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Tuberculosis infection via the emergency department among inpatients in South Korea: a propensity score matched analysis of the National Inpatient Sample

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SUMMARY

Background: Emergency departments (EDs) carry a high risk of infectious disease transmission and have also been implicated in tuberculosis (TB) outbreaks.

Aim: To determine if patients who visit EDs have an increased risk of TB infection. Using South Korean inpatient sample data (2012), the risk of TB occurrence during 90 days after hospitalization for patients admitted via EDs was compared with that for patients admitted via outpatient clinics.

Methods: The data of the 2012 Health Insurance Review and Assessment Service – National Inpatient Sample were used. TB diagnosis was based on International Classification of Diseases Version 10 [all TB (A15–A19), pulmonary TB (A15–A16) and extrapulmonary TB (A17–A18)].

Findings: After propensity score matching using the demographic and clinical characteristics of the patients, 191,997 patients (64,017 patients admitted via EDs and 127,908 patients admitted via outpatient clinics) were included in this study. There was no significant difference in baseline patient characteristics between the two groups. The percentage of patients with TB admitted via EDs was higher than that of patients admitted via outpatient clinics. The likelihood of active TB occurrence was 30% higher for all TB [hazard ratio (HR) 1.30; 95% confidence interval (CI) 1.12–1.52] and pulmonary TB (HR 1.30; 95% CI 1.10–1.53) in patients admitted via EDs compared with patients admitted via outpatient clinics; this difference was significant. However, no difference in the occurrence of extrapulmonary TB was observed between the two groups.

Conclusions: The likelihood of TB infection was greater in patients admitted via EDs than in patients admitted via outpatient clinics.

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Introduction

Healthcare-associated infections (HAIs) are a major health problem worldwide. A recent study by the World Health Organization (WHO) estimated that the prevalence of HAIs in hospitalized patients ranges from 3.5% to 12% in developed countries, and from 5.7% to 19.1% in low- and middle-income countries [1]. HAIs negatively affect patient outcomes (i.e. high morbidity and mortality, and extended hospital stays) and increase healthcare costs [2]. The pathogenesis of HAIs is complex and associated with many factors, including patient-specific factors (i.e. age and medical conditions), medical interventions (i.e. urinary and central venous catheters and surgical procedures) and healthcare delivery methods (i.e. inadequately cleaned, disinfected and/or sterilized equipment) [2]. Additionally, there is a risk for person-to-person transmission of infectious agents in healthcare facilities [3].

Tuberculosis (TB) is a communicable infectious disease caused by the bacterium *Mycobacterium tuberculosis* [4]. South Korea has a relatively high prevalence of TB, with an incidence of 108 cases/100,000 persons in 2012, which is seven times higher than the average incidence across Organisation for Economic Co-operation and Development countries [5]. In healthcare settings, TB is transmitted from person to person, specifically when droplet nuclei generated by patients with infectious TB are inhaled by another person [4]. Emergency departments (EDs) are high-risk areas for disease transmission [6,7], and are associated with TB outbreaks [8–11]. Given that EDs are often overcrowded and patients with undifferentiated illnesses remain in EDs for a long time, possibly in close proximity to each other [6,7], acutely ill or injured patients who visit EDs may be particularly vulnerable to TB infection.

This study aimed to determine whether patients who visit EDs have an increased risk of TB infection. Using South Korean inpatient sample data (2012), the risk of TB occurrence during 90 days after hospitalization in patients admitted via EDs was compared with that in patients admitted via outpatient clinics. A propensity score matched analysis was used to reduce the effects of confounding factors on observational data.

Methods

Data source

South Korea has a universal healthcare coverage system with a compulsory national health insurance (NHI) system, which covers approximately 98% of the South Korean population. Claims data are sent to the Health Insurance Review and Assessment Service (HIRA), which reviews the claims and renders reimbursement decisions. HIRA claims data comprise detailed information from 46 million patients per year (90% of the total population); these details include patients' diagnoses, treatments, procedures, surgical histories and prescription drugs [12]. However, for research purposes, this vast volume of claims data is unsuitable and cannot be used efficiently; therefore, HIRA developed the patient samples data set using a randomized sampling method, with the resultant data passing a validity test [12]. The HIRA National Inpatient Sample (HIRA-NIS, serial number: HIRA-NIS-2012-0051) is a comprehensive inpatient data set that includes 700,000 inpatients per year (13% of the total inpatient population) and

approximately 400,000 outpatients per year (1% of the total outpatient population).

Selection of study subjects

From the 2012 HIRA-NIS, 667,637 patients aged >20 years were selected as the study population. Assuming that the recorded responses were generated within 2–12 weeks after patients inhaled droplet nuclei containing *M. tuberculosis* [13], patients were followed-up regarding TB development for 15–90 days after the date of their first hospitalization. In total, 172,385 patients were excluded, including those who could not be followed-up for 90 days ($N=167,144$), those who had a diagnosis code of TB [International Classification of Diseases Version 10 (ICD-10) codes A15–A19] on the day of hospitalization ($N=4545$), those who developed TB within 15 days of hospitalization ($N=696$), and those who presented with respiratory symptoms (ICD-10 codes R04–R09, $N=34,454$). The remaining 460,798 patients were eligible for subsequent analyses.

To ensure relative homogeneity among inpatients who were admitted via EDs with inpatients who were admitted via outpatient clinics, the distribution of inpatients that developed TB within and after 15 days was checked between those admitted via EDs and those admitted via outpatient clinics (Table A, see online supplementary material). No between-group differences were observed, suggesting that the distribution of TB cases between ED and outpatient admissions in excluded patients may not differ significantly from that in included patients in the current study. However, when the included inpatients who visited EDs were compared with those who visited outpatient clinics (Table B, see online supplementary material), systematic differences ($P<0.0001$) were found in all baseline characteristics between the two inpatient groups. Thus, propensity score matching was used to reduce the effects of confounding by the measured covariates [14], in which the matching ratio was 1:2 (inpatients admitted via EDs were matched with inpatients admitted via outpatient clinics). After propensity score matching with baseline characteristics [i.e. age, sex, type of beneficiary, residential area, type of hospital and Charlson Comorbidity Index (CCI)] known to be associated with TB [15], 191,997 inpatients (64,017 inpatients admitted via EDs and 127,980 inpatients admitted via outpatient clinics) were finally included in the study. Within these matched inpatient groups, standardized differences (Table C, see online supplementary material) turned out to be less than 0.1, which indicates negligible differences in the baseline characteristics between the two inpatient groups [16].

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital. The requirement for informed consent was exempted by the committee.

Exposure and outcome variables

Inpatients admitted via EDs and those admitted via outpatient clinics from the 2012 HIRA-NIS were included in this study. If a patient was hospitalized more than once in 2012, only the first hospitalization was included in this study, and the TB diagnosis was traced to either an ED or outpatient clinic during the 90 days from the first day of hospitalization. To ensure patient-specific characteristics exerted minimal effects on the risk of new TB infections, the patients were matched according

to baseline characteristics. The baseline characteristics were as follows: inpatients were divided into 10-year groups based on age (20–29, 30–39, 40–49, 50–59, 60–69, 70–79 or ≥ 80 years) and sex. The type of health insurance beneficiary was classified as 'health insurance' (general health insurance beneficiary covered by NHI) and 'medical aid' (beneficiary of a public assistance programme targeted at economically disadvantaged individuals who are covered by NHI). Residential areas were categorized as 'urban' (large cities and metropolitan cities) or 'rural' (cities, counties and districts). Hospitals were divided into 'university hospitals' and 'clinics/hospitals'. The CCI was used to examine physical health status, in which the scores proposed by Quan *et al.* (2005) were calculated based on medical records, and were classified according to three categories (0, 1 or ≥ 2) [17]; higher scores indicated greater comorbidity.

As an outcome variable, TB diagnosis was defined by a diagnostic code (based on ICD-10, available at <http://apps.who.int/classifications/icd10/>), as follows:

- A15, respiratory tuberculosis, bacteriologically and histologically confirmed;
- A16, respiratory tuberculosis, not confirmed bacteriologically or histologically;
- A17, tuberculosis of nervous system;
- A18, tuberculosis of other organs; and
- A19, miliary tuberculosis.

The code was classified into two types: pulmonary TB (A15–A16) and extrapulmonary TB (A17–A18).

Statistical analysis

Propensity score matching was conducted using a greedy nearest neighbour matching method. Propensity scores were estimated with logistic regression models in which TB occurrence was regressed according to baseline characteristics (i.e. age, sex, type of beneficiary, residential area, type of hospital and CCI). In particular, to reduce the bias from unmeasured characteristics associated with hospitals (i.e. university hospitals and clinics/hospitals), patients were assigned to clusters by hospitals, and then inpatients admitted via EDs were matched with those admitted via outpatient clinics within the same hospitals. Once the matched samples were obtained, the baseline characteristics of the two inpatient groups – 'hospitalization after ED visit' and 'hospitalization after outpatient visit' – were compared. Statistical differences were determined using the Chi-squared test. Balance in baseline characteristics was evaluated by examining standardized differences between the two inpatient groups (Table C, see online supplementary material). TB was categorized into three types: all TB (ICD-10 codes A15–A19), pulmonary TB (ICD-10 codes A15–A16) and extrapulmonary TB (ICD-10 codes A17–A18). Within the propensity score matched samples, inpatients were followed-up to determine the new incidence of TB diagnosis for 90 days from the first day of hospitalization. Kaplan–Meier survival curves were estimated separately for inpatients admitted via EDs and those admitted via outpatient clinics. A stratified log-rank test was used to compare group survival curves [18]. A Cox proportional hazard regression analysis with a robust sandwich covariance estimate was used to calculate the risk of TB infection [19]. Hazard ratios (HR) and 95%

confidence intervals (CI) were used to estimate the risk of TB occurrence between 15 and 90 days after the first day of hospitalization among inpatients admitted via EDs compared with that among inpatients admitted via outpatient clinics (reference group). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA), and the statistical significance level was set at $\alpha=0.05$.

Results

Significant differences in patient characteristics were observed (all $P<0.0001$) before propensity score matching (Table A, see online supplementary material). Inpatients admitted via EDs were more likely to be older and male, have medical aid, live in rural areas, visit university hospitals and have higher CCI scores than those admitted via outpatient clinics.

Table I compares the baseline characteristics of the two inpatient groups after propensity score matching. In total, 64,017 inpatients admitted via EDs were matched with 127,980 inpatients admitted via outpatient clinics, where the matching ratio was 1:2. There were no significant differences between the two inpatient groups in terms of age, sex, type of beneficiary, residential area, type of hospital and CCI ($P>0.05$). The matched samples showed negligible imbalance in the baseline characteristics between the two inpatient groups (standardized difference <0.1) (Table C, see online supplementary material). Regarding disease prevalence, the highest proportion of patients were hospitalized via EDs because of trauma (18.4%), followed by gastrointestinal disease (15.2%) and cardiovascular disease (12.3%). In contrast, the highest proportion of patients were hospitalized via outpatient clinics because of musculoskeletal disease (14.9%), followed by trauma (11.1%) and cardiovascular disease (10.8%). The proportion of inpatients hospitalized via EDs because of pulmonology disease (ICD-10 codes J00–J99) was higher (7.3% vs 6.6%) than that of patients hospitalized via outpatient clinics (Tables D and E, see online supplementary material).

Table II shows HRs for TB occurrence (ICD-10 codes A15–A19) between 15 and 90 days after the first day of hospitalization. The HR increased with the increase in each 10-year age category. For sex and type of beneficiary, females (HR 1.42; 95% CI 1.22–1.65) and inpatients with medical insurance (HR 2.28; 95% CI 1.86–2.80) had higher HRs than their counterparts. HRs for TB occurrence increased gradually with CCI: HR=1.98 (95% CI 1.51–2.60) for a score of 1, and HR=5.24 (95% CI 4.15–6.63) for a score >2 .

Table III shows the percentage of cases and HRs for the occurrence of TB in inpatients who were hospitalized via EDs between 15 and 90 days after the first day of hospitalization. The percentage of inpatients with TB admitted via EDs was higher than that of inpatients admitted via outpatient clinics: 0.42% vs 0.35% for all TB (ICD-10 codes A15–A19), 0.35% vs 0.30% for pulmonary TB (ICD-10 codes A15–A16) and 0.07% vs 0.07% for extrapulmonary TB (ICD-10 codes A17–A18). Compared with inpatients admitted via outpatient clinics, inpatients admitted via EDs had significantly higher HRs for the occurrence of all TB (HR 1.30; 95% CI 1.12–1.52) and pulmonary TB (HR 1.30; 95% CI 1.10–1.53). In contrast, no significant risk was detected for the occurrence of extrapulmonary TB.

Table 1
Baseline characteristics of inpatients after propensity score matching (N=191,997)

Characteristics	No. (%) of inpatients		P-value
	Hospitalization after ED visit (N=64,017)	Hospitalization after outpatient clinic visit (N=127,980)	
Age (years)			
20–29	6804 (33.8)	13,341 (66.2)	0.5216
30–39	9520 (33.3)	19,050 (66.7)	
40–49	9997 (33.5)	19,805 (66.5)	
50–59	12,607 (33.0)	25,593 (67.0)	
60–69	10,234 (33.1)	20,653 (66.9)	
70–79	10,566 (33.5)	20,981 (66.5)	
≥80	4289 (33.4)	8557 (66.6)	
Sex			
Male	30,935 (33.3)	62,011 (66.7)	0.5463
Female	33,082 (33.4)	65,969 (66.6)	
Type of beneficiary			
Medical aid	4964 (33.4)	9884 (66.6)	0.8099
Medical insurance	59,053 (33.3)	118,096 (66.7)	
Residential area			
Urban area	31,205 (33.2)	62,712 (66.8)	0.2891
Rural area	32,812 (33.5)	65,268 (66.5)	
Type of hospital			
University hospital	19,815 (33.4)	39,540 (66.6)	0.7980
Clinic/hospital	44,202 (33.3)	88,440 (66.8)	
CCI			
0	22,151 (33.5)	44,037 (66.5)	0.5894
1	18,694 (33.4)	37,304 (66.6)	
≥2	23,172 (33.2)	46,639 (66.8)	

CCI, Charlson Comorbidity Index.

Figure 1 shows the survival curves for TB occurrence in inpatients admitted via EDs or outpatient clinics between 15 and 90 days after the first day of hospitalization. The Kaplan–Meier survival analysis indicated that the difference in cumulative probability of TB occurrence between the two hospitalized groups was significant for all TB (stratified log-rank test; $P=0.0008$) and pulmonary TB (stratified log-rank test; $P=0.0025$), but not extrapulmonary TB (stratified log-rank test; $P=0.2048$).

Discussion

Based on a representative inpatient sample data set obtained from HIRA, inpatients who were hospitalized via EDs were found to have a higher risk of acquiring active TB during the subsequent 90 days than inpatients hospitalized via outpatient clinics. After propensity score matching using the demographic and clinical characteristics of the inpatients, the likelihood of the occurrence of active TB increased by 30% for both TB (ICD-10 codes A15–A19) and pulmonary TB (ICD-10 codes A15–A16); the difference between the two groups was significant. However, there were no differences in the occurrence of extrapulmonary TB between the two groups. Pulmonary TB is a bacterial infection that most commonly affects the lungs, whereas extrapulmonary TB infections occur in organs other than the lungs (i.e. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones or meninges) [4]. Pulmonary TB infection is transmitted from person to person via

droplet nuclei containing *M. tuberculosis*, which eventually reach the lung alveoli; however, extrapulmonary TB (except for laryngeal TB) is rarely infectious [4]. These results suggest that airborne transmission of TB infection may be a key factor related to increased TB occurrence associated with ED visits.

To the best of the authors' knowledge, this is the first study to report the potential association between visiting an ED and the risk of TB infection in inpatients. However, some studies have considered the risk of infection with other respiratory diseases among patients who visited EDs. In a Canadian study of elderly residents in long-term care facilities, Quach *et al.* (2012) examined the risk of acute respiratory and gastrointestinal infections following ED visits, and found that the risk of acute infection was three times higher in elderly residents who visited EDs (odds ratio 3.9; 95% CI 1.7–8.6) compared with those who did not visit EDs [20]. Among children from the USA, the risk of infection with measles was significantly higher among those who visited EDs [21,22]. Recent research has suggested that outbreaks of emerging infectious diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), are associated with EDs [23,24]. At the National Taiwan University Hospital, one-third of SARS cases occurred after exposure to an index case (a known SARS patient) in the ED [23]. Infectious MERS was also transmitted from a single patient who visited the ED (index case), and was confirmed in 82 individuals (including 33 patients) who had visited the ED where the index case was hospitalized [24]. Thus, although the medical care systems, ED conditions and occurrence rates of infectious diseases vary between

Table II

Hazard ratios (HRs) (95% confidence interval) for the occurrence of tuberculosis (TB) according to the baseline characteristics of inpatients

Characteristics	HRs for TB occurrence	P-value
	HR (95% CI)	
Age (years)		
20–29	Reference	<0.0001
30–39	0.99 (0.59–1.68)	
40–49	1.66 (1.03–2.67)	
50–59	2.64 (1.70–4.09)	
60–69	3.59 (2.33–5.55)	
70–79	5.68 (3.73–8.67)	
≥80	6.42 (4.11–10.04)	
Sex		
Male	Reference	<0.0001
Female	1.42 (1.22–1.65)	
Type of beneficiary		
Medical aid	Reference	<0.0001
Medical insurance	2.28 (1.86–2.80)	
Residential area		
Urban area	Reference	0.7226
Rural area	1.03 (0.88–1.19)	
Type of hospital		
University hospital	Reference	0.3278
Clinic/hospital	1.08 (0.92–1.27)	
CCI		
0	Reference	<0.0001
1	1.98 (1.51–2.60)	
≥2	5.24 (4.15–6.63)	

CCI, Charlson Comorbidity Index.

countries, previous findings have consistently highlighted the potential risk of transmitting infectious respiratory diseases in EDs.

EDs are considered to be the highest-risk areas for TB transmission among various healthcare facilities [25]. Therefore, there is great concern about the risk of ED-acquired TB infection in healthcare workers [9,11,26]. For example, Haley *et al.* (1989) reported TB transmission at Parkland Memorial Hospital in the USA, where five ED workers acquired TB within one year (out of a total of six ED workers to develop TB within this period) after exposure to an index case (a patient with severe cavitary TB who visited the ED) [9]. In addition, 16 ED workers (out of a total of 112 workers with tuberculin-negative skin tests) progressed from negative to positive skin tests [9]. Sokolove *et al.* (1994) conducted a questionnaire survey on

self-reported purified protein derivative (PPD) skin test results and TB exposure among nurses and physicians working in an urban ED [11]. Of 81 respondents, 25 (31%) workers responded that they converted to PPD positive, with most converting during the first six months of 1993 while working in the ED [11]. In a one-year cohort study of 70 healthcare workers at a university hospital in Lima, Peru, Escombe *et al.* (2010) found that 39 (56%) healthcare workers were culture positive at baseline; after one year, 27/31 workers who tested culture negative at baseline consented to follow-up. Of these, eight tested culture positive, indicating the acquisition of TB infection [26]. Compared with the general population of Lima, these workers had a higher TB incidence rate of 1.46–1.72% [26]. These findings suggest that visiting an ED can lead to the acquisition of TB infection from ill inpatients with existing TB infections.

To the authors' knowledge, this is the first study to show a significant risk of TB infection (especially the occurrence of pulmonary TB) among inpatients as a result of visiting EDs. However, critical issues that might affect the interpretation of these findings warrant consideration. Of these, one of the most important is the presence of latent TB. Latent TB is a persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB [27]. WHO estimated that nearly one-third of the world's population had latent TB in 2010 [28], and that people with latent TB exhibited no physical signs and symptoms but were at high risk of developing active TB and becoming infectious [29]. South Korea is considered to be an intermediate TB burden country, where the recorded annual incidence of TB was 97/100,000 in 2013 [30]. It has also been suggested that South Korea has a high prevalence of latent TB [31]; thus, it is possible that TB infections associated with visits to EDs could have been due to the re-activation of latent TB rather than recent transmission via EDs. Clearly, inpatients who visit EDs are more likely to progress to active TB than outpatients because ED patients are more prone to numerous medical conditions, malnutrition, high comorbidity index, low socio-economic status and immunocompromised status [6,32–34], which are known risk factors for developing active TB [30]. The NHIS-NIS data set did not provide detailed information about whether inpatients had been diagnosed previously (before 2012) or treated for TB, whether any of their family members had TB, or whether they had a human immunodeficiency virus infection, because this is sensitive personal information. It was not possible to identify inpatients with untreated latent TB or to control all pathways, such as household contacts and the potential risks associated with active TB infection. Furthermore, it was considered that inpatients who were admitted via EDs include inpatients who were exposed to EDs for treatment, examination, diagnosis or

Table III

Matched Cox-proportional hazard regression analysis of the risk of tuberculosis (TB) infection after visiting an emergency department (ED)

	% of cases infected with TB		Cox model	
	Hospitalization after ED visits	Hospitalization after outpatient visits	HR (95% CI)	P-value
All TB (A15–A19)	0.42	0.35	1.30 (1.12–1.52)	0.0008
Pulmonary TB (A15–A16)	0.35	0.30	1.30 (1.10–1.53)	0.0025
Extrapulmonary TB (A17–A18)	0.07	0.07	1.26 (0.88–1.81)	0.2059

HR, hazard ratio; CI, confidence interval.

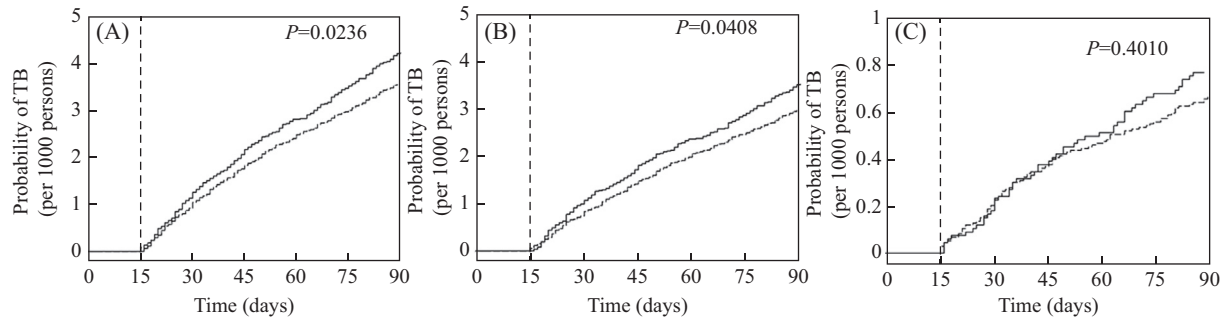


Figure 1. Survival curves for tuberculosis (TB) infection in patients hospitalized via emergency departments (EDs) or via outpatient clinics. Bold line, patients hospitalized via EDs; dotted line, patients hospitalized via outpatient clinics. (A) All TB (A15–A19), (B) pulmonary TB (A15–A16) and (C) extrapulmonary TB (A17–A18).

other medical procedures, as well as those exposed to EDs while waiting to be hospitalized or to start emergency treatment; however, the authors could not be certain of the transmission routes of TB infection. Thus, the results cannot be generalized to different population, years or types of medical care settings.

The current study applied the propensity score matching method to balance the potential risk of TB infection in the two inpatient groups (i.e. inpatients admitted via EDs and inpatients admitted via outpatient clinics). Nevertheless, as mentioned above, patients who visited EDs are more likely to exhibit an emergency/acute severe illness, and the HIRA-NIS data lack information on several factors that could influence the risk of TB. Hence, the results may be confounded by acute illnesses that increase the risk of TB. It should be noted that it is unlikely that the results are free of unmeasured confounders. Given that there is no immediate host response to infection after inhalation of droplet nuclei containing *M. tuberculosis*, and that the responses occurred over two to 12 weeks [13], inpatients with TB diagnosis within 14 days from the first ED visit were excluded, and the remaining inpatients were followed-up for 90 days from their first ED visit. This study also found that there was no significant difference in TB cases between excluded and included inpatients, regardless of whether they were hospitalized via EDs or outpatient clinics (Table A, see online supplementary material). This suggests that TB cases admitted via EDs and outpatient clinics in the excluded patients may not differ significantly from TB cases in the included patients in the current study. The results do not appear surprising, given previous evidence on the high risk of TB transmission among healthcare workers in EDs and within the ED environment (i.e. shared sources of air, prolonged hospital stay, and close proximity to undiagnosed or unsuspected TB patients). Thus, the risk of airborne transmission of droplet nuclei and the acquisition of active TB may affect healthcare workers in EDs, as well as the inpatients who visit EDs. In conclusion, this study found that the likelihood of TB infection was greater in inpatients admitted via EDs than in inpatients admitted via outpatient clinics. These results require confirmation using more detailed data regarding patient characteristics and ED conditions (i.e. the degree of overcrowding and waiting time). Also, a screening test for TB upon admission to EDs or outpatient clinics is needed. Given a recent series of outbreaks of infectious respiratory diseases associated with EDs, the effective and rapid isolation of

inpatients with suspected or confirmed respiratory diseases in EDs, and strategies to identify and block possible transmission sources (i.e. contaminated medical devices and specimen collection) in EDs may be necessary to reduce the risk of transmitting infectious diseases, which would also prevent the transmission of TB infection in EDs.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jhin.2018.03.031>.

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