Original Article

Risk factors of latent tuberculosis infection and immune function in health care workers in Suzhou, China

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Background: The Chinese government has pay attention about tuberculosis infection among medical staff in infectious disease hospitals, but the effects have not yet been reported. This study will explore latent infection and immune function in the medical staff and systematically analyze the associated influencing factors.

Methods: Ninety-four medical staffs were enrolled and 20 medical staffs were defined as low risk group and others were high risk group. We used IFN-γ release assay and flow cytometry to analyze the latent TB infection status and immune function. Logistic regression analyses were performed to identify the independent risk factors of latent TB infection.

Results: This study explored and compared the infection status of medical workers and found that the rate of positive TB-IGRA results was higher among high risk group than in low risk group. Working environment, occupational history and work type were risk factors for TB infection in hospital. This study also found that high risk group had higher IFN-γ expression and a lower ratio of CD4+ to CD8+ T cells and further analysis found that this immune disorder is associated with wards and occupations.

Conclusions: This study through rigorous sample collection and analysis found the risk factors of latent tuberculosis infection in health care workers. This finding may provide a theoretical basis to be used by the countries with a high TB burden to further improve their strategies for the prevention of TB infections in hospitals and may give an indication for improving the personal health of medical staff in infectious disease hospitals.

Keywords: Medical staff; tuberculosis; immune function; hospital infection

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Introduction

Tuberculosis (TB) has existed for millennia and remains a major global health problem. In 2016, 6.3 million new cases of TB were reported (up from 6.1 million in 2015) (1). The medical staffs in medical institutions that treat TB who come in contact with many patients or are directly exposed to samples containing TB are at a high risk of biological contamination and occupational exposure (2). The risk of TB transmission is higher among patients and medical staff and in the laboratory than among the general population. Some studies suggest that general medical staff and staff

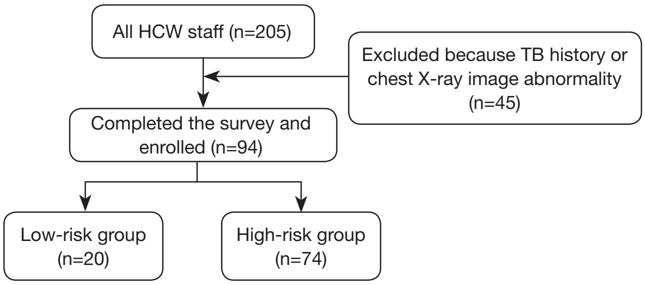

Figure 1 Study flow diagram. Of 114 HCWs answered the questionnaire and agreed to be tested for LTBI. HCWs, health care workers; LTBI, latent tuberculosis infection; CT, computed tomography; TB, tuberculosis.

involved in TB prevention and control are in a high-risk environment and clearly have higher rates of TB infection and TB incidence than does the general population (3-6). Medical staff who participate in TB-related work for more than 1 year have a relative risk of infection 1.5–2.4 times the risk of other groups (7). In high-income countries such as the United States, Canada, and France (2), which implement early TB infection control measures including special TB clinics and triage systems, negative pressure isolation wards and mechanical ventilation devices, and medical respirators or masks for medical staff, etc., the infection rate of TB is between 1.2% and 50%, and the incidence of TB is 130 per 10,000 in Portugal. However, in low- and middle-income countries such as Brazil (8), India, Vietnam (9) and Uganda (10), etc., the infection rate of TB is between 41% and 72%, and the incidence of TB is between 558 and 600 per 10,000 (7). The conditions of implementation of TB infection control measures vary. High-income countries implemented standard infection control measures earlier; however, although low- and middle-income countries have also implemented TB infection control measures to a certain extent, the measures lack normalization and comprehensiveness (5,11,12). The World Health Organization launched new "TB infection control guidelines" in 2009, and has called on countries to make plans, to regularly perform TB screening of medical staff, and to include in the record the date and results of screenings. China has a large number of TB cases; additionally, half of these new cases are infectious. Therefore, this important and urgent public health problem necessitates analysis of the current TB infection status of Chinese medical staff, improvement of the understanding of TB among these workers, and implementation of the required measures to strengthen TB understanding and prevention. In 2010 and 2011, China conducted related studies on the TB infection status of medical staff in specialized TB hospitals (13,14). However, China has allocated a large amount of manpower and financial resources to TB prevention and control in the past 5 years, and the protection and control measures in specialized TBs hospitals have been greatly improved. There have been no studies on tuberculosis hospital infections in the past five years, and the immune status of tuberculosis medical staff has not been studied also. Therefore, it is important to re-analyze the TB infection conditions of medical staff in specialized TB hospitals to provide effective methods for other high-burden countries to better prevent TB infection in hospitals.

Methods

The study was approved by the Research Ethics Committees of the Fifth People's Hospital of Suzhou (No. 2017003), informed consent was respectively obtained from all participants before their enrollment in this study and all methods were performed in accordance with relevant guidelines and regulations.

Subjects

The epidemiological method of cluster sampling was adopted in this study (*Figure 1*); all medical staff members (n=205) in our specialized TB hospital were chosen as the experimental group; 139 completed the questionnaire (*Figure 2*) but 45 were excluded because TB history or chest X-ray image abnormality; the 94 medical staff were enrolled finally.

Exclusion criteria applied to staff who could not participate in the physical examination because of vacation or allergies and staff who were pregnant or lactating.

All the research subjects met the following criteria: (I) no history of TB; (II) no recent symptoms or signs of active TB; and (III) no active or obsolete lesions identified by chest X-ray examination.

The research subjects were divided into the following two groups according to their degree of exposure to TB: (I) the high-risk population group (high-risk group), which included medical staff from the TB department and laboratory of the Suzhou Fifth People's Hospital; and (II) the low-risk population group (low-risk group), which

Personal protective questionnaire for hospital medical personnel

The purpose of this survey is to understand the occupational protection practices of TB medical staff at designated hospitals.to offer the policy basis for the tuberculosis infection control of Medical staff .Please fill in the information according to your actual situation. We will keep your personal information strictly confidential. Thanks for your cooperation!

Work unit : ________________________ number:______________________

1. General condition

1.1 gender : ① male ② female

1.2 date of birth: _____year _____month

1.3 degree of education :

① primary School or Below ②junior high school ③ senior high school/ vocational high school/technical secondary school ④ junior college ⑤ undergraduate college or above

1.4 marital status: ①married ② unmarried ③ divorced ④ widowed

1.5 Your residence is in : ① urban areas ② rural areas

1.6 The total number of people living in a family:_____

1.7 Estimated total household income in 2017 _____thousand yuan

1.8 height ____cm, weight _____kg

2. TB prevention work

2.1 work place

① tuberculosis clinic ② tuberculosis ward ③ tuberculosis laboratory ④ radiology department ⑤ pharmacy ⑥ cashier ⑦ others

2.2 post status

① administrator ② doctor ③ laboratory detection ④ nurse ⑤ nursing workers ⑥ radiology doctors ⑦ charge for personal ⑧ pharmacist ⑨ others

2.3 your professional title ① director ② vice director ③ intermediate ④ junior or below

2.4 work _____ days a week ; work _____hours a day

2.5 Estimate daily contact time with TB patients (or specimens) ____hours

2.6 Time for medical work: ____years ____ months; Time to work on TB control: ____years_____ months

2.7 The area of working area of contact TB person (or specimen) is approximately:_____m2

3.TB control knowledge

3.1 Do you think you are at a high risk of infection with TB bacillus ①no risk ② have some risk ③ great risk

3.2 If you are infected with TB, do you feel the consequences are serious? ① not serious ②a little serious ③ very serious

3.3 Do you think you can prevent the infection by wearing a medical mask (such as N95)? ① yes ② no

3.4 Do you think you can prevent TB infection by wearing gauze mask? ① yes ② no

3.5 Do you think you can prevent TB infection by wearing a surgical mask? ① yes ② no

3.6 Do you think regular ventilation (such as open window ventilation or mechanical ventilation) can prevent the infection of mycobacterium tuberculosis?

① yes ② no

3.7 Do you think that frequent disinfection (such as uv disinfection) can prevent the infection of mycobacterium tuberculosis? ① yes ② no

3.8 Do you think it is important to train regularly for infection control? ① unimportant ② important

4. Personal protective practice

4.1 You estimate the number of TB patients (or specimens) in contact in one day:______; How many TB patients (or specimens) are exposed at most times______

4.2 What mask do you wear when you are in contact with a patient?

① don't wear a mask ②surgical mask ③sand cloth mask ④ protective mask for medical use (such as N95)

4.3 The most common ventilation modes in the working area:

①natural ventilation ②mechanical ventilation such as exhaust fan ③central air-conditioning and ventilation system ④ air cleaner

4.4 The most common use of air disinfection in the working area:

①disinfection by ultraviolet light ② circulating air UV air sterilizer③ electrostatic absorption air sterilizer ④ chemical disinfection

4.5 The frequency of your work area is ventilated every day :

① not open ②one to two times ③ three to five times ④ it's open all the way

4.6 Whether or not the patients you contacted always wear with a mask (at least surgical mask)

① don't wear ② occasionally wear ③ most of the time ④ all the time

4.7 How often do you train for TB control?

① no training ② once a year ③ once during two years ④once during three years or above

investigation date : ______year ______ month ______day **the investigator checked and signed:_________________**

Figure 2 Personal protective questionnaire for hospital medical personnel.

was consisted of the medical staff from administrative department who did not have a chance to contact TB patients, we set this group as the general population. The high-risk group was further divided into the ward A subgroup, the ward B subgroup, the ward C subgroup and the laboratory department subgroup according to specific high-risk working environment. In addition, the high-risk group was divided into the doctor subgroup, the nurse subgroup and the laboratory staff subgroup according to profession and into the >5 years subgroup and the ≤5 years subgroup according to occupational history. The basic conditions and infection control parameters of each group are shown in *Table 1*.

QuantiFERON-Gold In-Tube assay

Blood samples were obtained after fasting and before 9 AM. Three heparin tubes were collected: (I) a negative-control tube (NIL tube), (II) an antigen tube (AG tube; contained a coating of specific M. tuberculosis antigens (ESAT-6, CFP-10, TB 7.7) that came into contact with the patient's T cells in the blood sample), and (III) a positive-control tube containing phytohaemagglutinin-P (PHA) (MIT tube). The concentration of IFN-γ secreted by the cells was measured by ELISA. The results were measured in IU/ml and interpreted in accordance with the manufacturer's recommendations as negative, positive, or indeterminate.

Flow cytometric analysis

The fluorochrome-labeled monoclonal antibodies CD3-APC, CD4-PerCP, and CD25-FITC were purchased from BD Pharmingen (San Diego, CA, USA), and IFN-γ-FITC was purchased from Cell Signaling Technology (Danvers, MA, USA). For each test, 50 mL of fresh heparinized whole blood of patients or healthy donors was incubated with the indicated antibodies (10 mL) for 15 minutes and then lysed with FACSTM lysing solution (BD Biosciences, San Jose, CA, USA). Samples were subsequently washed with phosphate buffered saline, fixed and eventually detected by a BD FACSAria supporting BD FACSDiva software.

Enzyme-linked immunosorbent assay (ELISA)

The serum samples were collected in serum separator tubes and allowed to clot for 2 hours at room temperature. Then, they were centrifuged at 3,000 rpm for 15 minutes and stored at −80 ℃ for the ELISA assay. The levels of IFN-γ in the serum were analyzed using ELISA kits (BlueGene Co., Ltd., Shanghai, China) according to the manufacturer's instructions.

Statistical analysis

The data were analyzed by GraphPad Prism 5.0 software and SPSS and were presented as the mean ± standard error of the mean (SEM). For comparisons of the collected data, a nonparametric test (Mann-Whitney U test), Student's *t* test or Chi-square test was performed, the bar in each group in the figures represents the mean ± SEM. The association between risk factors and the TB-IGRA results was assessed by multinomial logistic regression, and two-tailed values of P<0.05 were considered statistically significant.

Results

Study population

A total of 94 participants who completed the questionnaires and participated in the TB-IGRA test were enrolled in this study. These participants included 31 men and 63 women and had an average age of 33.10 years and average occupational history of 14.53 years. Among these participants, 20 subjects (15 women and 5 men) were in the low-risk group, with an average age of 33.05 years, whereas 74 subjects (53 women and 21 men) were in the high-risk group, with an average age of 37 years; there were no statistically significant differences between the two groups regarding gender or age. The high-risk group was further divided into four wards: 23 cases in the ward A subgroup, 17 cases in the ward B subgroup, 18 cases in the ward C subgroup and 16 cases in the laboratory subgroup. When divided according to profession, the high-risk group was divided into the doctor subgroup (n=23 cases), the nurse subgroup (n=32 cases), and the laboratory subgroup (n=19 cases). The high-risk group was also divided into the >5 years subgroup (n=43) and <5 years subgroup (n=31) according to occupational history. Finally, the high-risk group was divided into the lower-value subgroup (n=37) and the high-value subgroup (n=37) according to peripheral IFN-γ levels (*Table 1*).

TB-IGRA test results

Two cases in the low-risk group had positive TB-IGRA results, resulting in a positive rate of 10%, whereas 32

Table 1 Description of study population

Groups	n	Age (years)	Gender (male, female)	Positive of TB-IGRA (n, %)	Risk factors	Infection control measures		
						Management measures	Environmental engineering control	Personal protection
Low-risk group	20	33.05±0.969	5, 15	2, 10	No contact with TB patients	Has a tuberculosis infection control system, time to check the sputum system, all employees have received tuberculosis infection control training	Independent administrative building with well ventilation	None
High-risk group	74	37.00±1.713	21, 53	32, 43.2	Tuberculosis patients and Mycobacterium tuberculosis		The hospital is obsolete and lack of floor space; the layout is unreasonable and with general ventilation; has conventional UV lamp maintenance and regular maintenance the exhaust fan	Use surgical or N95 masks for protection
Ward								
A ward	23	33.04±0.722	5, 18	16, 69.6	Tuberculosis patients		Well ventilation	Use surgical masks for protection
B ward	17	33.35±2.239	1, 16	7, 41.2	Tuberculosis patients		Poor ventilation	Use surgical masks for protection
C ward	18	34.28±1.833	3, 15	7, 38.9	Tuberculosis patients		General ventilation	Use surgical masks for protection
Laboratory	16	30.13±1.772	12, 4	2, 12.5	Tuberculosis patients and Mycobacterium tuberculosis		P2 Laboratory	Use N95 masks for protection
Profession								
Physician	23	37.25±1.766	8, 15	16, 69.6	Tuberculosis patients		Normal	Poor awareness of protection and use surgical masks for protection
Nurse	32	30.66±1.310	1, 31	14, 43.6	Tuberculosis patients		Normal	Good awareness of protection and use surgical masks for protection
Laboratory staff	19	31.79±1.833	12, 7	2, 10.5	Tuberculosis patients and Mycobacterium tuberculosis		P2 Laboratory	Use N95 masks for protection
Working seniority								
>5 years	43	26.64±0.442	13, 30	26, 60.5	Tuberculosis patients and Mycobacterium tuberculosis		P2 Laboratory or normal	Use surgical or N95 masks for protection
≤5years	31	38.97±1.195	8, 23	6, 19.4				
IFN-γ								
Low	37	28.66±2.330	8, 29	9, 24.3	Tuberculosis patients and Mycobacterium tuberculosis		P2 Laboratory or normal	Use surgical or N95 masks for protection

Table 2 Univariate analysis (Chi-square test, Mann-Whitney test) of the differences between the TB-IGRA positive and negative in sex, working seniority, profession, ward and IFN-γ

Risk factors	TB-IGRA		χ^2/z	P
	Positive, n=32	Negative, n=42		
Sex (male, female)	10, 22	11, 31	χ^2=0.228	0.632
Working seniority (>5/≤5 years)	26, 6	17, 25	χ^2=12.404	<0.001
Profession (physician, nurse, laboratory staff)	16, 14, 2	7, 18, 17	χ^2=16.316	<0.001
Ward (A ward, B ward, C ward, laboratory medicine)	16, 7, 7, 2	7, 11, 10, 14	χ^2=13.815	0.003
IFN-γ (low, high)	9, 23	28, 14	χ^2=10.785	<0.001

TB, tuberculosis.

Table 3 Multivariable analysis (logistic) of the differences between the TB-IGRA positive and negative in sex, working seniority, profession, ward and IFN-γ

Risk factors	TB-IGRA		P
	Positive, n=32	Negative, n=42	
Sex (male/female)	10, 22	11, 31	0.082
Working seniority (>5/≤5 years)	26, 6	17, 25	0.002
Profession (physician, nurse, laboratory staff)	16, 14, 2	7, 18, 17	0.152
Ward (A ward, B ward, C ward, laboratory medicine)	16, 7, 7, 2	7, 11, 10, 14	0.024
IFN-γ (low, high)	9, 23	28, 14	0.037

TB, tuberculosis.

cases had positive TB-IGRA results in the high-risk group, resulting in a positive rate of 43.2% (χ^2=7.52, P<0.01). The incidence was obviously higher among medical staff who were in close contact with TB patients than in the general population (*Table 1*). Subgroup analyses of the high-risk group according to profession, occupational history and work environment found that the positive rate among medical staff with an occupational history of more than 5 years was 60.5%, which was significantly higher than the rate among those with an occupational history of less than 5 years (19.4%) (χ^2=12.404, P<0.001), even after the logistic analysis adjustment was adjusted (P=0.002). The positive rate was 69.6% in the doctor subgroup, 43.6% in the nurse subgroup and 10.5% in the laboratory subgroup, and there were significant differences among these three subgroups in the single-factor analysis of variance (χ^2=16.316, P<0.001). However, these differences disappeared after the logistic analysis was adjusted (P=0.152), and the positive rate was essentially the same in the laboratory subgroup and the healthy control group (10%). The positive rate of the ward A subgroup (69.6%) was significantly higher than those of the other wards, while the positive rate of the laboratory subgroup (12.5%) was significantly lower than those of other wards; the single-factor analysis of variance showed a statistically significant difference (χ^2=13.815, P=0.003). After the logistic analysis was adjusted, there was still a statistically significant difference (P=0.024). In addition, the positive rate was essentially the same in the laboratory subgroup and the healthy control group (10%). An analysis of positive values in high- and low-IFN-γ subgroups found that the positive rate of the low-IFN-γ subgroup (24.3%) was significantly lower than that of the high-IFN-γ group (62.1%), and both the single-factor analysis of variance (χ^2=10.785, P<0.001) and the logistic analysis showed statistically significant differences (P=0.037) (*Tables 1-3*).

Correlations between the levels of serum albumin, IFN-γ, CD4+ T cells, CD8+ T cells and TB infection

Analysis of the correlation between risk of exposure/

infection and immune function found that medical staff in the high-risk group had higher IFN-γ levels, a higher proportion of CD4+ T cells, and a lower proportion of CD8+ T cells than the low-risk group (all $P<0.05$), while the other comparisons did not identify any differences (*Figure 3*).

Further analysis of the differences between the positive TB-IGRA subgroup and negative TB-IGRA subgroup within the high-risk group found statistically higher IFN-γ values in the positive TB-IGRA subgroup compared with those in the negative TB-IGRA subgroup ($P<0.05$); however, no difference was found in the other comparisons (*Figure 3*).

Correlations of levels of serum albumin, IFN-γ, CD4+ T cells, and CD8+ T cells with occupation, working environment and occupational history

The correlation analysis of occupation and immune function found statistically higher IFN-γ values in the nurse subgroup ($P<0.05$) (*Figure 4*). The correlation analysis of working environment and immune function found that IFN-γ levels were the highest in the ward C subgroup compared with those of the ward A subgroup ($P<0.01$), ward B subgroup ($P<0.001$) and laboratory subgroup ($P<0.001$), with all differences being statistically significant (*Figure 4*). Additionally, the proportion of CD4+ T cells was higher in the ward C subgroup than in the laboratory subgroup, and the CD4+ T cell proportion of the ward A subgroup was lower than those of the ward B ($P<0.01$) and ward C ($P<0.01$) subgroups (*Figure 4*). No other differences were found.

Discussion

Since 2010, the Chinese government has invested a significant amount of money into the prevention and control of TB infections in hospitals and has formulated standardized TB infection control measures by referring to the experiences of developed countries. These measures included establishing special TB clinics, establishing negative pressure isolation wards with ≥12 air changes per hour (AHC), and providing N95 respirators to medical staff. In 2010 and 2011, China conducted related studies on the TB infection status of medical staff in specialized TB hospitals (13,14), but these studies could not have reflected the achievements of the hospital infection control scheme that has been systematically implemented in China in recent years. Therefore, it is important to reanalyze the TB infection status of the medical staff in specialized TB hospitals. This study is also the first to systematically discuss the immune status of medical staff in a specialized TB hospital, and the results may help to provide more effective methods to reduce TB infections in hospitals for other countries with a high TB burden.

This study compared the TB-IGRA results of medical staff members and found the results were significant improved in the past five years in China. However, this study also found that medial staff still had obviously higher positive rates than low-risk groups; these results were similar to those of the investigation by the Beijing Tuberculosis Hospital in 2011 (13) but better than the survey results in Henan (14) and Inner Mongolia (15) in 2010. Due to the particular status of Beijing in China and the different methods adopted by the Henan research, we are more inclined to select the research from Inner Mongolia as a reference, and the above results suggest that the measures adopted for the prevention of TB infection in hospitals are very efficient but require further improvement. We conducted a further analysis of whether factors related to the working environment, occupational history and type of work, were risk factors for TB infection in hospitals. Notably, infection rates of staff working in P2 laboratories and wearing N95 respirators, particularly in the study of the working environment, were significantly decreased to levels as low as those of the non-close-contact population, whereas staff wearing surgical masks had no corresponding change. This study also found huge differences in infection rates among different wards, and different ventilation conditions may be responsible for these findings based on our questionnaire analysis. This study also found that infection rates were significantly higher among doctors than individuals of other professions. The survey results demonstrated that protective consciousness was significantly lower in doctors than in the nurses and laboratory staff, which we think is the reason for the differing infection rates.

This study also systematically analyzed hospital infections and the immune function of medical staff in TB hospitals and analyzed the associated factors. Moreover, this study found that the problem of immune system disorders and health problems among the medical staff of TB hospitals should be noted by hospital administrators and medical staff.

Due to the small number of cases and single-center study, this study also has its limitation and the results

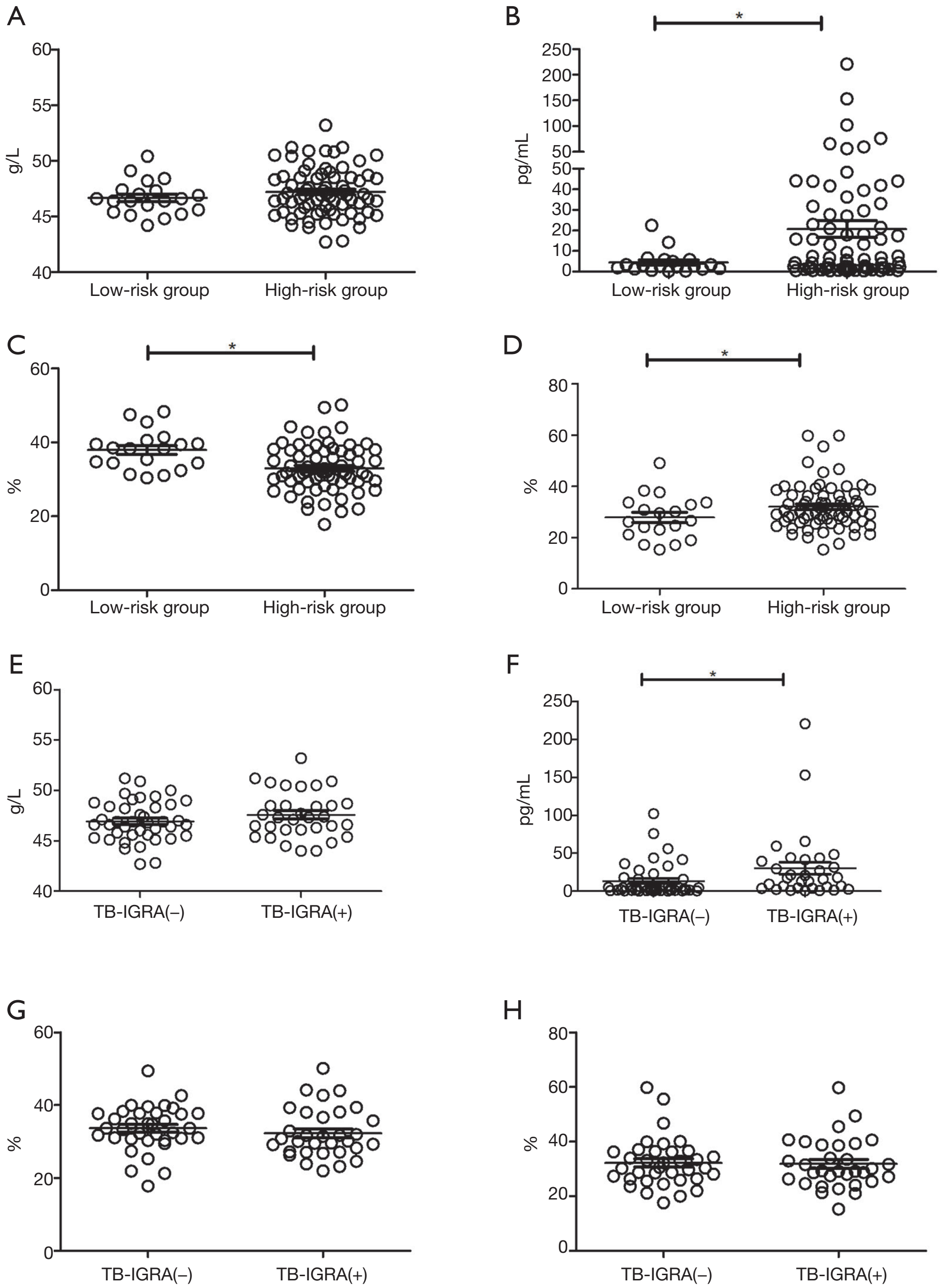

Figure 3 Analysis of the correlation between tuberculosis infection and immune function. (A) The expression levels of albumin in the low-risk and high-risk groups; (B) the expression levels of IFN-γ in the low-risk and high-risk groups; (C) the percentages of $CD4^+$ T cells in the low-risk and high-risk groups; (D) the percentages of $CD8^+$ T cells in the low-risk and high-risk groups; (E) the expression levels of albumin in the TB-IGRA(–) and TB-IGRA(+) groups; (F) the expression levels of IFN-γ in the TB-IGRA(–) and TB-IGRA(+) groups; (G) the percentages of $CD4^+$ T cells in the TB-IGRA(–) and TB-IGRA(+) groups; (H) the percentages of $CD8^+$ T cells in the TB-IGRA(–) and TB-IGRA(+) groups. *, $P<0.05$.

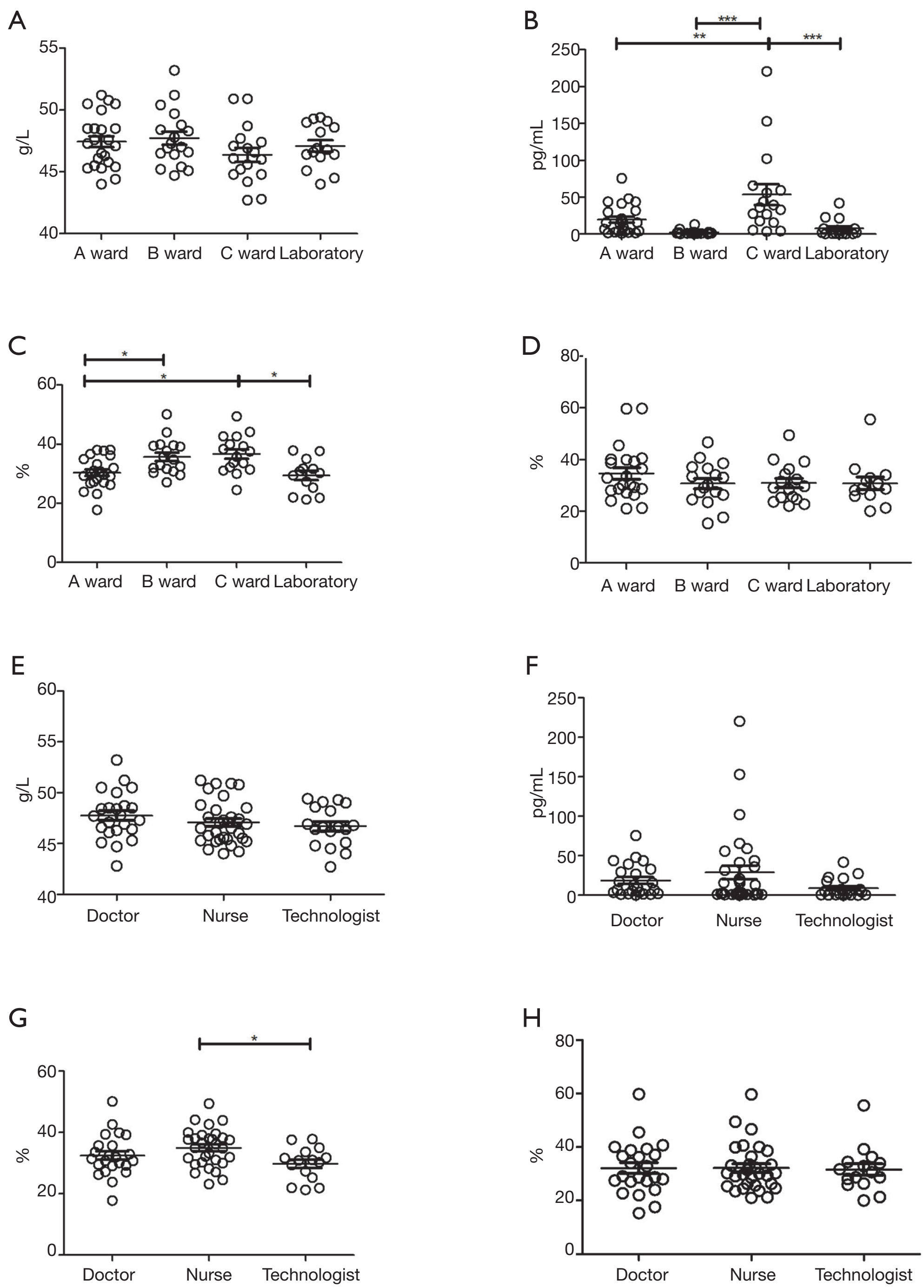

Figure 4 Abnormal immune factors among health care workers. (A) The expression levels of albumin in different wards; (B) the expression levels of IFN-γ in different wards; (C) the percentages of $CD4^+$ T cells in different wards; (D) the percentages of $CD8^+$ T cells in different occupations; (E) the expression levels of albumin in different occupations; (F) the expression levels of IFN-γ in different occupations; (G) the percentages of $CD4^+$ T cells in different occupations; (H) the percentages of $CD8^+$ T cells in different wards. *, P<0.05; **, P<0.01; ***, P<0.001.

may not generalizable. So we compare the low risk group between our study and others (2,7,13,15) and found there is no statistical difference. Even though, the results of this study still only consider as an indication for the prevention and possible strategies and more cases and multi-centers study still need.

This study systematically analyzed the status and factors of tuberculosis hospital infection of the medical staff and the immune charge in long-term exposure to tuberculosis. Although this study has limitations, its results still have special value. It may provide a theoretical basis for China and other countries with a high TB burden to further improve their strategies regarding the prevention of TB infection in hospitals and may give an indication for the improvement of the personal health of medical staff in infectious disease hospitals.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Research Ethics Committees of the Fifth People's Hospital of Suzhou (No. 2017003), informed consent was respectively obtained from all participants before their enrollment in this study.

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