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Estimating the burden of nosocomial exposure to tuberculosis in South Korea, a nationwide population based cross-sectional study

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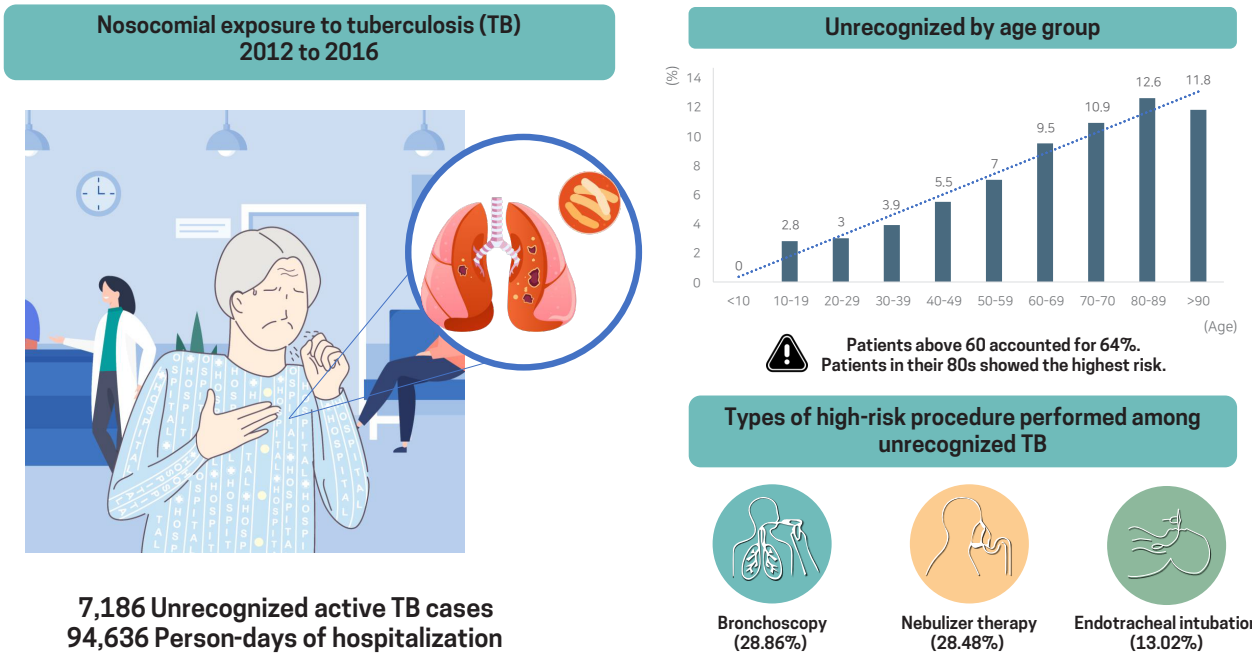

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Background/Aims: The aim of the study was to investigate the current nationwide burden of nosocomial exposure to tuberculosis (TB) using national health insurance claims data.
Methods: All patients who had claims for drug susceptibility testing for TB from 2012 to 2016, which indicated culture-proven TB, were included. The first day of the infectious period was defined as 3 months before a doctor's suspicion of TB in patients with respiratory symptoms and 1 month before in patients without symptoms. The last day of the infectious period was defined as one day before the prescription of anti-TB medications. Patients hospitalized during infectious periods were investigated and their hospitalization days were calculated. Records of medical procedures which increased the risk of nosocomial transmission by generating aerosols were also investigated.
Results: A total of 7,186 cases with 94,636 person-days of hospitalization with unrecognized active TB were found. Patients above 60 years of age accounted for 63.99% of the total number and 69.70% of the total duration of hospitalization. TB patients in the older age group showed a trend toward higher risks for hospitalization with unrecognized active TB. Patients in their 80s showed the highest risk (12.65%). Bronchoscopy (28.86%), nebulizer therapy (28.48%), and endotracheal intubation (13.02%) were common procedures performed in these patients during hospitalization.
Conclusions: The burden of nosocomial exposure to TB in South Korea is still substantial. Hospitalization with unrecognized active TB, especially among the elderly TB patients could be a serious public health issue in South Korea.

Keywords: Pulmonary tuberculosis; Nosocomial infection; Infectious disease transmission; Epidemiology; Korea

INTRODUCTION

South Korea is a country with an intermediate tuberculosis (TB) burden. The incidence rate was 66 cases per 100,000 population in 2018 [1]. The burden of TB in South Korea is disproportionately high considering the nation's sociodemographic index, an indicator reflecting income, education level, and fertility rate [2]. One reason for the high TB burden is the high incidence of TB in the elderly population [3,4]. Although the total incidence of TB is decreasing, the number of reported cases and the proportion of TB in the elderly is rising, from 6,547 new TB cases out of 34,123 total cases (19.2%) in 2001 to 14,193 cases out of 30,304 total cases (46.8%) in 2019 [5]. Elderly TB patients often present with atypical symptoms, so the diagnosis of TB can be delayed [6-8]. They also show atypical radiologic manifestations, misdiagnosed as pneumonia [9,10], and often need hospitalization indicated by CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥ 65) scores.

As hospitals are overcrowded, the risk of TB transmission is higher than in the community [11-13]. Moreover, the delay in a TB diagnosis in hospitalized patients can lead to a nosocomial TB outbreak [14-16]. In a population based TB investigation using molecular epidemiological techniques, a substantial proportion of TB transmissions occurred in hospitals [17]. The hospital environment in South Korea is especially vulnerable to the transmission of respiratory infections, which was one of the reasons for the Middle East respiratory syndrome outbreak in 2015. More than 50% of the wardrooms in South Korea are multiple occupancies with more than four beds per room and the rooms are overcrowded with family members of patients or privately hired aides who take care of the patients [18].

National Institute for Health and Care Excellence guidelines recommend that patients who spent more than 8 hours in the same wardroom with a smear-positive TB patient with a cough should be considered at risk for infection [19]. Several studies have reported that even smear-negative TB patients were infectious [20,21]. In Europe, close non-household contact is defined as those persons with a cumulative exposure time of 40 hours with sputum culture-positive TB patients, regardless of smear results [22]. Therefore, nosocomial transmission can result from smear-negative but culture-positive TB patients who are unexpectedly diagnosed with TB from the results of sputum or bronchial washing fluid cul-

tures reported several weeks later [23,24].

The present study aimed to investigate the current nationwide burden of nosocomial exposure to TB using national health insurance claims data.

METHODS

Data sources

Nationwide data collected between 2007 and 2016 derived from the Korean Health Insurance Review and Assessment (HIRA) database was analyzed. National health insurance in Korea is a mandatory program with universal health coverage system that covers almost 98% of the Korean population [25]. The HIRA database provides sociodemographic information on the insured, diagnoses described with International Classification of Diseases, 10th Revision (ICD-10) codes, and drugs, diagnostic examinations, and therapeutic procedures ordered by medical doctors.

Definition of pulmonary TB

To estimate the minimal burden of TB exposure, only culture-proven TB patients were included. Because the culture results were unavailable in the claims data, an operational definition of at least one prescription record for phenotypic drug susceptibility testing (DST) was used. Since 2005, the Korean TB guidelines have recommended that all TB patients undergo DST with the first culture-positive specimen [26]. However, the actual prescription rate for DST among culture-proven TB patients was suboptimal [27]. Since the introduction of private-public mix (PPM) in 2007 and nationwide expansion in 2011, the continuous monitoring of clinical practice by PPM nurses raised prescription rate for DST to a current level. Therefore, only patients who were diagnosed with TB from 2012 to 2016 were finally included to avoid underestimation of TB cases due to suboptimal prescription rates for DST. The records of individuals with ICD-10 codes of pulmonary TB (A15, A16, or A19) in addition to prescription records of phenotypic DST between 2007 to 2016 were extracted from HIRA database.

To estimate the actual burden of TB exposure, multiple episodes of treatment in a TB patient were analyzed as separate cases, if only DST was prescribed in treatment period. To define culture-confirmed TB cases, the operational definition of 'treatment case' and 'DST case' were used. All prescription records of at least three anti-TB medications (rifampin, rifabutin, isoniazid, ethambutol, pyrazinamide, kanamycin or streptomycin, levofloxacin or moxifloxacin, prothionamide, cycloserine, para-aminosalicylic acid) in each TB patient were sorted in time order, and any consecutive records with more than 180 days of interval were defined as separate 'treatment case.' Likewise, prescription records of DST in each TB patient were sorted, and any consecutive records with more than 90 days of interval were defined as separate 'DST case.' After applying clearing period of 2007 to treatment cases, incident treatment cases between 2008 to 2016 were identified. Then, treatment cases and DST cases were matched in each TB patients, and only cases with prescription records of DST within 6 months after treatment initiation were defined as culture-confirmed pulmonary TB cases. For a reason that described above, only cases from 2012 to 2016 were included in this study, finally (Fig. 1).

Definition of infectious period

Although there is no method to determine the start day of an infectious period, the Center for Disease Control and Prevention recommends the practical estimation of the start day by TB symptoms, smear results, and the presence of a cavity on chest X-ray [28]. Because the results of smears and chest X rays were not available in the claims data, a simple operational definition was used. The date of TB diagnosis (Point C) was defined as the time point when at least three kinds of anti-TB medication were first prescribed (Fig. 2). The timepoint of the clinician's first suspicion of TB (Point B) was defined as the date when TB-specific examinations (acid-fast bacilli smear, culture, nucleic acid amplification tests) were first ordered. For patients with prescription records of antitussive or mucolytic medications within 3 months before Point B, the first day of the infectious period (Point A) was defined as 90 days before Point B. For patients without those prescriptions, the Point A was defined as 30 days before. The last day of the infectious period was defined as one day before Point C. Though at least 2 weeks of anti-TB treatment is needed to be non-infectious, as mentioned in Korean guidelines for TB [29], in our study, confirmed TB patients were regarded as non-infectious, as they were isolated

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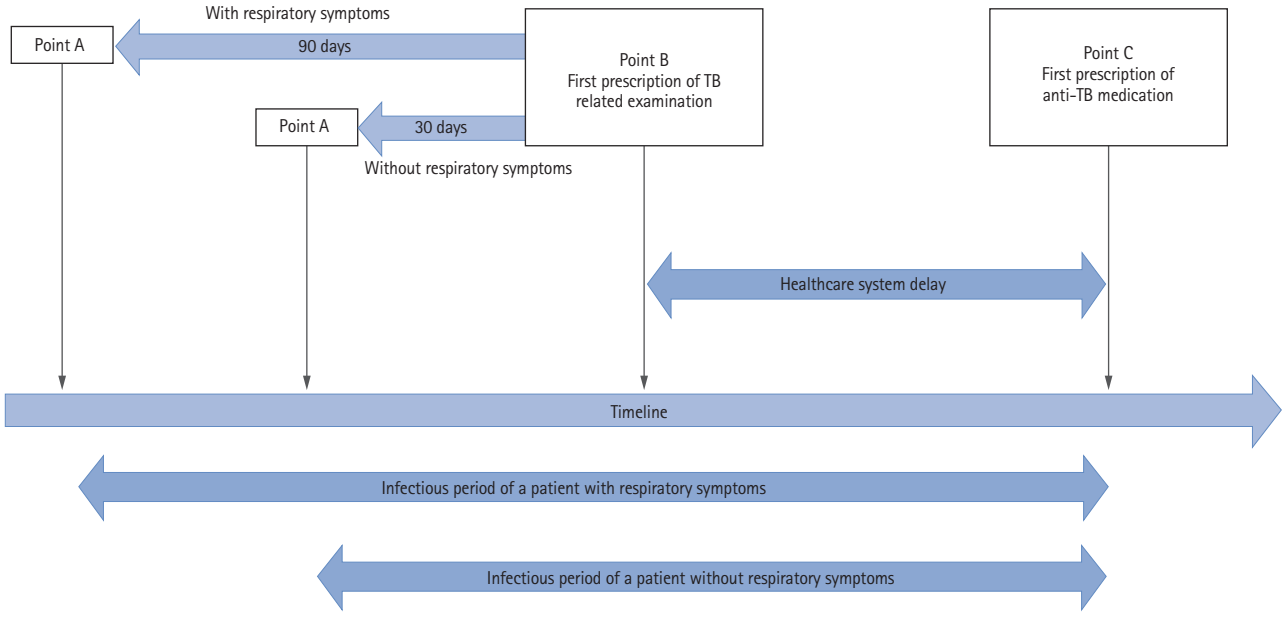

Figure 1. Flow chart of cases included in this study from the national health insurance claims data. Treatment case was defined with prescription records of at least three anti-tuberculosis (TB) medications. Any consecutive prescription records with more than 180 days of interval were defined as separate treatment cases. Likewise, drug susceptibility testing (DST) cases was defined with prescription records of DST. Any consecutive prescription records with more than 90 days of interval were defined as separate DST cases. After applying clearing period of 2007 to treatment cases, treatment cases and DST cases were matched in each TB patients, and only cases with prescription records of DST within 6 months after treatment initiation were defined as culture-confirmed pulmonary TB cases.

immediately after diagnosis of TB. The time interval between Point B and Point C was defined as the 'healthcare system delay.' Any hospitalizations during the infectious periods were totaled as person-days. There may be hospitalizations in isolated room before initiation of anti-TB treatment, in cases of suspected TB. Therefore, claims records for a charge for use of an isolation room during the infectious period were also investigated. Isolated hospitalization days were subtracted from the total hospitalization days during the infectious period, which defined hospitalization with unrecognized TB.

Data collection

For external validation of total number of extracted TB cases from HIRA database, the total identified cases were sorted by year of diagnosis and compared with annual cases reported by the Korean government, and those estimated by the World Health Organization (WHO). To investigate the clinical characteristics of TB patients hospitalized during infectious periods, comorbidities expressed by ICD-10 codes in the claims data were compared between hospitalized patients and those not hospitalized. The Charlson comorbidity index (CCI) was used as a tool to describe the comorbidities [30,31]. The 17 comorbidities which comprise CCI were defined with ICD-10 codes presented in Supplementary Table 1. Patients with more than three claim records with specific ICD-10 codes representing each comorbidity within 2 years before TB diagnosis were considered as having that comorbidity. The total number of hospitalizations with unrecognized TB and their person-days were analyzed in each age group. Records of medical procedures which increase the risk of nosocomial transmission by generating aerosols—bronchoscopy, laryngoscopy, endotracheal intubation, tracheostomy, cardiopulmonary resuscitation, use of a nebulizer, use of a high flow oxygen cannula, or mechanical ventilation—were investigated among the cases. Those performed during intensive care unit (ICU) admissions were counted separately.

Statistical analysis

For continuous variables, independent *t* tests or the

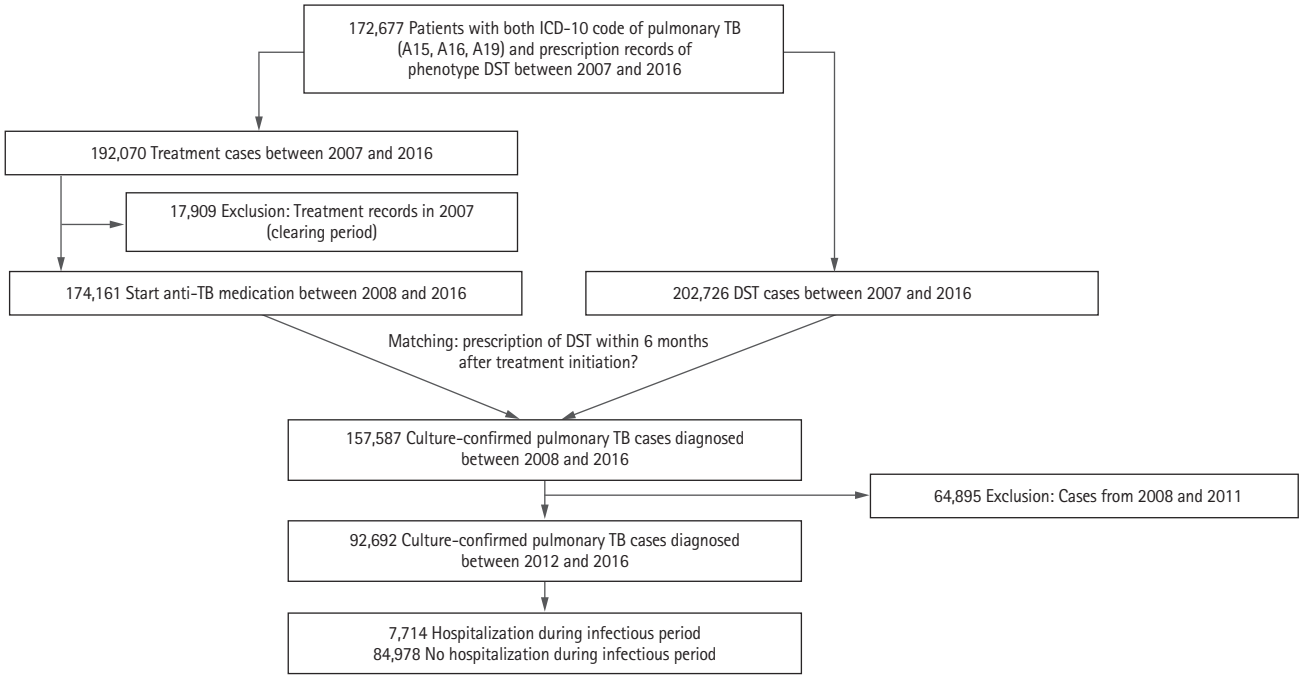

Figure 2. Operational definition of infectious period. The infectious period was defined as the term between Point A (presumed timepoint that the first transmission of *Mycobacterium* occurred) and a day before Point C (day of initiation of anti-tuberculosis [TB] medication). Healthcare system delay was defined as the interval between Point B (the first day when the clinical doctor suspected TB) and Point C. ICD-10, International Classification of Diseases, 10th Revision; DST, drug susceptibility testing.

Wilcoxon rank sum test were used for comparison. For categorical variables, the chi-square test or Fisher's exact test was used. Trends across ordinal variables were tested with the Cochran-Armitage test for trend. A $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics statements

Ethics approval was obtained from the Institutional Review Board of Incheon St. Mary's Hospital, Incheon, Korea (IRB No. OC17ZESE0085). The requirement for informed consent was waived by the Board.

RESULTS

From 2012 to 2016, a total of 92,692 cases of culture-proven pulmonary TB cases were identified (Fig. 1). The total number of extracted cases sorted by year of diagnosis, nationally-reported pulmonary TB cases [5], and bacteriologically confirmed pulmonary TB cases reported by WHO [1] were compared (Table 1).

The median infectious period of the total identified cases (n = 92,692) was 90 days (interquartile range [IQR], 90 to 98). That of patients with respiratory symptoms (n = 69,745) and without symptoms (n = 22,947) were 92 days (IQR, 90 to 104) and 34 days (IQR, 30 to 47) The healthcare system delays of patients hospitalized (n = 7,714) and those not hospitalized (n = 84,978) were compared (Fig. 3). The median healthcare system delay in the hospitalized cases was 23 days (IQR, 3 to 60), which was longer than that of those not hospitalized (2 days; IQR, 0 to 12; $p < 0.001$).

Characteristics of TB patients hospitalized during the infectious period

A total of 7,714 cases with 108,631 person-days of hospitalization during the infectious period was identified between 2012 to 2016. The mean age of the hospitalized group was higher than the non-hospitalized group ($p < 0.001$) and the proportion of males was lower in the

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Table 1. Comparison between cases identified, total national reported cases and bacteriologically confirmed cases estimated by WHO

Year	No. of cases identified	National notified pulmonary TB cases	TB cases estimated by WHO[a]
2012	19,261	31,075	28,397
2013	19,290	28,720	21,817
2014	19,266	27,906	21,489
2015	18,144	25,550	20,055
2016	16,731	24,696	20,072
Total	92,692	137,947	111,830

WHO, World Health Organization; TB, tuberculosis.
[a]Bacteriologically confirmed pulmonary TB cases (smear-positive or culture-positive or positive by WHO-recommended rapid diagnostic tests) which includes both new and relapsed cases.

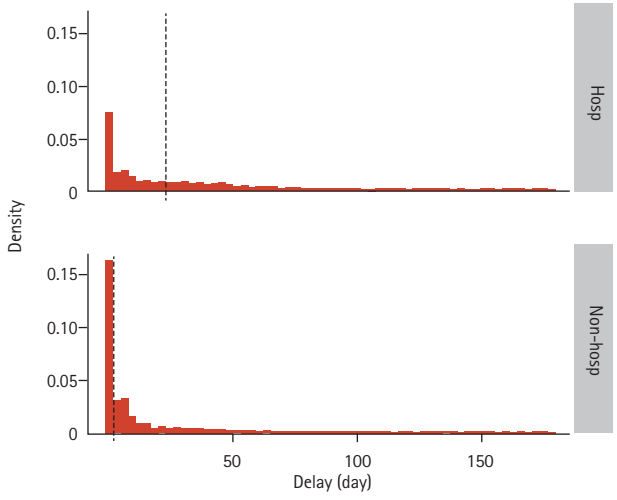

Figure 3. Density plots of healthcare system delays in hospitalization group (hosp) and non-hospitalization group (non-hosp). Dashed line represents median healthcare system delay 23 days in hospitalization group, whereas 2 days in non-hospitalization group.

hospitalized group ($p = 0.009$) (Table 2). The mean total CCI scores of the hospitalized group was higher than the non-hospitalized group ($p < 0.001$), implying that chronic diseases were more prevalent in the hospitalized group. In all comorbidities except 'any tumor' and 'acquired immune deficiency syndrome,' hospitalized patients showed a higher prevalence than non-hospitalized patients.

Burden of nosocomial exposure to pulmonary TB

After excluding cases with admissions to an isolation room, a total 7,186 cases with 94,636 person-days of hospitalization with unrecognized TB, which represented the nationwide burden of nosocomial exposure to TB, were identified. When the cases were classified into age groups, groups above 60 years of age accounted for 63.99% of the total number and 69.70% of the total duration of hospitalizations with unrecognized TB (Table 3). Patients in the older age group ($p < 0.001$) showed a trend toward a higher risk for hospitalization with unrecognized TB. The highest risk was noted in TB patients in their 80s (12.65%), which implies that among the culture-positive pulmonary TB patients in their 80s, 12.65% of patients were hospitalized without awareness of an active TB.

In the analysis of high-risk procedures, the most common procedures performed during hospitalization in infectious periods were bronchoscopies (28.86%) and nebulizer therapy (28.48%) (Table 4). When the cases were confined to hospitalization in the ICU, the proportion of patients who underwent high-risk procedures increased in all procedures, except bronchoscopy and laryngoscopy, suggesting that the ICU was a more vulnerable place for the nosocomial transmission of TB than general wards.

DISCUSSION

In this study, the nationwide burden of nosocomial exposure to TB in South Korea was estimated. Hospitalized patients were older and had more comorbidities compared to those not hospitalized. Elderly TB patients accounted for a substantial proportion of that burden,

Table 2. Characteristics and comorbidities of culture-proven pulmonary TB cases with and without hospitalization during the infectious period

Characteristic	Hospitalization (n = 7,714)	Non-hospitalization (n = 84,978)	*p* value
Age, yr	64.50 ± 16.78	56.08 ± 19.84	< 0.001
Male sex	4,618 (59.87)	52,154 (61.37)	0.009
Total CCI score	2.98 ± 2.56	2.04 ± 2.16	< 0.001
Categories of CCI			
Respiratory diseases			
Chronic pulmonary disease	3,021(39.16)	28,080 (33.04)	< 0.001
Cardiovascular diseases			
Myocardial infarction	315 (4.08)	1,666 (1.96)	< 0.001
Congestive heart failure	1,379 (17.88)	7,656 (9.01)	< 0.001
Peripheral vascular disease	204 (2.64)	1,344 (1.58)	< 0.001
Malignant neoplasms			
Any malignancy, including lymphoma and leukemia	298 (3.86)	3,094 (3.64)	0.320
Metastatic solid tumor	560 (7.26)	3,179 (3.74)	< 0.001
Endocrine diseases			
Diabetes without chronic complication	4,405 (57.10)	35,122 (41.33)	< 0.001
Diabetes with chronic complication	813 (10.54)	5,851 (6.89)	< 0.001
Renal diseases			
Renal disease	255 (3.31)	1,508 (1.77)	< 0.001
Gastrointestinal diseases			
Peptic ulcer disease	491 (6.37)	3,833 (4.51)	< 0.001
Mild liver disease	4,940 (64.04)	44,519 (52.39)	< 0.001
Moderate or severe liver disease	119 (1.54)	654 (0.77)	< 0.001
Psychological diseases			
Dementia	759 (9.84)	3,428 (4.03)	< 0.001
Neurological diseases			
Cerebrovascular disease	98 (1.27)	667 (0.78)	< 0.001
Hemiplegia or paraplegia	313 (4.06)	1,471 (1.73)	< 0.001
Musculoskeletal and connective tissue diseases			
Connective tissue disease	157 (2.04)	1,140 (1.34)	< 0.001
Infectious diseases			
AIDS	20 (0.26)	225 (0.26)	0.928

Values are presented as mean ± SD deviation or number (%).
TB, tuberculosis; CCI, Charlson comorbidity index; AIDS, acquired immune deficiency syndrome.

which demonstrated that TB in the elderly is a serious public health issue in South Korea.

Previous studies regarding the nosocomial transmission of TB in South Korea have focused on latent tuberculosis infections (LTBI) only in healthcare workers [32-35]. In a recently published study covering the results of an expanded contact investigation, which included inpatients and visitors, more close contacts were identified among them than among the healthcare workers [36]. Korean guidelines for national tuberculosis control

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Table 3. Hospitalization with unrecognized tuberculosis by age group

Age, yr	Total cases	No. of cases with unrecognized hospitalization	Sum of unrecognized hospitalization, person-day	Prevalence of unrecognized hospitalization, %	Unrecognized hospitalization, day
< 10	39	0	0	0	0
10–19	2,544	73 (1.02)	493 (0.52)	2.87	6.75 ± 3.44
20–39	8,821	268 (3.73)	1,776 (1.88)	3.04	6.63 ± 3.71
30–39	9,597	381 (5.30)	3,337 (3.53)	3.97	8.76 ± 8.16
40–49	13,081	724 (10.08)	8,240 (8.71)	5.53	11.38 ± 10.69
50–59	16,203	1,142 (15.89)	14,830 (15.67)	7.05	12.99 ± 12.88
60–69	13,886	1,321 (18.38)	19,117 (20.20)	9.51	14.47 ± 15.16
70–79	19,232	2,108 (29.33)	31,898 (33.71)	10.96	15.13 ± 15.95
80–89	8,538	1,080 (15.03)	13,921 (14.71)	12.65	12.89 ± 15.69
≥ 90	751	89 (1.24)	1,024 (1.08)	11.85	11.51 ± 14.45
Total	92,692	7,186 (100.00)	94,636 (100.00)	7.75	13.17 ± 14.26

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

Table 4. High-risk procedures performed during hospitalization in infectious periods

Variable	Total hospitalization[a] (n = 7,714)	Hospitalization in ICU (n = 2,263)
Bronchoscopy	2,226 (28.86)	561 (24.79)
Laryngoscopy	317 (4.11)	73 (3.23)
Endotracheal intubation	1,004 (13.02)	365 (16.13)
Tracheostomy	74 (0.96)	65 (2.87)
Cardiopulmonary resuscitation	19 (0.25)	12 (0.53)
Nebulizer therapy	2,197 (28.48)	948 (41.89)
High flow oxygen cannula	31 (0.40)	26 (1.15)
Mechanical ventilation	447 (5.79)	368 (16.26)

Values are presented as number (%).
ICU, intensive care unit.
[a]Hospitalizations in ICU were included.

recommend that contact investigations in nosocomial settings are needed when active TB in healthcare workers is identified [37]. Therefore, when inpatients are diagnosed with TB later during hospitalization, contact investigation of other inpatients and hospital visitors is not obligatory in South Korea. Lately, a few hospitals have initiated expanded contact investigation programs, including inpatients and visitors. However, considering the high LTBI prevalence in South Korea [38], diagnostic tests for LTBI have limited roles in demonstrating recent infections.

One of the epidemiologic features of TB in South Korea is the generation gap in the TB burden. As the incidence of TB in the younger generation decreases and TB in the elderly with various comorbidities increases [4-6], hospitals could be a major place for TB transmission, as in Japan [17]. The results of our study support that possibility. Elderly TB patients accounted for 64% of total burden of nosocomial TB exposure. Prevalence of unrecognized hospitalization was more than 10% among the elderly TB patients, which was higher than that in younger TB patients.

In addition to diagnostic difficulties which result from atypical clinical presentations and radiologic fea-

tures among elderly TB patients, poor adherence to anti-TB treatment is also an important public health issue in elderly TB patients [39]. Higher risk for experiencing adverse effects in elderly TB patients may be a reason for their poor adherence [40,41]. Also, mortality rate among elderly TB patients was high in South Korea—up to 26% in those age 75 or older in a citywide study [42]. In these backgrounds, management of elderly TB became one of key strategies of national TB control program in South Korea [38]. Pilot projects of active case finding among elderly population were implemented in 2017, which can reduce the current abundant burden of nosocomial TB exposure through early detection of elderly TB patients [43]. In addition, though it is not feasible so far [44], strategies of screening and treatment of LTBI among the elderly population have been investigated [45].

In several studies recently published in South Korea, hospitalization to a department other than a pulmonology or infectious diseases department, suggesting non-respiratory related hospitalization was a significant risk factor delayed isolation of hospitalized TB patients [46-48]. In those studies, more comorbidities such as malignancy, cardiovascular disease, chronic kidney disease were identified among the delayed isolation groups. Although the main reason for hospitalization were not investigated in our study, a substantial proportion of those hospitalizations might be attributable to non-respiratory related hospitalization associated with their comorbidities. Moreover, in previous studies mentioned above, typical symptoms of pulmonary TB were less prominent among the delayed group. These factors may bring about low index of suspicion for TB among physicians.

For a long time, chest X-ray has been used as a screening tool for TB. Although there are limitations of chest X-ray as a screening tool [49], it is noteworthy that approximately half of delayed cases were diagnosed with chest radiographs retrospectively interpreted by radiologists, in the previous study [48]. Recently developed automatic detection algorithm using artificial intelligence can be a useful tool for early detection of TB [50], when combined with automatic alarming systems reporting to physicians. Further studies investigating whether those new tools can shorten the healthcare system delay of TB diagnosis are needed.

Xpert MTB/RIF assay which was introduced to South Korea in 2013 provides faster, more accurate results than smear microscopy [51]. In our study, median time from physicians' suspicion of TB to prescription of anti-TB medication was only 2 days (IQR, 0 to 15) among the total cases, which might reflect the widespread use of Xpert MTB/RIF assay. However, as elderly TB patients often have difficulty in producing adequate sputum specimens [52], new diagnostic tools complementary to sputum-based diagnosis should be investigated, considering increasing proportion of the elderly TB patients. Currently investigated diagnostic methods using serum or plasma which detect components of *Mycobacterium tuberculosis* (Mtb) or host immune response to Mtb may be useful especially among the elderly TB patients [53].

The proportion of patients who underwent bronchoscopies during hospitalization with unrecognized TB was 28.86%, which was compatible with previous reports in South Korea [54]. Bronchoscopy is not a routine method for diagnosing TB, but our results showed that bronchoscopies were frequently performed in TB patients in South Korea. In a previous study, approximately 4.6% of the patients who underwent bronchoscopies after computed tomography scans for diagnosis pulmonary disease other than TB, were eventually and unexpectedly, diagnosed with TB [23]. Another remarkable finding was that records of endotracheal intubations were identified in 1,004 cases (13.02%) among total hospitalized cases. In general, endotracheal intubation is performed to protect the patency of airway in situations of clinical deterioration, or electively before general anesthesia. In our study, among 1,004 cases (13.02%), 374 cases (4.85%) were the former and 630 cases (8.17%) were the latter. These 630 cases might represent the burden of nosocomial exposure to TB in operating rooms.

The claims data has several strengths. Exact timepoints, such as the date of admission, outpatient visits, and prescriptions for anti-TB medication or diagnostic examinations could be identified without bias. In contrast to hospital-based cohort studies, in which the medical records in participating institutions are collected, all records of medical utilization in the country were included in this population-based cohort study using claims data. A limitation of our study was that information on the infectivity of the index cases (smear status and presence of pulmonary cavity) was unavailable in the claims data. To overcome this limitation, only

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pulmonary TB patients with records of DST, meaning culture-proven TB cases, were included in this study. Although a consensus definition was used, the uncertainty of the exact infectious period remains a limitation of this study. In addition, the primary endpoint of this study was the burden of nosocomial TB exposure, not actual transmission. Further studies on transmission in nosocomial settings are needed.

In conclusion, the burden of nosocomial exposure to TB in South Korea was still substantial. As the proportion of elderly TB patients increases, hospitals could be the most important place for TB transmission in the near future. Comprehensive national TB control programs to reduce the nosocomial transmission of TB should be implemented.

KEY MESSAGE

1. Total burden of nosocomial exposure to tuberculosis (TB)–7,186 cases with 94,636 person-days of hospitalization with unrecognized TB between 2012 to 2016 were identified.
2. TB patients who were hospitalized during infectious period were elder and had more comorbidities than those who were not.
3. High-risk medical procedures for TB transmission were performed frequently, especially in intensive care unit.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. ICD-10 codes representing each category of Charlson comorbidity index

Categories of Charlson comorbidity index	ICD-10 code
Respiratory diseases	
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Cardiovascular diseases	
Myocardial infarction	I21.x, I22.x, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Malignant neoplasms	
Any malignancy, including lymphoma and leukemia	C00.x–C26.x, C30.x–C34.x, C37.x– C41.x, C43.x, C45.x–C58.x, C60.x– C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
Metastatic solid tumor	C77.x–C80.x
Endocrine diseases	
Diabetes without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complication	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2– E13.5, E13.7, E14.2–E14.5, E14.7
Renal diseases	
Renal disease	I12.0, I13.1, N03.2–N03.7, N05.2– N05.7, N18.x, N19.x, N25.0, Z49.0– Z49.2, Z94.0, Z99.2
Gastrointestinal diseases	
Peptic ulcer disease	K25.x–K28.x
Mild 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
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Psychological diseases	
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1
Neurological diseases	
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Musculoskeletal and connective tissue diseases	
Connective tissue disease	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
Infectious diseases	
AIDS	B20.x–B22.x, B24.x

ICD-10, International Classification of Diseases, 10th Revision; AIDS, acquired immune deficiency syndrome.

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