─────── **Memorial Lecture by the Imamura Award Winner**───────

RISK OF *MYCOBACTERIUM TUBERCULOSIS* INFECTION AMONG EMPLOYEES AT A GENERAL HOSPITAL WITHOUT WARDS FOR TUBERCULOSIS PATIENTS

─ A Study of Interferon-Gamma Release Assay Positivity ─

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Abstract [Objective] Risk of exposure to *Mycobacterium tuberculosis* among hospital workers was retrospectively evaluated using interferon-gamma release assay (IGRA) positivity as an indicator of exposure. We hypothesized that exposure to a hospital environment posed a risk of exposure to *M.tuberculosis*. [Subjects] The subjects were 870 employees who underwent IGRA from December 2010 to April 2012. They were divided into the following groups based on exposure in the hospital environment: 161 new employees who were evaluated at hiring (non-exposure group) and 709 existing employees including those who had undergone contact examinations (exposure group). [Methods] QuantiFERON-TB Gold®3G was used for IGRA. Logistic regression analysis was used to calculate the odds ratios for positivity in the exposure group compared to that in the non-exposure group. [Results] The overall positivity rate was 6.7%, with a significant difference between the groups (1.9% and 7.8% in the non-exposure and exposure groups, respectively) (P＝0.005). After adjusting for gender, years of employment, smoking history, and alcohol intake, the exposure group's odds ratio (95% confidence interval) for positivity compared to that in the non-exposure group was 4.1 (1.4−17.6) (P＝0.007). [Conclusion] These results suggest that exposure to a hospital working environment could present a risk of tuberculosis infection, regardless of years of employment.

Key words: Tuberculosis, Hospital-acquired infection, Contact examination, Interferon-gamma release assay, QuantiFERON

INTRODUCTION

Among medical professionals, nurses have higher relative risks of tuberculosis infection[1], and a tendency for a higher risk of tuberculosis has been observed in clinical laboratory technicians.[2]−[6] The main reason for this increased risk may be their close contact with patients or patient specimens that can produce aerosols in their work,[7] which suggests a risk of exposure to *Mycobacterium tuberculosis* in hospital environments (hereinafter abbreviated as "exposure to a hospital environment" or "exposure").

Interferon-gamma release assay (IGRA) is a method of diagnosing tuberculosis infection, including latent tuberculosis infection (LTBI), with high levels of sensitivity and specificity,[8] and is a leading method for hospital-acquired tuberculosis infection control.[9] Knowing the baseline level can raise the sensitivity and specificity of LTBI diagnosis

in health checks for people who have been in contact with tuberculosis (contact examinations), thus greatly contributing to the early diagnosis and treatment of infections.

In 2010, a medical worker at our hospital experienced a hospital-acquired infection from a patient with miliary tuberculosis. Because of this, baseline IGRA using QuantiFERON-TB Gold®3G (QFT, Japan BCG Laboratory) was performed in all hospital employees as part of hospital-acquired infection control. Thereafter, IGRA was performed in all new employees upon hire. This study retrospectively analyzed these results to compare the IGRA positivity of a post-employment group (baseline group ＋ contact-examination group: hospital-environment exposure group) to that of a new-employee group (non-hospital environment exposure group) to determine whether exposure to the environment of our hospital was a risk factor for tuberculosis infection among employees. We also examined how job type and years

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of employment affected this risk.

METHODS

The subjects included 870 employees of Tohoku Pharmaceutical University Hospital (formerly Tohoku Welfare Pension Hospital) who underwent IGRA for health checks at hire (new-employee group), for baseline measurements (baseline group), or for contact examinations (contact-examination group) from December 2010 to April 2012 (Table 1). During this period, seven patients were diagnosed with tuberculosis at our hospital and contact examinations including IGRA were performed for all cases. IGRA for the 582 people in the baseline group were performed all at once in February 2011. All employees, except for those who had undergone IGRA for contact examination, were subject to testing. All new employees, regardless of job or department, were placed in the new-employee group. The hospital's infection control team determined which employees should undergo contact examinations by following a proposed method.[10] For contact examinations, blood was collected for IGRA 2−3 months after contact.

The QFT test was used for IGRA and assessments were made according to its specifications.

The primary outcome was the adjusted odds ratio (OR) for IGRA positivity among the baseline and contact-examination groups (exposure group) compared to the new-employee group (non-exposure group). The regression models were adjusted for smoking history, alcohol intake, sex, and years of employment (one-year increases). The secondary outcomes were (1) the OR for IGRA positivity by profession and (2) the OR for IGRA positivity when the exposure group was divided into three equal groups based on years of employment (10 professions with IGRA-positive members; see below).

JMP 10.0.0 (SAS Institute Inc., USA) was used for the statistical analysis and $P < 0.05$ was considered statistically significant. Chi-square tests were used to compare IGRA positivity between the non-exposure and exposure groups. The adjusted ORs for IGRA positivity were calculated using logistic regression analysis (model 1: adjusted for smoking history, alcohol intake, sex; model 2: model 1 variables ＋ years of employment). Unless otherwise noted, the ORs are shown with confidence intervals (CI) and P values (OR [CI], P value).

The hospital paid for the QFT testing and contact examinations.

This retrospective clinical analysis of employee IGRA results was approved by the Tohoku Pharmaceutical University Hospital ethics screening committee (February 12, 2013).

RESULTS

Table 1 shows the subjects' basic characteristics. Significant differences were not observed between the new employee, baseline, and contact-examination groups in sex, proportion with a smoking habit, and proportion who consumed alcohol; however, due to the large number of new graduates in the new-employee group, significant differences were observed in age and years of employment (both $P < 0.0001$) (Table 1). The IGRA positivity rates in the new-employee, baseline, and contact-examination groups were 1.9%, 8.2%, and 5.5%, respectively, which represents a significant difference ($P = 0.01$) (Table 1).

Next, the ORs for IGRA positivity were calculated for the baseline and contact-examination groups using the two adjusted logistic regression models (Table 2). The OR for IGRA positivity in the baseline group was significantly higher than that of the new-employee group (5.0 [1.8−20.8], $P = 0.0009$) (model 1). This significance was maintained when years of employment was added in model 2 (4.4 [1.5−18.6], $P = 0.005$) (Table 2). In the contact-examination group, however, while the OR for IGRA positivity tended to be higher in both models, the differences were not signifi-

Table 1　Baseline characteristics according to IGRA for hospital workers
(new employees, baseline, and contact examination)

Characteristics	Groups				P value
	Total (N＝870)	New employees (N＝161)	Baseline assay (N＝582)	Contact examination (N＝127)	
Age (years) [18−74 years]	35±11	26.8±6.7	37.0±11.2	36.1±9.2	＜0.0001
Gender (male) (%)	25.3	28.0	26.3	17.3	0.08
Smoking history (%) (N＝802)	11.6	8.7	12.6	10.9	0.4
Alcohol intake (%) (N＝802)	67.5	71.3	67.4	63.0	0.4
Years of employment (years) [1−44 years]	8.8±9.3	1.0±0.5	10.5±9.6	10.7±8.8	＜0.0001
IGRA					
Positive [N (%)]	58 (6.7)	3 (1.9)	48 (8.2)	7 (5.5)	0.01
Negative [N (%)]	664 (76.3)	148 (91.9)	420 (72.2)	96 (75.6)	
Suspended [N (%)]	145 (16.7)	10 (6.2)	113 (19.4)	22 (17.3)	
Failure [N (%)]	3 (0.3)	0 (0)	1 (0.2)	2 (1.6)	

Values are expressed as mean ± standard deviation or percentage. P values were calculated using analysis of variance (ANOVA) for continuous variables or chi-square test for categorical variables.
IGRA: interferon-gamma release assay,　N: subject numbers

cant (model 1: 3.5 [0.9−16.3], P＝0.06) (model 2: 3.0 [0.8−14.6], P＝0.1) (Table 2). Moreover, when the baseline and contact-examination groups were combined to form the hospital-environment exposure group, its ORs for IGRA positivity were significantly higher, independent of the adjustment factors (model 1: 4.7 [1.7−19.7], P＝0.001) (model 2: 4.1 [1.4−17.6], P＝0.007) (Table 2). Significant differences between the adjustment factors and the ORs for IGRA positivity were not observed for smoking history, alcohol intake, or years of employment (one-year increases), although men exhibited a significantly higher OR for IGRA positivity than that in women (Table 2).

Table 3 shows the IGRA positivity rates among hospital employees by profession. IGRA positivity was observed among new employees and in the following nine professions:

clinical laboratory technicians, doctors, nurses, radiology technicians, pharmacists, assistant nurses, cooks, assistant cooks, and medical clerks. The ORs for IGRA positivity were calculated for these professions (Table 4). The results showed that three professions (clinical laboratory technicians, doctors, and nurses) had significantly higher ORs for IGRA positivity compared to those of new employees in both models. The results for model 2 are as follows: clinical laboratory technicians 13.2 [3.0−69.7], P＝0.0006; doctors 4.7 [1.4−22.1], P＝0.01; and nurses 3.9 [1.2−17.6], P＝0.02 (Table 4).

Table 2 suggests that adding years of employment (one-year increases) as a variable in model 2 did not increase the ORs for IGRA positivity. However, as a secondary outcome, we also examined the OR for IGRA positivity after dividing

Table 2 Adjusted odds ratios for IGRA positivity between the new employees (reference) and each group of hospital workers

Variables	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
New employees	1 [Ref]		1 [Ref]	
Baseline assay	5.0 (1.8−20.8)	0.0009	4.4 (1.5−18.6)	0.005
Contact examination	3.5 (0.9−16.3)	0.06	3.0 (0.8−14.6)	0.1
Baseline assay ＋ Contact examination ("Post-employment" group)	4.7 (1.7−19.7)	0.001	4.1 (1.4−17.6)	0.007
Smoking history	0.5 (0.1−7.5)	0.1	0.5 (0.1−1.2)	0.1
Alcohol intake	0.9 (0.5−1.7)	0.8	0.9 (0.5−1.6)	0.8
Gender (male)	2.3 (1.3−4.0)	0.006	2.3 (1.3−3.9)	0.006
Years of employment (1-year increase)	N/A	N/A	1.0 (0.99−1.04)	0.3

Model 1 includes variables of smoking history, alcohol intake and gender (male).
Model 2 includes variables in Model 1 plus years of employment (1 year increase).
OR: odds ratio, CI: confidence interval, Ref: reference, N/A: not applicable

Table 3 Stratified analyses of IGRA among the professions of the hospital workers

Profession	N	Result of IGRA			
		Positive (%)	Suspended (%)	Negative (%)	Failure (%)
New employees	161	1.9	6.2	91.9	0
Laboratory technicians	30	23.3	3.3	73.3	0
Doctors	96	12.5	20.8	66.7	0
Nurses	391	6.4	18.2	74.7	0.8
Radiology technicians	18	11.1	11.1	77.8	0
Pharmacists	18	11.1	11.1	77.8	0
Assistant nurses	22	9.1	45.5	45.5	0
Cooks	11	9.1	0	90.9	0
Assistant cooks	15	6.7	20	73.3	0
Medical clerks	55	5.5	21.8	72.7	0
Physical therapists	15	0	26.7	73.3	0
Occupational therapists	10	0	40	60	0
Dietitians	7	0	0	100	0
Clinical engineers	6	0	16.7	83.3	0
Speech therapists	4	0	50	50	0
Boiler engineers	2	0	0	100	0
Orthoptists	2	0	50	50	0
Dental hygienists	2	0	50	50	0
Associate nurses	2	0	0	100	0
Dental technician	1	0	0	100	0
Driver	1	0	100	0	0
Clinical psychologist	1	0	0	100	0

the hospital-environment exposure group (baseline ＋ contact-examination groups) into three equal groups based on years of employment (distribution: 1−44 years, ＜3.7 years, 3.7−13.9 years, and ≧13.9 years) (Table 5). The results showed that all groups exhibited significantly higher ORs for IGRA positivity than those of the new-employee group and that the differences between the groups were not significant (4.3 [1.4−18.8], P＝0.008; 4.8 [1.6−20.8], P＝0.004; and 5.1 [1.7−22.0], P＝0.002, respectively) (Table 5).

DISCUSSION

With declining incidence rates of tuberculosis, so are the numbers of hospital beds for tuberculosis patients and medical professionals who either specialize in or have experience treating this disease.[11] As a result, some tuberculosis patients are likely transitioning from receiving care from specialists at medical institutions dedicated to tuberculosis to care under non-specialists at general community hospitals. If this inference is correct, the risk of tuberculosis infection for medical professionals at community hospitals may be increasing. In the present study, we retrospectively examined IGRA positivity at baseline and in contact examinations performed as part of hospital-acquired tuberculosis infection control and compared this to the IGRA positivity at hiring to evaluate the risk of tuberculosis infection among medical professionals continuously employed at a community hospital. The results showed that, compared to the new-employee group (non-hospital environment exposure group) who underwent IGRA at hiring, the OR for IGRA positivity was significantly higher in the post-employment group (hospital environment exposure group). Moreover, when IGRA positivity was examined by profession and years of employment, clinical laboratory technicians, doctors, and nurses had significantly higher ORs for IGRA positivity. The ORs of the post-employment group were significantly higher regardless of the years of employment.

A higher risk of tuberculosis among medical professionals has been reported in several studies.[1]−[6] The tuberculin test or IGRA have been used to evaluate the risk of infection. A higher risk has been associated with professions frequently in contact with tuberculosis patients and with medical procedures that discharge *M.tuberculosis* (tracheal intubation, bronchial suctioning); infection control measures to address these areas have been shown to be effective at reducing the risk of infection.[12]−[14] However, previous studies compared current hospital employees who had already been exposed to a hospital environment, which was treated as the hypothetical risk in our study. Because these studies did not perform comparisons with a control group that had not been exposed to a hospital environment, their results may have been underestimated. The present study used a population believed to have not been exposed to a hospital environment as a control group. To our knowledge, our comparison of IGRA positivity among new employees to baseline IGRA positivity among existing employees was the first statistical examination of the potential risk of tuberculosis infection following exposure to a hospital environment. Previous research on this topic includes studies that used estimated and

Table 4 Multivariate analyses for IGRA positivity between the new employees (reference) and each profession

Professions with positive IGRA	Model 1 OR (95% CI)	Model 1 P	Model 2 OR (95% CI)	Model 2 P
New employees	1　[Ref]		1　[Ref]	
Laboratory technicians	17.5 (4.4−87.3)	＜0.0001	13.2 (3.0−69.7)	0.0006
Doctors	5.2 (1.5−24.0)	0.007	4.7 (1.4−22.1)	0.01
Nurses	4.7 (1.5−20.4)	0.005	3.9 (1.2−17.6)	0.02
Radiology technicians	5.0 (0.6−33.2)	0.1	3.5 (0.4−25.4)	0.2
Pharmacists	5.4 (0.7−35.8)	0.1	4.1 (0.5−29.1)	0.2
Assistant nurses	6.3 (0.8−41.4)	0.08	4.8 (0.6−33.1)	0.1
Cooks	5.7 (0.3−53.5)	0.2	4.2 (0.2−41.7)	0.3
Assistant cooks	4.7 (0.2−41.1)	0.3	4.3 (0.2−38.1)	0.3
Medical clerks	2.8 (0.5−15.5)	0.2	2.2 (0.4−12.7)	0.4

Model 1 includes variables of smoking history, alcohol intake and gender (male).
Model 2 includes variables in Model 1 plus years of employment (1 year increase).

Table 5 The association of the length of employment and IGRA positivity

	Years after employment (years)	Ratio of positive IGRA (%)	OR (95% CI)	P
New employees	＜1.0	1.9	1 [Ref]	
Baseline assay ＋ Contact examination ("Post-employment" group)	＜3.7	7.5	4.3 (1.4−18.8)	0.008
	3.7−13.9	7.5	4.8 (1.6−20.8)	0.004
	13.9≦	8.3	5.1 (1.7−22.0)	0.002

The adjusted model includes variables of smoking history, alcohol intake and male gender.

observed tuberculosis infection rates[15] and IGRA positivity[16] among the general populace as controls compared to the infection rates and IGRA positivity[17] among hospital workers at hospitals with tuberculosis wards. In contrast, the control group in the present study actually underwent IGRA and the hospital environment where the latent risk of infection was evaluated was a general hospital without a tuberculosis ward. The population that was analyzed exhibited a lower overall positivity rate (6.7%) than that reported among the general populace (7.1%) (Table 1).[16] Still, the OR of the baseline group was significantly higher independent of the adjustment factors, including years of employment, which suggests that exposure to a hospital environment increases the risk of tuberculosis infection even among a population with low IGRA positivity. That said, the IGRA positivity of the contact-examination group (5.5%) was lower than that of the baseline group (8.2%) (Table 1). The groups' mean ages did not differ significantly and the OR for IGRA positivity in the contact-examination group alone was not significantly different (3.0 [0.8−14.6]) (Table 2). Therefore, the IGRA positivity was lower in the contact-examination group because (1) contact examinations were performed in only seven tuberculosis patients during the study period; thus, there was a small number of hospital-acquired infections among employees, and (2) the proportion of people already infected with tuberculosis in the baseline group was higher than that in the contact-examination group. The overall low rate of IGRA positivity was likely influenced by the low incidence of tuberculosis in Sendai City and Miyagi Prefecture, where our hospital is located (2013 fiscal year $<$ 10 patients/100,000 people per year).[18] Moreover, while age-related differences in IGRA positivity have been reported,[16] considering the mean age of the subjects in this study (35 years) and the possibility of multicollinearity with years of employment, age was not included in the variables when evaluating OR.

Clinical laboratory technicians, doctors, and nurses exhibited significantly higher ORs for IGRA positivity (Table 3), a finding consistent with previous studies on tuberculosis infection risk among different professions. Years of employment, or the length of exposure to a hospital workplace environment (per year), did not affect the OR for IGRA positivity (Table 2). This indicates that hospital employees might incur a risk of tuberculosis infection within the first year of employment. This has already been noted in research on workers at hospitals that accept tuberculosis patients[19] and suggests that employees of general hospitals without tuberculosis wards may also be at risk of tuberculosis infection soon after starting work.

The present study was a retrospective study of baseline IGRA results performed as part of hospital-acquired infection control, which limited our ability to set adjustment factors (for example, medical history, smoking index, and amount of alcohol intake). Moreover, background characteristics such as

age and level of obesity (BMI) were not included in the variables. Furthermore, the suspended results of IGRA testing were not followed-up for positivity after several months to confirm the result. A prospective study is warranted to identify additional candidate and assumed adjustment factors; in workplaces (other than hospitals) without the risks of a hospital environment as a control so that IGRA could be performed at hiring and after one year or longer of employment; and to analyze only subjects from both workplaces who were IGRA-negative at hiring.

CONCLUSION

Baseline IGRA was performed among all employees of a general community hospital without a tuberculosis ward. A retrospective analysis of these results suggested that exposure to a hospital environment represents a risk of tuberculosis infection independent of years of employment and other variables. This finding demonstrates the importance of preventing exposure to tuberculosis from the beginning of employment and in ways that are suited to the profession.

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