A Study on the Relapse Rate of Tuberculosis and Related Factors in Korea Using Nationwide Tuberculosis Notification Data

Hyungmin Lee a,*, Jusang Kim b

aDivision of Epidemic Intelligence Service, Korea Centers for Disease Control and Prevention, Cheongju, Korea.
bDepartment of Internal Medicine, College of Medicine, Catholic University of Korea, Seoul, Korea.

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Abstract
Objectives: From the perspective of public health, tuberculosis (TB) remains an important issue that threatens health. Korea is an intermediate burden country with a TB incidence of 97/100,000 individuals. Among many TB control measures, a relapse rate of TB is one indicator that can be used to indirectly assess the level of TB control in countries and in communities. Relapse TB has an approximately 12% yearly incidence in Korea. This study aims to estimate the relapse rate of TB and to investigate the associated factors by using nationwide TB notification data in Korea.

Methods: The nationwide TB notification data in 2005 was used with the exclusion criteria of duplicated reporting, foreign-born patients, outcome—died, and outcome—diagnosis changed. The data were double-checked as to whether they were reported again during 2006–2010 and the estimated relapse rate of TB. Associated factors were analyzed by multivariate logistic regression with the variables of age, sex, registration type, results of sputum smear test, medication, and outcome of treatment.

Results: Among 45,434 TB patients in 2005, 4,371 patients were again reported as TB patients from 2006 to 2010. Five hundred and sixty-four patients were reported more than twice and the cumulative number of relapses was 5,072 cases. The 5-year relapse rate was estimated as 9.62%. The relapse rate decreased yearly: 4.8% in 2006, 2.4% in 2007, 1.6% in 2008, 1.4% in 2009, and 1.0% in 2010. Age, sex, registration type, tuberculosis type, and medication were independently associated with a relapse of TB. In the multivariate logistic regression analysis, the following factors were related: male sex, 40–49 years old; registration type, relapse, treatment after failure, treatment after default, transfer in, and other, the sputum smear-positive pulmonary TB, and medications (including individuals taking 2–5 drugs).

*Corresponding author.
E-mail: sea2sky76@gmail.com

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Conclusion: This study has estimated a 5-year relapse rate of TB in Korea that is slightly lower than the rate of relapse TB in the annual reports. This study could be conducted and cross-checked with data from the National Health Insurance in the future.

1. Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. It primarily infects the lungs, but it can also infect the digestive organs, lymph, and bones. Approximately 10% of the *M. tuberculosis*-infected people develop tuberculosis. The onset of tuberculosis is more frequent in men and tends to increase with aging. People with lower immunity, old age, diabetes; who use immunosuppressive drugs; and people with HIV/AIDS infection are more likely to develop tuberculosis [1].

Tuberculosis remains an important problem that threatens public health throughout the world, including Korea. Tuberculosis-infected people in Korea number an estimated 15 million, which is one-third of the total population [2]. Each year Korea witnesses 30,000–35,000 newly diagnosed cases of TB, which is the highest incidence among infectious diseases in Korea, and approximately 75,000 people are treated [3,4]. The World Health Organization (WHO) reports a TB incidence rate of 97 per 100,000 people in Korea, and Korea is among the intermediate burden countries [1].

Since 1962, Korea has begun to control TB on a national basis with its National Tuberculosis Control Plan. The national tuberculosis status survey has been conducted every 5 years since 1965 until 1995. During this period, the incidence rate has sharply decreased and the prevalence rate has also decreased from 5% to 1% [2]. With a decrease of TB patients and low responding rate of the national survey, the national TB status has been identified on a report basis since 2000 [5]. The scale of TB patients has not been decreased, but remains steady [3,4] (Figure 1).

Deaths and the incidence rate caused by TB are also the highest among all infectious diseases. In fact, because of TB infection, Korea has the highest incidence and deaths among the 36 Organisation for Economic Co-operation and Development (OECD) countries and is 70th–90th among WHO member states [1]. The patients are mostly distributed in their 20–40s (40%), which is a typical aspect of developing countries. Tuberculosis in Korea was mostly controlled by public health centers, but private hospitals have gradually taken over this role since the mid-1990s, and above 85% of TB patients are treated and controlled in private hospitals since 2010 [3,4,6].

Tuberculosis relapse is divided into two classes: (1) a patient in whom the initial onset has been treated, but the existing *M. tuberculosis* reactivates into a second onset of TB; and (2) a patient with reinfection with new *M. tuberculosis* [7,8]. To distinguish between these two classes, genotyping is necessary but unfeasible for every patient. Korea does not identify these two classes [i.e., relapse (reactivated onset) and reinfection] [9]. The relapse rate differs by a country’s incidence and control: 0–27% of TB relapses occur within 2 years after treatment completion and most relapses occur within 5

![Figure 1. Number and rate of tuberculosis notification in 2001–2010.](image-url)
years; however, some relapses occur 15 years after treatment. In low incidence countries, most relapses occur within 2 years of treatment completion; however, in high incidence countries, relatively high relapse 2 years after treatment completion can be attributed to the relatively high chance of reinfection [10–12].

Among many indicators to control TB, the relapse rate is an indicator that can be used to evaluate a community’s level of tuberculosis control [13]. According to the Korea Tuberculosis Annual Report, approximately 12% of annual reported cases are reported as relapse tuberculosis [3,4]. However, no national level study has been conducted with the exception of studies on specific medical institution or TB patients with antimicrobial resistance. This study aims to estimate the relapse rate of TB in Korea by using national data on reported cases and find factors related to the relapse of TB.

2. Materials and methods

2.1. Study participants

The data source is the national reported cases of TB patients registered in the TB Integrated Information System (TBnet). The study participants were TB patients registered in TBnet in 2005. The exclusion criteria were patients with duplicate reports, foreigners, chronic TB cases, death after treatment, and changed diagnosis. Among 46,969 patients registered in TBnet in 2005, the following were excluded: 718 duplicate reports, 388 foreigners, 49 changed diagnosis, 262 deaths after treatment, and 118 chronic cases. In this study, 45,434 TB patients were analyzed (Figure 2).

2.2. Methods

We checked whether the patients in the study had been reported again in the TBnet during the following 5 years (i.e., 2006–2010). We selected the following variables as related factors in the reported data: age, sex, region, registration type, disease code (based on the International Classification of Disease-10, available at http://apps.who.int/classifications/icd10/), medicine, and treatment results. The region was classified and coded from 1 to 16 with no specific region name. Registration types were “new case”, “relapse”, “treatment after failure”, “treatment after default”, “transfer in”, or “other”. The disease codes of the ICD-10 were reclassified as follows: “sputum smear-positive pulmonary TB” (A15.0); “sputum smear-negative pulmonary TB” (A15.1, A15.2, A15.3, A16.0, A16.1, A16.2, A19.0-A19.9); and “extrapulmonary TB” (A15.4-A15.9, A16.3-A16.9, A17.x, A18.x). Based on the medication, patients were divided into five groups: Group 1 patients were treated with isoniazid, rifampin, pyrazinamide, and ethambutol. Groups 2–5 patients were classified according to the other medicines. Treatment results were classified as “cure”, “complete”, “failure”, “default”, “transfer out”, and “others”.

The data used in this study did not require the submission of informed consent from the patients because the report is mandatory by the tuberculosis prevention law. The author received the data with no personal information and the computer to access the data was not connected with an outside network. This study was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention, Cheongju, Korea (No. 2012-05CON-15-P).

2.3. Data analysis

Descriptive epidemiological analysis was conducted for the general characteristics of study patients. The Chi-square test was performed for major variables and relapse with 0.05 significance level. Multivariate logistic regression analysis was conducted to analyze factors associated with relapse of TB. SAS 9.2 for Windows (SAS Inc., Cary, NC, USA) was used for data analysis.

3. Results

3.1. General characteristics and variables

The characteristics of TB patients registered in TBnet 2005 were the following. More than one-half (62.1%) of the patients were men. The average age was 47.5 ± 19.8 years. Most patients were above the age of 20 years: 214 patients were aged <10 years; 2,443 patients were aged 10–19 years; 8134 patients were aged 20–29 years; 7,299 patients were aged 30–39 years; 7,338 patients were aged 40–49 years; 5,675 patients were aged 50–59 years; 6,293 patients were aged 60–69 years; and 8,038 patients were aged ≥70 years. The registration types were the following: 34,569 new cases; 5611 relapses; 654 re-registration after cease; 1,812 move-in; and 2,505 others. There were 15,745 sputum smear-positive pulmonary TB cases; 23,437 sputum smear-negative pulmonary TB cases; and 6,216 extrapulmonary TB cases. Group 1 medicines alone were used by 43,276 patients, but 2,158 patients used the other medicine groups. Based on age, location of medical
The number of male patients was statistically significantly greater than the number of women (Table 1).

### 3.2. Factors associated with the relapse rate

Among 45,434 patients in 2005, 4,371 persons were re-reported during the following 5-year period (i.e., 2006–2010). The total number of re-reported cases was 5,072 reports with the exclusion of 564 duplicate reports. Therefore, the 5-year relapse rate of TB was 9.62, based on the number of patients. The annual relapse rate decreased yearly: 2,189 (4.8%) patients in 2005; 1,082 (2.4%) patients in 2007; 714 (1.6%) patients in 2008; 615 (1.4%) patients in 2009; and 472 (1.0%) patients in 2010. The first 2 years had 65% of relapses in the 5-year period (Figures 3 and 4).

The Chi-square test showed that the relapse rate and study variables were all independently related. Men (10.86%) more frequently relapsed, compared to women (7.59%). The relapse rate was highest among patients in their 40s (11.50%), followed by patients in their 50s (10.27%), 60s (10.03%), 30s (9.81%), 20s (8.81%), 70s (8.53%), 10s (7.65%), and < 10 years (3.27%). Patients (9.87%) in private medical institutions had slightly more relapses than patients (8.97%) in public health centers. Patients with re-registration after cease showed the highest relapse rate (25.08%), followed by failure of the first treatment (21.55%), relapse (14.95%), others (12.14%), move-in (10.49), and new cases (8.14%). The highest relapse rate occurred with sputum smear-positive pulmonary TB (12.37%), followed by sputum smear-negative pulmonary TB (8.72%) and extrapulmonary TB (6.05%). More relapsed patients (15.89%) had used medicines from Group 2 to Group 5, compared to patients using Group 1 medicines (9.31%). The location of the medical institutions also showed a

| Table 1. General characteristics of the study population. |
|---------------------------------|------------|-----------|-------|---------|
| Age (y) | Total (no.) | Men (no.) | Women (no.) | p |
| 0–9 | 214 | 113 | 101 | < 0.0001 |
| 10–19 | 2,443 | 1,490 | 953 | |
| 20–29 | 8,134 | 4,263 | 3,871 | |
| 30–39 | 7,299 | 4,510 | 2,789 | |
| 40–49 | 7,338 | 5,251 | 2,087 | |
| 50–59 | 5,675 | 4,148 | 1,527 | |
| 60–69 | 6,293 | 4,236 | 2,057 | |
| ≥ 70 | 8,038 | 4,197 | 3,841 | |
| Region | Total (no.) | Men (no.) | Women (no.) | p |
| 1 | 12,085 | 7,309 | 4,776 | < 0.0001 |
| 2 | 4,531 | 2,799 | 1,732 | |
| 3 | 2,155 | 1,364 | 791 | |
| 4 | 1,854 | 1,186 | 668 | |
| 5 | 1,386 | 850 | 536 | |
| 6 | 1,048 | 637 | 411 | |
| 7 | 681 | 432 | 249 | |
| 8 | 6,747 | 4,221 | 2,526 | |
| 9 | 2,130 | 1,206 | 924 | |
| 10 | 1,265 | 787 | 478 | |
| 11 | 1,841 | 1,205 | 636 | |
| 12 | 2,101 | 1,329 | 772 | |
| 13 | 1,946 | 1,247 | 699 | |
| 14 | 2,106 | 1,284 | 822 | |
| 15 | 3,157 | 2,089 | 1,068 | |
| 16 | 401 | 263 | 138 | |
| Registration Type | Total (no.) | Men (no.) | Women (no.) | p |
| New | 34,569 | 20,631 | 13,938 | < 0.0001 |
| Relapse | 5,611 | 4,095 | 1,516 | |
| T.A.F. | 283 | 214 | 69 | |
| T.A.D. | 654 | 496 | 158 | |
| T.I. | 1,812 | 1,125 | 687 | |
| Other | 2,505 | 1,647 | 858 | |
| Tuberculosis type | Total (no.) | Men (no.) | Women (no.) | p |
| Sputum smear (+) pul TB | 15,745 | 10,251 | 5,494 | < 0.0001 |
| Sputum smear (−) pul TB | 23,437 | 14,773 | 8,700 | |
| Extrapulmonary TB | 6,216 | 3,184 | 3,032 | |
| Medication | Total (no.) | Men (no.) | Women (no.) | p |
| Only Group 1 drugs | 43,276 | 26,757 | 16,519 | < 0.0001 |
| With Groups 2–5 drugs | 2,158 | 1,451 | 707 | |
| Total | 45,434 | 28,208 | 17,226 | |

pul = pulmonary; T.A.D. = treatment after default; T.A.F. = treatment after failure; T.I. = transfer in.
significant difference: the highest rate was 14.01% and the lowest rate was 6.93% (Table 2).

Among TB patient data of public health centers for which treatment results were available, the relapse rate was independently associated with sex, age, registration type, TB type, treatment result and region, based on the Chi-square test. The relapse rate was higher in men (10.0%) than in women (6.8%). The age-related relapse rate showed that the <10 years age group had the highest rate (20.0%), followed by patients in their 20s (8.4%); 30s (9.3%); 40s (10.2%); 50s (10.3%); 60s (10.0%); and 70s (7.8%). However, the <10 year age group size was only five patients; therefore, the relapse rate of the group could not be an effective value. Patients with first treatment failure experienced the greatest relapse (40%), followed by re-registration (21.2%), relapse (14.9%), others (10.8%), new cases (7.5%), and move-out (7.4%). However, the size of first treatment failure group was also small and insufficient to justify the results.

Based on the tuberculosis type, the relapse rate of sputum smear-positive pulmonary TB was 11.8%; sputum smear-negative pulmonary TB, 7.0%; and extrapulmonary TB, 5.4%. Treatment results showed that patients with treatment failure had the highest relapse rate (50%), followed by treatment cease (24.0%), others (17.1%), move-out (11.4%), completion (11.1%), and full recovery (7.3%). The regional relapse rate showed a difference: the highest rate was 12.32% and the lowest rate was 5.42%.

The Chi-square test showed that the relapse rate in public health center patients with treatment results were associated with age, sex, registration type, TB type, and medicine. With these variables, multivariate logistic regression was performed to confirm that most related variables in the Chi-square test were also related.

The relapse rate for all study patients was higher in men than in women with an odds ratio of 1.33 [95% confidence interval (95% CI), 1.24–1.43]. Because of the small size of the <10-year-old group, the reference was patients in the 10s age group and the odds ratio of relapse in the 40s age group was significant at 1.20 (95% CI, 1.01–1.42); however, the other age groups did not show a significant difference. Compared to users of private medical institutions, public health center users were more likely to relapse with an odds ratio of 1.23.

**Figure 3.** Relapse rate of tuberculosis by year (2006–2010).

**Figure 4.** Proportion of relapse of tuberculosis by year (2006–2010).
(95% CI, 1.14–1.33). Re-registration after first treatment failure had the highest odds ratio of 3.18 (95% CI, 2.64–3.83), followed by first treatment failure [odds ratio of 2.02 (95% CI, 1.50–2.72); and relapse registration [odds ratio of 1.76 (95% CI, 1.61–1.91)]. Move-out and other reasons were associated with an odds ratio of 1.23 (95% CI, 1.05–1.44) and 1.51 (95% CI, 1.33–1.71), respectively. Patients with sputum-positive TB had more relapses than patients treated by Groups 2–5 medicines with an odds ratio of 1.32 (95% CI, 1.16–1.50). The region also showed various associations (odds ratio of 0.85–1.85; Table 3).

For patients in public health centers, all dropout records were input and a multivariate logistic regression was performed. Public health centers rarely used Group 2 medicines (<1%); therefore, they were excluded in the analysis. In the multivariate analysis among the patients in public health centers, the relapse rate was not associated with age. This finding was different from the analysis

Table 2. Relapse rate of tuberculosis by the characteristics of the study population.

| Relapse   | No   | Yes   | p     |
|-----------|------|-------|-------|
| Sex       |      |       |       |
| Men       | 25,145 (89.14) | 3,063 (10.86) | < 0.0001 |
| Women     | 15,918 (92.41) | 1,308 (7.59) |       |
| Age (y)   |      |       |       |
| 0–9       | 207 (96.73) | 7 (3.27) | < 0.0001 |
| 10–19     | 2,256 (92.35) | 187 (7.65) |       |
| 20–29     | 7,417 (91.19) | 717 (8.81) |       |
| 30–39     | 6,583 (90.19) | 716 (9.81) |       |
| 40–49     | 6,494 (88.50) | 844 (11.50) |       |
| 50–59     | 5,092 (89.73) | 583 (10.27) |       |
| 60–69     | 5,662 (89.97) | 631 (10.03) |       |
| ≥ 70      | 7,352 (91.47) | 686 (8.53) |       |
| Medical Facilities |      |       |       |
| Public    | 11,412 (91.03) | 1,124 (8.97) | 0.0004 |
| Private   | 29,651 (90.13) | 3,247 (9.87) |       |
| Registration Type |      |       |       |
| New       | 31,756 (91.86) | 2,813 (8.14) | < 0.0001 |
| Relapse   | 4,772 (85.05) | 839 (14.95) |       |
| T.A.F.    | 222 (78.45) | 61 (21.55) |       |
| T.A.D.    | 490 (74.92) | 164 (25.08) |       |
| T.I.      | 1,622 (89.51) | 190 (10.49) |       |
| Other     | 2,201 (87.86) | 304 (12.14) |       |
| TB type Sputum smear (+) pul TB | 13,797 (87.63) | 1,948 (12.37) | < 0.0001 |
| Sputum smear (−) pul TB | 21,426 (91.28) | 2,047 (8.72) |       |
| Extra–pul TB | 5,840 (93.95) | 376 (6.05) |       |
| Medication Only Group 1 drugs | 39,248 (90.69) | 4,028 (9.31) | <.0001 |
| With Groups 2–5 drugs | 1,815 (84.11) | 343 (15.89) |       |
| Region 1   | 11,139 (92.17) | 946 (7.83) | < 0.0001 |
| 2         | 3,896 (85.99) | 635 (14.01) |       |
| 3         | 1,946 (90.30) | 209 (9.70) |       |
| 4         | 1,671 (90.13) | 183 (9.87) |       |
| 5         | 1,290 (93.07) | 96 (6.93) |       |
| 6         | 943 (89.98) | 105 (10.02) |       |
| 7         | 617 (90.60) | 64 (9.40) |       |
| 8         | 6,228 (92.31) | 519 (7.69) |       |
| 9         | 1,899 (89.15) | 231 (10.85) |       |
| 10        | 1,156 (91.38) | 109 (8.62) |       |
| 11        | 1,658 (90.06) | 183 (9.94) |       |
| 12        | 1,930 (91.86) | 171 (8.14) |       |
| 13        | 1,690 (86.84) | 256 (13.16) |       |
| 14        | 1,892 (89.84) | 214 (10.16) |       |
| 15        | 2,735 (86.63) | 422 (13.37) |       |
| 16        | 373 (93.02) | 28 (6.98) |       |
| Total     | 41,063 (90.38) | 4,371 (9.62) |       |

Data are presented as n (%). T.A.D. = treatment after default; T.A.F. = treatment after failure; TB = tuberculosis; T.I. = transfer in; pul = pulmonary.
Table 3. Results of multivariate logistic regression analysis.

| Sex          | OR (95% CI) |
|--------------|-------------|
| Men          | 1.33 (1.24–1.43) |
| Women        | 1           |

| Age (y)      | OR (95% CI) |
|--------------|-------------|
| 0–9          | 0.43 (0.20–0.93) |
| 10–19        | 1           |
| 20–29        | 1.07 (0.91–1.27) |
| 30–39        | 1.10 (0.93–1.31) |
| 40–49        | 1.20 (1.01–1.42) |
| 50–59        | 1.02 (0.86–1.22) |
| 60–69        | 1.04 (0.87–1.23) |
| ≥70          | 0.90 (0.76–1.07) |

| Medical facilities | OR (95% CI) |
|--------------------|-------------|
| Public             | 1           |
| Private            | 1.23 (1.14–1.33) |

| Registration type | OR (95% CI) |
|-------------------|-------------|
| Relapse           | 1.76 (1.61–1.91) |
| T.A.F.            | 2.02 (1.50–2.72) |
| T.A.D.            | 3.18 (2.64–3.83) |
| T.I.              | 1.23 (1.05–1.44) |
| Other             | 1.42 (1.25–1.61) |

| Tuberculosis type | OR (95% CI) |
|------------------|-------------|
| Sputum smear     | 1.14 (1.33–1.52) |
| Pulmonary        | 1           |
| Sputum smear     | 1           |
| (-) pul TB       | 0.70 (0.62–0.78) |
| Extrapulmonary TB| 1           |

| Medication        | OR (95% CI) |
|-------------------|-------------|
| Only Group 1 drugs| 1           |
| With Groups 2–5   | 1.32 (1.16–1.50) |

| Region | OR (95% CI) |
|--------|-------------|
| 1      | 1.85 (1.66–2.06) |
| 2      | 1.19 (1.02–1.42) |
| 3      | 1.20 (1.01–1.42) |
| 4      | 0.85 (0.69–1.06) |
| 5      | 1.23 (0.99–1.52) |
| 6      | 1.20 (0.92–1.57) |
| 7      | 0.98 (0.87–1.10) |
| 8      | 1.42 (1.21–1.65) |
| 9      | 1.06 (0.86–1.30) |
| 10     | 1.29 (1.09–1.53) |
| 11     | 1.06 (0.90–1.26) |
| 12     | 1.71 (1.47–1.99) |
| 13     | 1.28 (1.09–1.50) |
| 14     | 1.66 (1.47–1.88) |
| 15     | 0.85 (0.58–1.26) |
| 16     |             |

CI = confidence interval; OR = odds ratio; T.A.D. = treatment after default; T.A.F. = treatment after failure; T.I. = transfer in; pul = pulmonary.

with total study subjects. The related variables [denoted by (odds ratio, 95% CI)] were men (1.32, 1.14–1.52), relapse (1.87, 1.60–2.18), and re-registration after cease (2.32, 1.64–3.29). However, there was no association with move-out or others. The treatment failure group was too small to confirm significance. Sputum-positive TB (1.66, 1.45–1.88), treatment failure (10.26, 5.95–17.68), treatment cease (3.77, 3.03–4.68), move-out (1.42, 1.17–1.73), and other dropout (2.41, 1.80–3.25) were associated with relapse (Table 4).

Table 4. Results of multivariate logistic regression analysis in public health centers.

| Sex          | OR (95% CI) |
|--------------|-------------|
| Men          | 1.32 (1.14–1.52) |
| Women        | 1           |

| Age (y)      | OR (95% CI) |
|--------------|-------------|
| 0–9          | 3.22 (0.32–32.27) |
| 10–19        | 1           |
| 20–29        | 1.02 (0.78–1.35) |
| 30–39        | 0.99 (0.75–1.32) |
| 40–49        | 0.96 (0.73–1.28) |
| 50–59        | 0.98 (0.73–1.33) |
| 60–69        | 1.02 (0.76–1.38) |
| ≥70          | 0.81 (0.60–1.09) |

| Registration type | OR (95% CI) |
|-------------------|-------------|
| Relapse           | 1.87 (1.60–2.18) |
| T.A.F.            | 3.35 (0.47–23.82) |
| T.A.D.            | 2.32 (1.64–3.29) |
| T.I.              | 1.09 (0.81–1.47) |
| Other             | 1.30 (0.85–1.98) |

| Tuberculosis type | OR (95% CI) |
|-------------------|-------------|
| Sputum smear (+) pul TB | 1.66 (1.45–1.88) |
| Sputum smear (-) pul TB | 1           |
| Extrapulmonary TB | 0.81 (0.45–1.48) |

| Outcome | OR (95% CI) |
|---------|-------------|
| Cure    | 1           |
| Failure | 10.26 (5.95–17.68) |
| Default | 3.77 (3.03–4.68) |
| Transfer out | 1.42 (1.17–1.73) |
| Other   | 2.41 (1.80–3.25) |

| Region | OR (95% CI) |
|--------|-------------|
| 1      | 1           |
| 2      | 1.23 (0.96–1.58) |
| 3      | 1.25 (0.89–1.75) |
| 4      | 0.77 (0.54–1.09) |
| 5      | 1.63 (1.03–2.57) |
| 6      | 1.40 (0.94–2.09) |
| 7      | 0.73 (0.40–1.31) |
| 8      | 1.03 (0.84–1.28) |
| 9      | 1.18 (0.84–1.68) |
| 10     | 0.99 (0.68–1.45) |
| 11     | 1.44 (1.05–1.97) |
| 12     | 0.90 (0.62–1.30) |
| 13     | 1.47 (1.10–1.96) |
| 14     | 1.35 (1.02–1.79) |
| 15     | 1.77 (1.35–2.32) |
| 16     | 0.57 (0.30–1.09) |

CI = confidence interval; OR = odds ratio; pul = pulmonary; T.A.F. = treatment after failure; T.A.D. = treatment after default, T.I. = transfer in.

4. Discussion

4.1. Interpretation of the results

This study aimed to identify factors associated with relapse of TB in Korea by using national reported case data. The relapse rate for a 5-year period in this study was 9.6%, which was lower than the rate reported in the Annual Report on the Notified Tuberculosis Patients in
Korea [3,4]. The relapse rate did not include relapse after the 5-year period. The reported rate of private medical institutions was estimated below 60%. The TB infection of risk groups such as residents in unauthorized facilities and homeless people was not identified. For various reasons, the relapse rate in this study was underestimated in comparison to the annual reported relapse rate. The relapse of TB can be divided into two categories: (1) recurrence by reactivation of same bacteria in the previous infection and (2) reinfection. These two factors can be confirmed with genotyping, but in this study with national reported cases, the patients’ clinical data could not be attained; therefore, recurrence and reinfection could not be identified [7,9]. Korea does not conduct TB DNA fingerprinting tests on TB patients, and a special methodology is necessary to distinguish between these two aspects. A literature review indicates that within 2 years of treatment more cases of recurrences result from reactivation of existing bacteria and more cases of reinfection occur after 2 years of treatment with another person’s TB bacteria. A high TB incidence rate is controversially associated with reinfection [10,14]. In this study, 42% of the relapsed TB patients had relapsed within 1 year and 65% of patients had relapsed within 2 years.

If we were to extend the follow-up period, the relapse rate within 2 years would be lower. This finding contrasted with the results of existing studies. A study conducted in one private hospital revealed that 80% of TB patients with completion of treatment needed additional treatment [8,9,15]. Compared to the existing study in Korea, the relapse rate in 2 years after treatment was lower and closer to the other country’s study results [8,9,15].

The relapse of TB was higher in men, which is the case with TB infection. The relapse rate by sex was higher in some studies, but other studies show no relation [16,17]. This study also confirmed that men relapsed more, based on Chi-square and multivariate regression analyses. Relapse occurred more in patients in the 40s, 50s, and 60s age groups. This may be associated with the increase of TB patients and latent tuberculosis infection. However, there was no relation between age and the relapse rate in this study’s multivariate logistic regression with patients registered in the public health centers with treatment results available. This suggests that previous treatment results, rather than age effect, affects the relapse of TB.

To confirm the same results in the all TB patients, it is necessary to secure treatment results in patients treated and controlled by private medical institutions. Among patients using private medical institutions, the relapse rate was higher compared to the rate of public health centers. This finding could be explained in that first infected TB patients treated by Group 1 medicines were mostly treated in public health centers, whereas incurable TB patients with relapsed TB or antimicrobial-resistant TB were treated in private medical institutions. Furthermore, treatment dropout is also relatively higher in private medical institutions [6].

Compared with new cases, relapsed patients, treatment failure patients, and re-registered patients after cease of treatment were more highly relapsed. It may be that patients with second treatment are more relapsed, compared to patients with new cases. In particular, patients with treatment failure could be relapsed again, even with full recovery after long-term treatment. These results corresponded with the results of existing studies that factor in relapse is previous TB infection [14].

The relapse of patients with treatment failures were also far higher (Tables 4 and 5). Treatment failure is mostly attributable to antimicrobial-resistant tuberculosis. The relapse could be high, even after full recovery after long-term treatment.

It could be a good method to lower the relapse by managing the first TB-infected patients to take medicine thoroughly and periodically not to fail treatment [15]. For convenience of intake, the everyday intake of medicines is better for lowering TB relapse, compared to taking medicines two or three times weekly. Directly observed therapy (DOT) in general lowers the relapse rate, but some researchers are suspicious of the effectiveness of DOT [8,18]. The relapse rate with short-term chemical therapy (e.g., rifampin) is < 5%; however, this study’s relapse rate of patients with full recovery using public health centers with treatment results was 7.3%. This rate was higher than the rate reported in existing studies [19]. Patients with an irregular medicine intake period, a cavity observed on chest X-ray, and sputum-positive results after a 2-month intake of medicine have a relapse rate >5%; however, in this study, no clinical data were secure and could not be confirmed [18]. The completion patients’ relapse rate was 11.7%, which is higher than the relapse rate of patients with full recovery.

Without confirming negative TB, completion patients, who were in reality treatment failures, could be reported as relapse patients [20]. Move-out patients also showed a higher relapse rate. This may be because the patients were no longer treated without move-in to other medical institutions. However, more study on conformity is needed.

4.2. Strength and limitations

Studies outside Korea indicate relapse factors of TB such as irregular intake of medicine, alcoholism, smoking, previous history of TB infection, and diseases accompanied by a decline in immunocompetence [15]. This study could not investigate the associated factors of behavior or clinical situations of patients and did not confirm factors. Furthermore, no questionnaires were conducted to investigate the behaviors and socioeconomic characteristics of patients and this study
Table 5. Relapse rate of tuberculosis in public health centers.

|                      | Relapse |          | p       |
|----------------------|---------|----------|---------|
|                      | No      | Yes      |         |
| Sex                  |         |          |         |
| Men                  | 7,511   | (90.0)   | 839     | (10.0)  | < 0.0001 |
| Women                | 3,901   | (93.2)   | 285     | (6.8)   |          |
| Age (y)              |         |          |         |
| 0–9                  | 4       | (80.0)   | 1       | (20.0)  | 0.002    |
| 10–19                | 1,115   | (93.5)   | 78      | (6.5)   |          |
| 20–29                | 2,377   | (91.6)   | 218     | (8.4)   |          |
| 30–39                | 1,855   | (90.7)   | 190     | (9.3)   |          |
| 40–49                | 1,762   | (89.8)   | 200     | (10.2)  |          |
| 50–59                | 1,195   | (89.7)   | 138     | (10.3)  |          |
| 60–69                | 1,411   | (90.0)   | 156     | (10.0)  |          |
| ≥ 70                 | 1,693   | (92.2)   | 143     | (7.8)   |          |
| Registration         |         |          |         |
| New                  | 8,684   | (92.5)   | 705     | (7.5)   | < 0.0001 |
| Type                 |         |          |         |
| Relapse              | 1,655   | (85.1)   | 289     | (14.9)  |          |
| T.A.F                | 3       | (60.0)   | 2       | (40.0)  |          |
| T.A.D                | 178     | (78.8)   | 48      | (21.2)  |          |
| T.I                  | 677     | (92.6)   | 54      | (7.4)   |          |
| Other                | 215     | (89.2)   | 26      | (10.8)  |          |
| TB type              |         |          |         |
| Sputum smear (+) pul TB | 4,585 | (88.2) | 616 | (11.8) | < 0.0001 |
| Sputum smear (−) pul TB | 6,615 | (93.0) | 496 | (7.0) |          |
| Extrapulmonary TB    | 212     | (94.6)   | 12      | (5.4)   |          |
| Outcome              |         |          |         |
| Cure                 | 9,366   | (92.7)   | 735     | (7.3)   | < 0.0001 |
| Complete             | 217     | (88.9)   | 27      | (11.1)  |          |
| Failure              | 28      | (50.0)   | 28      | (50.0)  |          |
| Default              | 428     | (76.0)   | 135     | (24.0)  |          |
| Transfer out         | 1,083   | (88.6)   | 139     | (11.4)  |          |
| Other                | 290     | (82.9)   | 60      | (17.1)  |          |
| Region               |         |          |         |
| 1                    | 2,109   | (91.54)  | 195     | (8.46)  | 0.0002   |
| 2                    | 967     | (89.37)  | 115     | (10.63) |          |
| 3                    | 430     | (89.77)  | 49      | (10.23) |          |
| 4                    | 606     | (93.66)  | 41      | (6.34)  |          |
| 5                    | 212     | (89.83)  | 24      | (10.17) |          |
| 6                    | 277     | (89.35)  | 33      | (10.65) |          |
| 7                    | 223     | (94.49)  | 13      | (5.51)  |          |
| 8                    | 2,422   | (92.09)  | 208     | (7.91)  |          |
| 9                    | 468     | (90.87)  | 47      | (9.13)  |          |
| 10                   | 438     | (92.41)  | 36      | (7.59)  |          |
| 11                   | 539     | (89.68)  | 62      | (10.32) |          |
| 12                   | 491     | (92.99)  | 37      | (7.01)  |          |
| 13                   | 667     | (89.65)  | 77      | (10.35) |          |
| 14                   | 716     | (89.50)  | 84      | (10.50) |          |
| 15                   | 655     | (87.68)  | 92      | (12.32) |          |
| 16                   | 192     | (94.58)  | 11      | (5.42)  |          |
| Total                | 11,412  | (91.0)   | 1,124   | (9.0)   |          |

Data are presented as n (%). pul = pulmonary; T.A.D. = treatment after default; T.A.F. = treatment after failure; T.I. = transfer in.

has limited variables [15]. Private medical institution had limited results after dropout of the registry; therefore, no relapse rate was calculated for the dropout patients.

Medical doctors and medical institution are required to report TB patients, but it is not mandatory to report treatment and control of TB patients. To overcome this limit, the National Health Insurance data should be utilized for the visit period, TB bacteria test date, medicine intake information, insurance type, and insurance premium. This current study’s limitation would also be overcome by surveying a sample representative population to cover health behavior and socioeconomic status. In the disease code after 2008, multidrug-resistant TB and extensively drug-resistant TB were introduced as “U88.0” and “U88.1”, respectively. Using reported cases after 2008, a study on the relapse of antimicrobial-resistant TB patients could be conducted, which this
study did not investigate. However, this study has a strong point in that it secured representativeness and confidence of data by using national TB reported cases, and calculated the relapse rate of tuberculosis in Korea, and identified factors associated with relapse of TB.

Conflicts of interest

The authors have no conflicts of interest to declare.

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