, treatment, and comorbidities including diabetes mellitus, AIDS, and alcohol consumption.

^{c)}The model was adjusted by age group and comorbidities including chronic obstructive pulmonary disease, rheumatic/collagen-vascular disease, and steroid use.

The odds of abnormal liver function resulting in treatment discontinuation were associated with an increased odds of 1.2, 4.7, 7.9, 5.5, and 8.2-fold in the age group of 5–18, 19–35, 36–65, 66–75, 76 years or above, respectively. Adverse skin reactions resulting in treatment discontinuation were only associated with the age group of 19–35 years, showing a 1.7-fold increase in odds (AOR 1.69, 95% CI 1.08–2.65). Regarding LTBI treatment, the use of 3HR and 4R was associated with lower odds of treatment discontinuation due to ADRs by 24% and 43%, respectively, compared to 6–9H (3HR: AOR 0.76, 95% CI 0.61–0.94; 4R: AOR 0.57, 95% CI 0.41–0.79). The risk reduction was significant for abnormal liver function resulting in treatment discontinuation, with a decrease in odds by 44% and 63% for participants prescribed 3HR and 4R, respectively (3HR: AOR 0.56, 95% CI 0.55–0.56; 4R: AOR 0.37, 95% CI 0.36–0.37). However, there was no association between LTBI treatment and adverse skin reactions resulting in treatment discontinuation.

DISCUSSION

This cohort study identified that 5.3% of HHCs (633 cases out of 11,913) discontinued treatment due to ADRs. The

most common ADRs resulting in treatment discontinuation were adverse skin reactions (2.0%), abnormal liver function (1.9%), and gastrointestinal disorders (0.4%). Our multivariable analysis found that female sex, any age group above 19 years, 6–9H therapy, and steroid use were associated with ADRs. The odds with ADRs and abnormal liver function resulting in treatment discontinuation consistently increased with age until 65 years, and HHCs between 66 and 75 years exhibited lower odds than those between 36 and 65, with a noticeable surge in odds for individuals 76 years and older. The odds of adverse skin reactions resulting in treatment discontinuation increased only in the 19–35 age group. Additionally, the 3HR and 4R exhibited lower odds of ADRs and abnormal liver function, which resulted in treatment discontinuation compared to the 6–9H.

The prevalence of abnormal liver function (1.9%) resulting in treatment discontinuation in this study was similar to that in previous studies. A nationwide cohort study in Norway reported hepatotoxicity resulting in treatment discontinuation at a rate of 2.2% (16 cases out of 726 patients); a post-hoc analysis of two multinational randomized controlled studies reported hepatotoxicity resulting in treatment discontinuation at a rate of 1.2% (76 cases out of 6,485 patients) [13,14]. However, adverse skin reactions resulting

in treatment discontinuation (2.0%) showed a higher incidence than previously reported rates. Prior reports indicated adverse skin reactions resulting in treatment discontinuation ranging from 0.6% (38 cases out of 6,485 patients) to 0.7% (5 cases out of 764 patients) [13-15]. Notably, a direct comparison with earlier studies was not feasible due to differences in the study design, data sources, the definition of ADRs, and the LTBI treatment used. Previous studies focused on monitoring skin rashes among individuals visiting tertiary hospitals, which could have contributed to the lower reported prevalence. Our study, which used the nationwide registry data and national claims database, may better represent the real-world prevalence of adverse skin reactions resulting in treatment discontinuation by detecting even the mildest forms of adverse skin reactions.

According to the 2022 South Korean national tuberculosis report, 56% of newly diagnosed patients are 65 years or older, emphasizing the importance of TB prevention among older adults [16]. However, the 2020 national tuberculosis treatment guidelines recommend primarily treating LTBI for individuals under 65 years, possibly due to concerns about potential ADRs in older individuals. This study addresses these concerns by revealing that the odds of overall ADRs and abnormal liver function resulting in treatment discontinuation among individuals aged 66 to 75 years is lower than those aged 36 to 65 years, with the highest odds reported at 76 years or above. These findings were drawn from indirect comparison; therefore, cautious interpretation is required. However, they align with a previous observational study conducted at eight referral medical centers in Taiwan, which reported similar rates of ADRs in both elderly (≥ 60 yr) and young patient (< 60 yr) groups [17]. A retrospective study at five university hospitals in Korea also found that LTBI treatment was relatively well-tolerated in persons in the 65–78 age group [18]. Notably, most treatment discontinuations were due to loss of follow-up rather than adverse effects of LTBI treatment. Current evidence suggests the potential to expand current Korean guidelines' age limitation of 65 years for the use of 9H, 4R, and 3HR, considering the high prevalence of TB in older populations [10].

In line with previous evidence, this study observed a favorable safety profile of 3HR and 4R compared to 6–9H [19,20]. The use of 3HR and 4R was significantly associated with lower odds of treatment discontinuation due to ADRs compared to 6–9H (3HR: AOR 0.76, 95% CI 0.61–0.94; 4R: AOR 0.57, 95% CI 0.41–0.79). In the univariate analysis,

the odds of 6–9H on treatment discontinuation due to ADR were higher than 3HR and 4R but decreased after accounting for other factors, particularly age (Supplementary Table 3). Notably, the study also found that 3HR or 4R were associated with lower odds for abnormal liver function that resulted in treatment discontinuation, further supporting the preference for these regimens over 6–9H due to their relatively lower hepatotoxicity (Supplementary Table 4) [20]. Conversely, adverse skin reactions resulting in treatment discontinuation were not significantly associated with LTBI treatment [13]. Instead, increased odds of adverse skin reactions resulting in treatment discontinuation were associated with comorbidities, such as rheumatic disease/collagen vascular disease, and prior steroid use (Supplementary Table 5). This finding emphasizes the need for cautious monitoring of adverse skin reactions in participants with a history of rheumatic disease/collagen vascular disease and steroid use.

To the best of our knowledge, this study is the first to use a nationwide HHC investigation database linked with a claims database to examine the prevalence of ADRs resulting in LTBI treatment discontinuation and investigate the association of age and LTBI treatment with these ADRs. The strength of this study is that the TB registry data represents the entire TB population in Korea, offering a real-world perspective. However, the authors acknowledge the potential for misclassification bias inherent in retrospective cohort studies. This study also provides insight into ADRs across age groups (ranging from infants to individuals 76 years or older) not previously studied.

However, a limitation of this study is that registry data contained no information on the classification, timing, severity of ADRs, and ADR-related mortality and morbidity. Moreover, including only primary ADRs resulting in treatment discontinuation may produce underestimation and exclusion of mild ADRs. The association between steroid use and adverse skin reactions poses challenges for interpretation due to the broad spectrum of conditions (ranging from mild skin diseases to respiratory diseases and autoimmune diseases) that necessitate steroids. Steroid use could exhibit adverse skin reaction resulting from LTBI treatment; however, further studies should explore this issue.

This study provided the real-world prevalence of ADRs resulting in treatment discontinuation among HHCs receiving LTBI treatment in Korea. The study confirmed that 3HR and 4R were associated with decreased odds of ADRs and abnormal liver function, which resulted in treatment discontinuation.

tinuation compared to 9H. While our results may not apply to all individuals aged 66–75 years, our findings suggest the potential use of LTBI treatment in this age group with appropriate population selection, and cautious use for those aged 76 or above. However, further studies are warranted to validate these results.

KEY MESSAGE

1. There is a limited real-world study with a sufficient sample size regarding ADRs in LTBI treatment. This study, using real-world data, identified 233 participants with adverse skin reactions (2.0%) and 230 participants with abnormal liver function (1.9%), resulting in treatment discontinuation.
2. The age group of 66–75 years demonstrated a lower odds of ADRs and abnormal liver function resulting in treatment discontinuation than 36–65 years age group. Thus, the use of LTBI treatment for individuals aged 66–75 years may be potentially appropriate, and caution is advised for individuals aged 76 or above. Further studies are necessary to draw a conclusive assessment.
3. Consistent with previous evidence, the 3HR and 4R were less associated with ADRs and abnormal liver function resulting in treatment discontinuation compared to the 6–9H.
4. Regarding adverse skin reactions resulting in treatment discontinuation, participants with rheumatic/collagen-vascular disease and previous steroid use showed a higher odds. Such participants may require cautious monitoring of adverse skin reactions when initiating LTBI treatment.

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Supplementary Table 1. Definition of treatment completion

Regimen	Definition	Treatment completion	Treatment discontinuation
Isoniazid (H)	Days of supply/ $180 \times 100 \geq$	$\geq 80\%$	$< 80\%$
Rifampicin (R)	Days of supply/ $120 \times 100 \geq$		
Isoniazid + Rifampicin (HR)	Days of supply/ $90 \times 100 \geq$		

Supplementary Table 2. Definition of comorbidities in ICD-10 codes

Comorbidities	Code
Chronic obstructive pulmonary disease	I278, I279, J40, J41.x–J47.x, J60.x–J66.x, J67, J684, J701, J703
Diabetes mellitus	E10.0, E10.1, E10.2–E10.8, E10.9, E11.0, E11.2–E11.8, E11.1, E11.9, E12.0, E12.1, E12.2–E12.8, E12.9, E13.0, E13.1, E13.2–E13.8, E13.9, E14.0, E14.1, E14.2–E14.8, E14.9
Renal failure	I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0–49.2, Z94.0, Z99.2
Liver disease	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
AIDS	B20.x–B22.x, B24.x
Malignancy	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C77.x–C80.x, C81.x–C85.x, C88.x, C90.0, C90.2, C96.x, C97.x
Rheumatic disease/ collagen–vascular disease	L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0–M31.3, M32.x–M35.x, M45.x, M46.1, M46.8, M46.9
Alcohol abuse	E52, F10, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1

ICD-10, International Classification of Disease, Tenth Revision; AIDS, acquired immune deficiency syndrome.

Supplementary Table 3. Univariable and multivariable logistic model for ADRs

Characteristic	Without ADRs (n = 9,584)	With ADRs (n = 633)	OR (95% CI)	aOR (95% CI)
Sex, female	5,286 (55.2)	408 (64.5)	1.47 (1.25–1.74)	1.27 (1.07–1.51)
Age (yr)	30.82 ± 23.26	43.39 ± 20.45		
≤ 5	1,835 (19.1)	48 (7.6)	1.00	1.00
6–18	2,254 (23.5)	50 (7.9)	0.85 (0.57–1.27)	0.91 (0.61–1.37)
19–35	1,247 (13.0)	100 (15.8)	3.07 (2.16–4.36)	3.56 (2.44–5.21)
36–65	3,811 (39.8)	380 (60.0)	3.81 (2.81–5.17)	4.38 (3.09–6.21)
66–75	337 (3.5)	32 (5.1)	3.63 (2.29–5.76)	3.82 (2.31–6.31)
≥ 76	100 (1.0)	23 (3.6)	8.79 (5.14–15.03)	9.09 (5.12–16.15)
Insurance level				
0–5th	2,014 (21.0)	157 (24.8)	1.00	1.00
5–10th	1,933 (20.2)	143 (22.6)	0.95 (0.75–1.20)	1.01 (0.79–1.28)
11–15th	2,721 (28.4)	179 (28.3)	0.84 (0.68–1.05)	0.98 (0.78–1.22)
16–20th	2,844 (29.7)	154 (24.3)	0.70 (0.55–0.87)	0.78 (0.61–0.98)
Missing	72 (0.8)	0 (0.0)	< 0.001 (0.0001–999.999)	< 0.0001 (0.0001–999.999)
LTBI regimen				
6–9H	3,613 (37.7)	169 (26.7)	1.00	1.00
3HR	5,121 (53.4)	407 (64.3)	1.68 (1.40–2.02)	0.76 (0.61–0.94)
4R	850 (8.9)	57 (9.0)	1.41 (1.04–1.92)	0.57 (0.41–0.79)
Comorbidities				
Chronic pulmonary disease	2,798 (29.2)	175 (27.6)	0.93 (0.78–1.11)	
Diabetes mellitus	789 (8.2)	98 (15.5)	2.00 (1.60–2.51)	1.21 (0.94–1.55)
Renal failure	46 (0.5)	5 (0.8)	1.69 (0.67–4.25)	
Liver disease	376 (3.9)	41 (6.5)	1.73 (1.25–2.41)	1.09 (0.77–1.53)
AIDS	3 (0.0)	1 (0.2)	5.28 (0.55–50.75)	
Malignancy	264 (2.8)	23 (3.6)	1.34 (0.87–2.07)	
Rheumatic disease/ collagen–vascular disease	162 (1.7)	24 (3.8)	2.28 (1.47–3.52)	1.41 (0.90–2.20)
Alcohol abuse	56 (0.6)	8 (1.3)	2.16 (1.03–4.53)	
Steroid use	3,668 (38.3)	297 (46.9)	1.43 (1.22–1.68)	1.31 (1.11–1.54)

Values are presented as number (%) or mean ± standard deviation.

ADR, adverse drug reaction; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; LTBI, latent tuberculosis infection; 6–9H, six to nine months of isoniazid; 3HR, three months of isoniazid/rifampin; 4R, four months of rifampicin; AIDS, acquired immune deficiency syndrome.

Supplementary Table 4. Univariable and multivariable logistic model for abnormal liver function

Characteristic	Without abnormal liver function (n = 9,987)	With abnormal liver function (n = 230)	OR (95% CI)	aOR (95% CI)
Sex, female	5,542 (55.5)	152 (66.1)	1.56 (1.19)	1.33 (1.33–1.34)
Age (yr)	31.24 ± 23.31	47.72 ± 15.96		
≤ 5	1,879 (18.8)	4 (1.7)	1.00	1.00
6–18	2,295 (23.0)	9 (3.9)	1.84 (0.57–5.99)	1.19 (1.18–1.20)
19–35	1,310 (13.1)	37 (16.1)	13.27 (4.72–37.31)	4.65 (4.61–4.68)
36–65	4,028 (40.3)	163 (70.9)	19.01 (7.04–51.33)	7.92 (7.89–7.95)
66–75	357 (3.6)	12 (5.2)	15.79 (5.06–49.23)	5.50 (5.43–5.57)
≥ 76	118 (1.2)	5 (2.2)	19.90 (5.28–75.09)	8.20 (8.04–8.36)
LTBI regimen				
6–9H	3,723 (37.3)	59 (25.7)	1.00	1.00
3HR	5,377 (53.8)	151 (65.7)	1.77 (1.31–2.40)	0.56 (0.55–0.56)
4R	887 (8.9)	20 (8.7)	1.42 (0.85–2.38)	0.37 (0.36–0.37)
Comorbidities				
Chronic pulmonary disease	2,916 (29.2)	57 (24.8)	0.80 (0.59–1.08)	
Diabetes mellitus	853 (8.5)	34 (14.8)	1.86 (1.28–2.69)	0.99 (0.98–1.00)
Renal failure	50 (0.5)	1 (0.4)	0.87 (0.12–6.31)	
Liver disease	406 (4.1)	11 (4.8)	1.19 (0.64–2.19)	
AIDS	3 (0.0)	1 (0.4)	14.56 (1.51–140.36)	< 0.001 (< 0.001–22.55)
Malignancy	279 (2.8)	8 (3.5)	1.25 (0.61–2.56)	
Rheumatic disease/ collagen–vascular disease	181 (1.8)	5 (2.2)	1.20 (0.49–2.96)	
Alcohol abuse	60 (0.6)	4 (1.7)	2.93 (1.06–8.13)	3.38 (3.32–3.44)
Steroid use	3,864 (38.7)	101 (43.9)	1.24 (0.95–1.62)	

Values are presented as number (%) or mean ± standard deviation.

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; LTBI, latent tuberculosis infection; 6–9H, six to nine months of isoniazid; 3HR, three months of isoniazid/rifampin; 4R, four months of rifampicin; AIDS, acquired immune deficiency syndrome.

Supplementary Table 5. Univariable and multivariable logistic model for adverse skin reactions

Characteristic	Without adverse skin reactions (n = 9,984)	With adverse skin reactions (n = 233)	OR (95% CI)	aOR (95% CI)
Sex, female	5,557 (55.7)	137 (58.8)		
Age	31.53 ± 23.29	34.94 ± 23.23	1.14 (0.87–1.48)	
≤ 5	1,843 (18.5)	40 (17.2)	1.00	1.00
6–18	2,272 (22.8)	32 (13.7)	0.65 (0.41–1.04)	0.70 (0.44–1.13)
19–35	1,303 (13.1)	45 (19.3)	1.56 (1.01–2.40)	1.69 (1.08–2.65)
36–65	4,093 (41.0)	98 (42.1)	1.10 (0.76–1.60)	1.12 (0.76–1.64)
66–75	355 (3.6)	14 (6.0)	1.82 (0.98–3.38)	1.70 (0.91–3.17)
≥ 76	118 (1.2)	5 (2.1)	1.95 (0.76–5.04)	1.68 (0.64–4.40)
LTBI regimen				
6–9H	3,699 (37.0)	83 (35.6)	1.00	
3HR	5,396 (54.0)	132 (56.7)	1.09 (0.83–1.44)	
4R	889 (8.9)	18 (7.7)	0.90 (0.54–1.51)	
Comorbidities				
Chronic pulmonary disease	2,890 (28.9)	83 (35.6)	1.36 (1.04–1.78)	1.24 (0.93–1.66)
Diabetes mellitus	871 (8.7)	16 (6.9)	0.77 (0.46–1.29)	
Renal failure	50 (0.5)	1 (0.4)	0.86 (0.12–6.23)	
Liver disease	402 (4.0)	15 (6.4)	1.64 (0.96–2.79)	
AIDS	4 (0.0)	0 (0.0)	< 0.001 (0–∞)	
Malignancy	279 (2.8)	8 (3.4)	1.24 (0.61–2.53)	
Rheumatic disease/ collagen–vascular disease	174 (1.7)	12 (5.2)	3.06 (1.68–5.58)	2.37 (1.29–4.38)
Alcohol abuse	64 (0.6)	0 (0.0)	< 0.001 (0–∞)	
Steroid use	3,837 (38.4)	128 (54.9)	1.95 (1.50–2.54)	1.79 (1.37–2.34)

Values are presented as number (%) or mean ± standard deviation.

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; LTBI, latent tuberculosis infection; 6–9H, six to nine months of isoniazid; 3HR, three months of isoniazid/rifampin; 4R, four months of rifampicin; AIDS, acquired immune deficiency syndrome.