Original Article

Prevalence of latent tuberculosis infection and its risk factors in Japanese hemodialysis patients

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Running title: Prevalence of latent tuberculosis in HD patients

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Abstract

Background

The majority of active tuberculosis (TB) cases develop from latent tuberculosis infection (LTBI). Since the risk of TB in hemodialysis (HD) patients is particularly high, interferon-gamma release assay (IGRA) for LTBI screening in HD patients is considered important. However, the prevalence and characteristics of LTBI in Japanese HD patients remain obscure.

Methods

We performed an observational cross-sectional study of LTBI using IGRA QFT-3G tests in 118 HD outpatients enrolled at 3 hospitals of varying location and function.

Results

Of the 118 patients, 96 were QFT negative, 7 were QFT indeterminate, 14 were QFT positive, and 1 was QFT judgment impossible. No patient had active TB. Confirmed (QFT positive) and possible (QFT positive+indeterminate) LTBI patients totaled 14 (11.9%) and 21 (17.8%), respectively. The LTBI possible group was significantly older and had a significantly higher rate of nephrosclerosis versus the QFT negative group. The indeterminate group had a significantly longer HD period. The QFT results were not remarkably affected by other clinical data, including hospital characteristics. The possible LTBI rate increased age-dependently, with higher values from 60 years of age.

Conclusions

The prevalence of LTBI is high in Japanese HD patients, especially from the age of 60 years. Older age was a significant risk factor for LTBI, with prediction difficult using other clinical data. Extended HD may mask IGRA results. Therefore, aggressive screening for LTBI is advised in all HD patients regardless of hospital region or type, especially in patients over 60 years of age or newly commencing HD.

Keywords Latent tuberculosis infection・Dialysis・Interferon-gamma release assay (IGRA)・QuantiFERON

Introduction

Tuberculosis (TB) is one of the most prominent infectious diseases in the world. The definition of a country with low TB incidence is one with a morbidity rate of less than 10 per 100 thousand population, which has been attained by many developed countries. In contrast, Japan's TB incidence was 11.5 per 100 thousand population in 2019 [1]. Since Japan remains a country with moderate TB incidence, the establishment of preventive strategies is of ongoing importance.

Most active TB cases reportedly develop from latent tuberculosis infection (LTBI). Therefore, effective LTBI treatment is an important step in halting the progression to active TB. The treatment guidelines for LTBI in Japan advise the appropriate selection of patients who are at high risk of developing active TB and whose treatment benefit will outweigh the side effects [2]. These guidelines also state that the relative onset risk of TB in hemodialysis (HD) patients is 10 to 25 times higher than in individuals without risk factors, that HD patient treatment recommendation is a level A priority, and that screening for and treating LTBI in HD patients should be actively considered [3-6].

Since the reaction to tuberculin skin test (TST) is known to be weakened in HD patients, the usefulness of interferon-gamma release assay (IGRA) for LTBI detection has been emphasized [7-9]. However, LTBI screening in HD patients remains uncommon in Japan, and LTBI prevalence and characteristics are obscure. To address these issues, the current study examined Japanese HD patients for LTBI using IGRA-based testing.

Materials and methods

Patients and study design

A total of 157 HD outpatients were enrolled from among 3 hospitals (Fig. 1). Each hospital was respectively located in a regional hub city, a regional small city, and a town and performed varying levels of treatment, from acute to chronic care. All patients were of Japanese ancestry. The exclusion criteria in this study were active TB, inpatient status, and poor general condition including active infection and terminal malignant disease. Since the outpatients in the night HD session at Hospital A were generally younger, healthier, and more active, and thus significantly different from the typical characteristics of HD patients in Japan, they were excluded from this study (n=20). Although no HD outpatients met the exclusion criteria, 19 declined to participate in the analysis, leaving 118 HD outpatients consenting to this observational cross-sectional study. We examined for the presence of LTBI in the subjects and investigated their clinical characteristics. Patient data were collected from medical records and included age, sex, body mass index (BMI), HD period, primary disease of end-stage kidney disease (ESKD), complications, smoking history, respiratory disease, use of immunosuppressants or steroids, and blood findings. Blood tests were taken at the first HD session of a week.

Diagnosis of LTBI

The gold standard diagnostic method for LTBI has not been established. Since the accuracy of TST is known to decrease in HD patients [9], we employed the QFT-3G Quantiferon® TB Gold IGRA (QIAGEN, Germantown, MD, USA). Specifically, TST is less sensitive and often provides false negative results from diminished immunocompetence or false positive results from the BCG vaccine. In contrast, many studies support the usefulness of QFT-3G for LTBI diagnosis in HD patients [7-11]. We defined QFT positive patients as having LTBI after excluding active TB. In the culturing process, blood samples were aliquoted into 3 dedicated QFT-Gold test tubes (negative control, positive control, and TB-antigen-coated tube). No antigens were coated on the negative control tube, while the mitogen phytohemagglutinin was coated on the

positive control tube. ESAT-6/CFP-10/TB 7.7 peptides (Mycobacterium tuberculosis-specific antigens) were coated on the TB-antigen-coated tube. Aliquoted samples were placed in an incubator for 16 to 24 hours at 37℃. After incubation, the blood samples were centrifuged (2000 g for 15 minutes), and collected supernatants were subjected to enzyme-linked immunosorbent assay testing to measure the concentration of lymphocyte-producing interferon gamma (IFN-γ). The IFN-γ level of each test tube was designated as follows:

Measured value A＝(concentration of IFN-γ in TB antigen tube) – (concentration of IFN-γ in negative control tube)

Measured value M＝(concentration of IFN-γ in positive control tube) – (concentration of IFN-γ in negative control tube)

A QFT positive result was defined as measured value A ≥ 0.35 IU/mL regardless of measured value M. A QFT indeterminate result was defined as measured value M ≥ 0.5 IU/mL along with 0.1 IU/mL ≤ measured value A ≤ 0.35 IU/mL). A QFT negative result was defined as measured value M ≥ 0.5 IU/mL along with measured value A < 0.1 IU/mL). A QFT judgment impossible result was defined as measured value M < 0.5 IU/mL along with measured value A < 0.35 IU/mL. QFT positive patients were checked for respiratory infectious symptoms and underwent chest X-ray examinations, chest computed tomography and mycobacterial cultures to exclude active TB.

Statistical analysis

Data are presented as the median (interquartile range) for continuous variables and the percentage for category variables. Continuous variables were compared for the QFT negative group vs. positive group, and the QFT negative group vs. positive+indeterminate group, and the QFT indeterminate group vs. negative+positive group by means of the Mann Whitney U test. Category variables were analyzed with Fisher's exact probability test. For multi-group comparison among three hospitals, continuous variables and category variables were adjusted by Steel-Dwass method and Bonferoni-type p-values, respectively. The risk

factors of possible LTBI were examined using logistic regression analyses. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R commander (The R Foundation for Statistical Computing, Vienna, Austria) with added statistical functions frequently used in biostatistics [12]. A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

Overall median subject age was 70 years (interquartile range [IQR]: 62-79 years) and 65% were men (Table 1). Median BMI was 21.8 (IQR: 19.5-24.2). Median dialysis period was 56 months (IQR: 26-142 months). The most common primary disease of ESKD was diabetic kidney disease (38%), followed next by chronic glomerulonephritis (19%). Approximately half of patients (47%) had diabetes mellitus, and 80% had hypertension.

Comparisons of QFT negative group vs. positive group

Of the 118 patients, 96 were QFT negative, 7 were QFT indeterminate, 14 were QFT positive, and 1 was QFT judgment impossible (Fig. 1). As none of the QFT positive patients had active TB, 14 patients were judged as LTBI confirmed patients.

We compared the patient characteristics of the QFT negative group vs. positive group (Table 2). Compared with QFT negative group patients, QFT positive subjects were significantly older, with the rate of nephrosclerosis as the primary disease of ESKD significantly higher ($p=0.005$ and 0.01, respectively).

Comparisons of QFT negative group vs. positive+indeterminate group

Although a QFT indeterminate result is generally treated as QFT negativity [13], it should be considered QFT positive in populations at high risk of TB (i.e., QFT positive rate $\geq 15\%$). Previous studies have reported high QFT positive rates in HD patients [6,7,14] and described HD patients as a population with a QFT positive rate $\geq 15\%$ [15,16]. Therefore, we compared the QFT positive+indeterminate group (LTBI possible group) with the QFT negative group. Significant differences were detected for age ($p=0.002$) and

primary disease of ESKD (Table 3).

Comparisons of QFT indeterminate group vs. negative+positive group

To examine the characteristics of the group with unclear QFT results (indeterminate group), we compared the indeterminate group with the group with clear QFT results (negative+positive group). Significant difference was detected for HD period (p=0.04) (Table 4).

Univariate and multivariate logistic regression analyses for risk factors of possible LTBI

Logistic regression analyses were conducted to evaluate the risk factors of possible LTBI (Table 5). Univariate analysis indicated age as a significant risk factor for possible LTBI. When the cohort was divided according to median age (70 years), the age ≥ 70 years group exhibited an extremely high LTBI risk (odds ratio 6.8, 95% confidence interval 1.88-24.6, p=0.004). In multivariate analysis, the number of explanatory variables should be set as less than one-tenth the number of events. Since 21 patients had possible LTBI, only 2 variables could be entered in this study. Multivariate analysis adjusted by the known risk factor of smoking history [17], sex, dialysis period, and nephrosclerosis demonstrated age to be the strongest independent risk factor for possible LTBI.

Characteristics of patients at each hospital and comparisons of hospital location and type

Hospital A was situated in regional hub city, hospital B was in regional small city, and hospital C was in town. In comparison analyses of patient characteristics between 2 hospitals (hospital A vs. B, A vs. C, and B vs. C), significant differences were not found except for BMI between hospital A and B (Table 6). QFT judgement results were comparable among the hospitals, regardless of location or type.

Relationship between QFT results and patient age

The number of patients stratified by age was 1 in the 30s, 6 in the 40s, 13 in the 50s, 35 in the 60s, 35 in the 70s, 26 in the 80s, and 2 in the 90s. The confirmed LTBI rate (i.e., QFT positive rate) was 0% for the 30s to 50s, 3% (1 patient) for the 60s, 23% (8 patients) for the 70s, 15% (4 patients) for the 80s and 50% (1 patient) for the 90s (Fig. 2 and 3). The LTBI possible rate (i.e., QFT positive+indeterminate rate) was 0% for the 30s to 50s, 9% (3 patients) for the 60s, 29% (10 patients) for the 70s, 27% (7 patients) for the 80s and 50% (1 patient) for the 90s. Both rates increased age-dependently, with the prevalence becoming markedly higher from the age of 60 years.

Discussion

An earlier study employing IGRA reported that the prevalence of LTBI was 17.9% in newly commencing HD patients in Japan [15]. Another Japanese study described that 22% of HD patients were positive for T-SPOT, another type of IGRA [16]. In the current investigation, the QFT positive rate among HD patients was 11.9% and the QFT indeterminate rate was 5.9%. The guidelines recommended that QFT indeterminate be treated as QFT positive in populations with high infectious prevalence, such as a QFT positive rate ≥ 15% [13]. Since previous studies found that HD patients exhibited a higher prevalence of LTBI and were at a higher relative risk of developing active TB [3-6], we treated the QFT indeterminate group of HD patients as an LTBI possible population. When the QFT indeterminate group was included with the QFT positive group, the LTBI possible rate in HD patients reached 17.8%, which was consistent with the results of previous reports [15,16]. These findings indicate that the prevalence of LTBI in Japanese HD patients is high and that active screening for LTBI is important.

To investigate the risk factors of LTBI, we conducted comparative examinations between the QFT negative group and the QFT positive group or the QFT positive+indeterminate group. Both analyses revealed significant differences for age and primary disease of ESKD. The QFT positive rate as well as the QFT positive+indeterminate rate increased age dependently from the age of 60 years, indicating increased LTBI risk in older adults. The respective incidence of TB in 1951 and 2019 in Japan was 698 and 11.5 per 100 thousand population [1,18]. Thus, older people have lived through a period of higher TB incidence, which might have influenced the results. Regarding the primary disease of ESKD, the percentages of nephrosclerosis and unknown kidney disease were significantly higher, whereas that of chronic glomerulonephritis was significantly lower, in the LTBI possible group. In older patients, nephrosclerosis is the most common kidney disease and the primary kidney disease is often unspecified, indicating that the impact of primary disease of ESKD is strongly confounded by age. The logistic regression analysis suggests that older age is the most prominent risk factor for LTBI, and so HD patients in their 60s and over should be more actively screened for LTBI. The known risk factors for LTBI in HD patients include age, smoking history, and TB history [15, 17].

In the current study, neither smoking history (current or past habit) nor TB history were remarkable risk factors for LTBI in HD patients. However, the very high rate of smoking history in the QFT negative and QFT positive+indeterminate groups (64% and 71%, respectively), as well as the very low rate of TB history in these groups (0% and 5%, respectively), might have masked significant results.

Since HD patients with a history of TB were also included in the cohort, the impact of TB history on IGRA results should be considered. In general patients with a TB history, the IGRA test often indicates positive results. When active TB infection is ruled out, LTBI retreatment is ineffective and considered unnecessary for those patients, which may reduce the usefulness of the IGRA test in such patients. However, Japanese guidelines state that retreatment may be considered for cases with an extremely high risk of TB development [2]. HD patients have weakened immunity, and their specific IFN-γ response to TB diminishes over time. Therefore, HD patients may be more likely to exhibit negative IGRA results despite a TB history. When IGRA positivity is detected in HD patients with TB history, the possibility of reactivation or reinfection of TB should be considered in addition to the possibility of an immune response to the prior TB, and retreatment may be considered out of a high risk for TB development. IGRA testing for HD patients with a TB history is thus considered useful. In the current study, one patient with a history of TB exhibited a QFT positive result and was placed into the LTBI group to consider retreatment after excluding active TB. Indeed, IGRA test interpretation should be done carefully in HD patients with a TB history.

As prior Japanese studies on LTBI in HD patients did not examine for the influence of hospital location or function, we included HD patients from 3 types of hospitals in differently sized municipalities: large hospital A in a core city, medium-sized general hospital B in a rural city, and small rural hospital C in a sparsely populated area. Hospitals A, B, and C were mainly responsible for acute phase care for critically ill patients, acute-to-chronic phase care for mildly to moderately ill patients, and chronic phase care, respectively. In hospital A, the turnover of HD patients was high due to the introduction of new patients, the referral of patients in acute and severe conditions from other hospitals, and the transfer of stable HD patients to other chronic care institutions. Since TB is an airborne infection and HD rooms are closed spaces, high

turnover situations may increase the probability encountering active TB patients. However, we observed no remarkable differences in IGRA results among the 3 hospitals, suggesting that hospital characteristics were not a significant factor impacting LTBI incidence. Accordingly, screening for LTBI in HD patients is advised for all types of hospitals.

The incidence of TB in the general population varies by region. LTBI prevalence in HD patients may be estimated by incidence of TB in the general population. To clarify this notion, we summarized reports concerning TB incidence in the general population and the IGRA positive rates among HD patients worldwide (Table7). TB incidence in Japan appeared to be lower than in Asian countries such as Taiwan and South Korea [1,6,15,19]. The incidence of TB in Nagano Prefecture was particularly lower [1]. However, the IGRA positive rate in Japanese HD patients is relatively high, as may be expected from the data in Asian regions. However, this result might have been influenced by the age of HD patients in Japan, which was older than in the cohort populations of the Asian regions. In spite of low TB incidences in such western countries as Canada, Germany, Belgium, and Switzerland, whose rates were equivalent to that in Nagano, the IGRA positive rates among HD patients were considerably higher than those in Japanese cities [20-23]. The reason for this is unclear, but may be related to greater population heterogenicity; several reports have indicated that the percentage of foreign-born cases among TB patients is extremely high in low TB incidence western countries (60%, 43% 51%, and 60% in Canada, Germany, Belgium, and Switzerland, respectively) [24,25]. According to a WHO report [26], TB incidence in those countries has stopped falling or has been increasing in recent years. Thus, the incidence of TB in western countries is currently maintained at low levels, although influxes in foreigners may increase LTBI prevalence. Related to those social conditions, the western reports also included data on the proportion of HD patients who were from or had lived in TB-endemic areas, showing that those cases had a potentially high TB risk rate (Table 7). In contrast, the proportion of immigrants and foreigners in Asian countries such as Japan and South Korea is relatively low (2.0 and 2.3%, respectively) [27]. It is noteworthy that the percentage of foreign-born TB patients increased in Japan in 2019, accounting for 10.9% of newly registered cases [28]. This novel social phenomenon will potentially increase the prevalence of LTBI in Japan as in western countries in the future. Taken together, the prevalence of LTBI

may not be predictable by local TB incidence in the general population due to a variety of factors. Even if the local TB incidence is low, IGRA testing remains a necessity, especially for HD patients.

Lastly, the QFT indeterminate group is considered QFT negative in the general population but QFT positive in populations with a high rate of QFT positivity, such as in HD patients. Since the QFT indeterminate group had a significant impact on the prevalence of LTBI, understanding the clinical characteristics of QFT indeterminate patients is important. A previous report found that a longer HD period was related to an indeterminate judgement [17]. The current study also demonstrated that the QFT indeterminate group had a significantly longer HD period than the QFT negative and positive groups, implicating HD period as a potential masking factor of the IGRA reaction. When Mycobacterium tuberculosis enters the body, it is first phagocytosed by macrophages. Its antigen information is then presented to T lymphocytes for sensitization followed by IFN-γ secretion. IGRA employs this immune response for the diagnosis of TB by measuring secreted IFN-γ. The QFT indeterminate group is a population maintaining some cellular immunity, which is presumably weak against Mycobacterium tuberculosis-specific antigens. Previous studies have indicated that the decrease in QFT response is dependent on the time after sensitization to Mycobacterium tuberculosis [29] and that cellular immunity deteriorates with prolonged dialysis [30]. Since the longer period of HD possibly weakened the QFT response, screening for LTBI should be conducted at the time of HD introduction.

Limitations

This study had several limitations. First, the mean age of the patients was higher than that of HD patients in Japan, and Nagano prefecture has one of the lowest incidences of TB incidence nationwide. It might therefore be difficult to generalize our results for all Japanese HD patients; however, our findings may predict the clinical features of Japanese HD patients in the future given current social trends. Second, this was a small-scale observational study. However, it included HD patients from different types of hospitals and

analyzed relatively many patients as compared with previous reports from Japan. Third, the newest generation of QFT-3G, QuantiFERON-TB Gold Plus (QFT-Plus), has recently become available. The results of this study may become more evident when QFT-Plus is used. Lastly, although the current study could not detect all known possible risk factors of LTBI, including smoking history and previous TB infection, their clinical importance cannot be denied.

Conclusion

The current study demonstrated that the prevalence of LTBI was high in HD patients and increased in older patients from their 60s. The most significant related factor to LTBI was older age, while LTBI prediction appeared difficult from blood data, comorbidities, hospital characteristics, and TB incidence in the general population of the patient's living region. HD period was a potential masking factor of the IGRA reaction. Since LTBI is a prominent risk factor for active TB development, aggressive screening for LTBI in HD patients is advisable regardless of hospital location or type. IGRA may be particularly beneficial for reliable LTBI judgement in HD patients over the age of 60 years as well as in those newly commencing HD.

Compliance with ethical standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at which the studies were conducted (Shinshu University Ethics Committee; IRB approval number 3320) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Written informed consent was obtained from all individual participants included in the study.

Conflict of interest: The authors have declared that no conflict of interest exists.

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Figure legends

Fig. 1 Flowchart of QFT results

The blood samples of 118 HD outpatients were analyzed using QFT-3G assays. Among them, 14 LTBI patients were detected. There were no active TB patients.

Fig. 2 Number of patients stratified by age

Black bars, dark gray bars, and light gray bars indicate the numbers of total patients, QFT indeterminate patients, and QFT positive patients, respectively.

Fig. 3 QFT positive rate and QFT positive+indeterminate rate stratified by age

The upper panel indicates the QFT positive rate and lower panel indicates the QFT positive+indeterminate rate. These rates increased age-dependently.

Table 1 Clinical characteristics of the study population

	N = 118
Age (years)	70 (62-79)
Male (%)	77 (65%)
BMI (kg/m^2)	21.8 (19.5-24.2)
Dialysis period (months)	56 (26-142)
Primary disease of end-stage kidney disease (%)	
Diabetic kidney disease	45 (38%)
Chronic glomerulonephritis	22 (19%)
Nephrosclerosis	12 (10%)
Polycystic kidney disease	7 (6%)
Rapidly progressive glomerulonephritis	3 (3%)
Lupus nephritis	1 (0.8%)
Unknown	28 (24%)
Complication (%)	
Diabetes mellitus	56 (47%)
Hypertension	94 (80%)
History of TB	1 (0.8%)
Smoking history (%)	77 (65%)
Respiratory disease (%)	5 (4%)
Use of steroids	4 (3%)
Use of immunosuppressants	0 (0%)

BMI: body mass index, TB: tuberculosis

Table 2 Comparisons between QFT negative group and positive group

	QFT negative N = 96	QFT positive N = 14	p-value
Age (years)	68.5 (61.0-76.3)	74.5 (73-82.5)	0.005
Male (%)	59 (61%)	12 (86%)	0.13
BMI (kg/m^2)	21.8 (19.7-23.9)	23.3 (19.0-24.8)	0.34
Dialysis period (months)	52.5 (24.5-138)	46.5 (17.25-102.75)	0.51
Primary disease of end-stage kidney disease (%)			
Diabetic kidney disease	39 (41%)	3 (21%)	0.24
Chronic glomerulonephritis	22 (23%)	0	0.07
Nephrosclerosis	7 (7%)	5 (36%)	0.01
Polycystic kidney disease	6 (6%)	0	1
Rapidly progressive glomerulonephritis	3 (3%)	0	1
Lupus nephritis	1 (1%)	0	1
Unknown	18 (19%)	6 (43%)	0.08
Complication (%)			
Diabetes mellitus	47 (49%)	5 (36%)	0.4
Hypertension	74 (77%)	13 (93%)	0.29
History of TB	0	1 (0.8%)	0.13
Smoking history (%)	61 (64%)	11 (79%)	0.37
Respiratory disease (%)	4 (4%)	1 (7%)	0.5
Use of immunosuppressants or steroids (%)	4 (4%)	0	1
Blood data			
WBC ($\times 10^2/\mu L$)	53.3 (45.8-65.93)	53.1 (44.25-68.75)	0.92
HGB (g/dL)	11.5 (10.5-12.1)	11.25 (10.6-11.65)	0.49
Alb (g/dL)	3.5 (3.2-3.725)	3.55 (3.4-3.7)	0.85
Ferritin (ng/mL)	72.05 (27.65-155.98)	62.0 (47.25-112.8)	0.89

QFT: quantiFERON, BMI: body mass index, TB: tuberculosis, WBC: white blood cell, HGB: hemoglobin, Alb: albumin

Table 3 Comparisons between QFT negative group and positive+indeterminate group

	QFT negative N = 96	QFT positive+indeterminate N = 21	p-value
Age (years)	68.5 (61-76.25)	74.0 (70-83)	0.002
Male (%)	59 (61%)	17 (81%)	0.13
BMI (kg/m^2)	21.8 (19.7-23.9)	23.1 (18.9-24.4)	0.93
Dialysis period (months)	52.5 (24.5-138)	73.0 (29.0-192)	0.59
Primary disease of end-stage kidney disease (%)			
Diabetic kidney disease	39 (41%)	5 (24%)	0.21
Chronic glomerulonephritis	22 (23%)	0	0.01
Nephrosclerosis	7 (7%)	5 (24%)	0.04
Polycystic kidney disease	6 (6%)	1 (5%)	1
Rapidly progressive glomerulonephritis	3 (3%)	0	1
Lupus nephritis	1 (1%)	0	1
Unknown	18 (19%)	10 (45%)	0.009
Complication (%)			
Diabetes mellitus	47 (49%)	8 (38%)	0.47
Hypertension	74 (77%)	19 (90%)	0.24
History of TB	0	1 (5%)	0.18
Smoking history (%)	61 (64%)	15 (71%)	0.62
Respiratory disease (%)	4 (4%)	1 (5%)	1
Use of immunosuppressants or steroids (%)	4 (4%)	0	1
Blood data			
WBC ($\times 10^2/\mu L$)	53.3 (45.8-65.9)	49.0 (43.9-71.2)	0.54
HGB (g/dL)	11.5 (10.5-12.1)	11.2 (10.5-11.7)	0.44
Alb (g/dL)	3.5 (3.2-3.73)	3.4 (3.3-3.6)	0.45
Ferritin (ng/mL)	72.05 (27.7-156.0)	74.2 (45.2-96.0)	0.9

QFT: quantiFERON, BMI: body mass index, TB: tuberculosis, WBC: white blood cell, HGB: hemoglobin, Alb: albumin

Table 4 Comparisons between QFT indeterminate group and negative+positive group

	QFT indeterminate N = 7	QFT negative+positive N = 110	p-value
Age (years)	73 (68.5-84)	70 (62.0-77.75)	0.19
Male (%)	5 (71%)	71 (65%)	1
BMI (kg/m^2)	19.73 (19.11-21.76)	21.85 (19.63-24.32)	0.21
Dialysis period (months)	192 (80-224)	50 (23.5-129)	0.04
Primary disease of end-stage kidney disease (%)			
Diabetic kidney disease	2 (29%)	42 (38%)	0.71
Chronic glomerulonephritis	0	22 (20%)	0.35
Nephrosclerosis	0	12 (11%)	1
Polycystic kidney disease	1 (14%)	6 (5%)	0.36
Rapidly progressive glomerulonephritis	0	3 (3%)	1
Lupus nephritis	0	1 (0.9%)	1
Unknown	4 (57%)	24 (22%)	0.06
Complication (%)			
Diabetes mellitus	3 (43%)	52 (47%)	1
Hypertension	6 (85%)	87 (79%)	1
History of TB	0	1 (1%)	1
Smoking history (%)	4 (57%)	72 (65%)	0.7
Respiratory disease (%)	0	5 (5%)	1
Use of immunosuppressants or steroids (%)	0	4 (4%)	1
Blood data			
WBC ($\times 10^2/\mu L$)	44 (40.95-62.05)	53.25 (45-65.98)	0.35
HGB (g/dL)	10.9 (10.6-11.55)	11.4 (10.5-12.0)	0.68
Alb (g/dL)	3.3 (3.1-3.4)	3.5 (3.3-3.7)	0.07
Ferritin (ng/mL)	74.2 (59.7-81.7)	71 (33.63-148.6)	0.66

QFT: quantiFERON, BMI: body mass index, TB: tuberculosis, WBC: white blood cell, HGB: hemoglobin, Alb: albumin

Table 5 Univariate and multivariate logistic regression analyses of QFT positive+indeterminate group

Univariable logistic regression analysis	Factors	OR	95% CI	p-value
	Age	1.08	1.03-1.14	0.003
	Male	2.67	0.83-8.54	0.10
	Smoking history	1.43	0.51-4.03	0.49
	Dialysis period	1	1.00-1.01	0.61
	Nephrosclerosis	3.97	1.12-14.10	0.03
Logistic regression analysis divided by median age				
	Age (< 70 years)	Reference	-	-
	Age (≥ 70 years)	6.8	1.88-24.60	0.004
Multivariate logistic regression analysis				
Model 1	Age (≥ 70 years)	7.29	1.99-26.70	0.003
	Smoking history	1.79	0.61-5.30	0.29
Model 2	Age (≥ 70 years)	6.85	1.87-25.00	0.004
	Male	2.70	0.81-9.02	0.10
Model 3	Age (≥ 70 years)	7.54	2.02-28.20	0.003
	Dialysis period	1.00	1.00-1.01	0.30
Model 4	Age (≥ 70 years)	6.00	1.63-22.10	0.007
	Nephrosclerosis	2.70	0.72-10.10	0.14

QFT: quantiFERON, OR: odds ratio, CI: confidence interval

Table 6 Comparisons of patient characteristics at each hospital

	Hospital A	Hospital B	Hospital C
	N = 64	N = 27	N = 27
Age (years)	70 (61.75-75.25)	70 (64.5-84.0)	74 (64.5-81.0)
Male (%)	41 (64%)	18 (67%)	18(67%)
BMI (kg/m^2)	22.391 (20.32-24.58)	20.41 (18.60-22.52)*	21.275 (18.77-23.35)
Dialysis period (months)	56 (27.75-123)	34 (20-174)	90 (31.00-147)
Primary disease of end-stage kidney disease (%)			
Diabetic kidney disease	27 (42%)	9 (33%)	9 (33%)
Chronic glomerulonephritis	14 (22%)	1 (4%)	7 (26%)
Nephrosclerosis	9 (14%)	1 (4%)	2 (7%)
Polycystic kidney disease	3 (5%)	3 (11%)	1 (4%)
Rapidly progressive glomerulonephritis	1 (2%)	1 (4%)	1 (4%)
Lupus nephritis	1 (2%)	0	0
Unknown	9 (14%)	12 (44%)*	7 (26%)
Smoking history (%)	45 (70%)	17 (63%)	15 (56%)
QFT			
Negative (%)	53 (83%)	21 (78%)	22 (81%)
Indeterminate (%)	3 (5%)	2 (7%)	2 (7%)
Positive (%)	7 (11%)	4 (15%)	3 (11%)
Impossible (%)	1 (2%)	0	0

BMI: body mass index, QFT: quantiFERON
*$p < 0.05$

Table 7 Positive and indeterminate IGRA rates among hemodialysis patients in different countries

Country	Tuberculosis incidence (2018)	IGRA positive or indeterminate rate in hemodialysis patients (research year or year of publication)	Age in years (hemodialysis patients)	Proportion of patients who are from or have lived in TB-endemic areas for an extended time
Current study: Nagano Prefecture, Japan	9	QFT positive: 11.9%, indeterminate: 6.8% (2016-2017)	70 (62-79) (median age interquartile range) 69.65±11.96 (mean±SD)	N/A
Tokyo, Japan	14.3	IGRA positive and indeterminate: 17.9% (2014-16) (including before hemodialysis)	71 (30-92) (median age, range)	N/A
Taiwan	53 (2013)	QFT positive: 34.4%, indeterminate: 10.8% (2010)	58.3±14.9 (mean±SD)	N/A
South Korea	66	QFT positive: 22.2% (2017-2019)	61.6±12.6 (mean±SD hemodialysis: 93.3%, peritoneal dialysis: 6.7%)	N/A
Canada	5.6	TSPOT positive: 35.5% (2005)	N/A	52.2% (born in tuberculosis-endemic country)
Germany	7.3	Positive: 40-60%, indeterminate: 0-1% (3 types of IGRA) (2015)	64.1±13.8 (mean±SD)	10.9% (long-term resident in tuberculosis-endemic country)
Belgium	9	QFT positive: 33.3% (excluding previous tuberculosis history) (2013)	66 (54-71) (median age interquartile range low tuberculosis prevalence) 59 (45-71) (median age interquartile range high tuberculosis prevalence)	48.3% (originated from high tuberculosis prevalence country)
Switzerland	6.4	QFT positive: 25.5%, indeterminate: 2.5% (2010)	64 (30-87) (median age interquartile range)	18.0% (originated from medium tuberculosis prevalence country)

IGRA: interferon-gamma release assay, QFT, quantiFERON, SD: standard deviation, N/A: not available

Fig. 1 Flowchart of QFT results

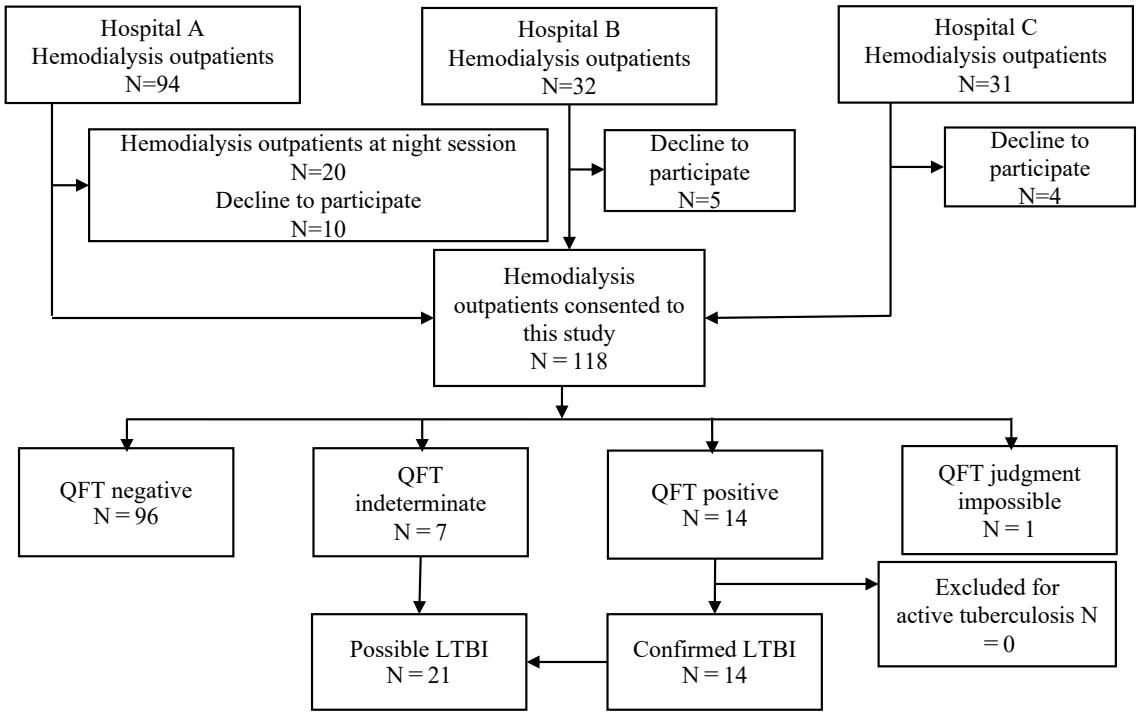

Fig. 2 Number of patients stratified by age

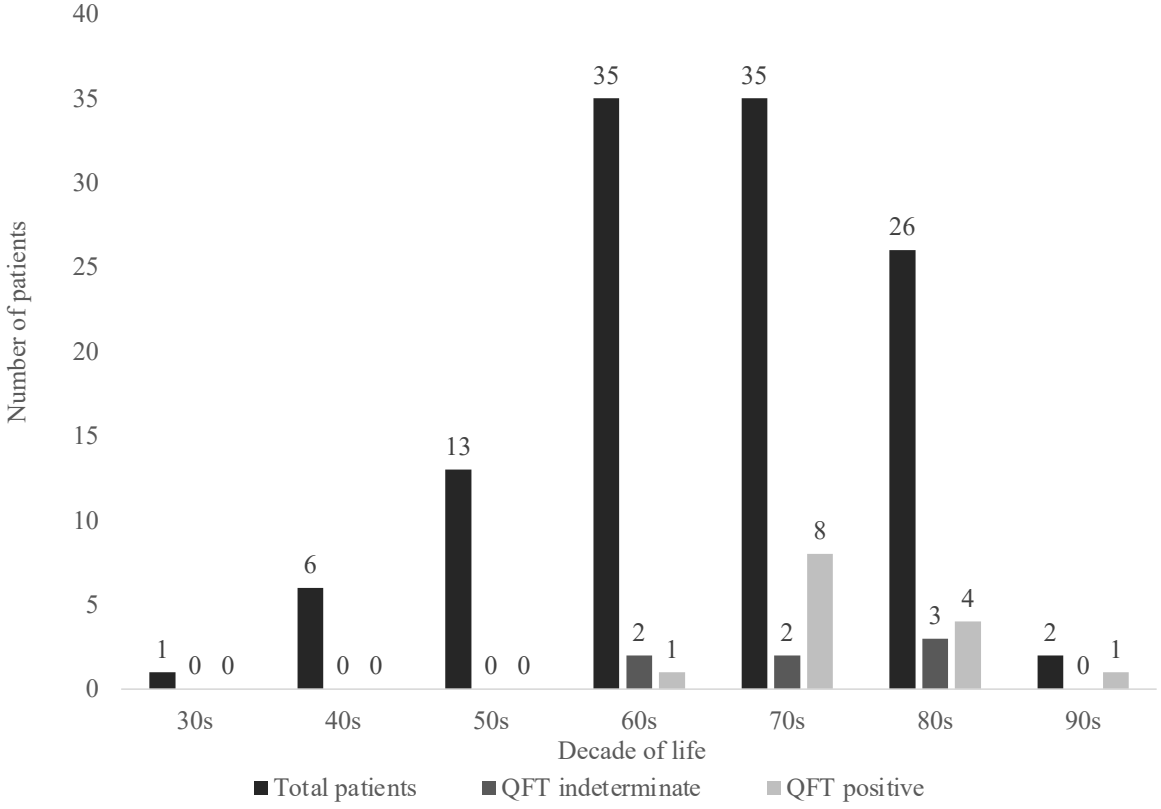

Fig. 3 QFT positive rate and QFT positive+indeterminate rate stratified by age