Comparison of the Prevalence of Latent Tuberculosis Infection among Non-Dialysis Patients with Severe Chronic Kidney Disease, Patients Receiving Dialysis, and the Dialysis-Unit Staff: A Cross-Sectional Study

Chin-Chung Shu¹,²,³*, Chia-Lin Hsu²,⁴, Chih-Yuan Lee⁵, Jann-Yuan Wang²,⁴, Vincent Wu²,⁴, Feng-Jung Yang⁷, Jann-Tay Wang²,⁴, Chong-Jen Yu²,⁴, Li-Na Lee²,⁴,⁶

¹ Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei City, Taiwan, ² School of Medicine, National Taiwan University, Taipei City, Taiwan, ³ Department of Traumatology, National Taiwan University Hospital, Taipei City, Taiwan, ⁴ Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan, ⁵ Department of Surgery, National Taiwan University Hospital, Taipei City, Taiwan, ⁶ Department of Laboratory Medicine, National Taiwan University Hospital, Taipei City, Taiwan, ⁷ Department of Internal Medicine, National Taiwan University Hospital, Yun-Lin Branch, Yun-Lin County, Taiwan

* ccshu139@ntu.edu.tw

Abstract

Background

Patients with renal failure are vulnerable to tuberculosis, a common worldwide infectious disease. In the growing dialysis population, the risk for tuberculosis among the associated sub-groups is important but unclear. This study investigated latent tuberculosis infection (LTBI) in patients with severe chronic kidney disease (CKD) and among dialysis-unit staff caring for patients on dialysis.

Methods

From January 2012 to June 2013, patients undergoing dialysis, those with severe CKD (estimated glomerular filtration rate <30ml/min/1.73 m²), and the dialysis-unit staff (nursing staff and doctors in hemodialysis units) in several Taiwan hospitals were prospectively enrolled. Interferon-gamma release assay (IGRA) through QuantiFERON-TB Gold In-tube was used to determine LTBI. Predictors for LTBI were analyzed.

Results

Of the 599 participants enrolled, 106 (25%) in the dialysis group were IGRA positive. This was higher than the seven (11%) among severe CKD patients and 12 (11%) in the dialysis-unit staff. Independent predictors of LTBI in patient with renal dysfunction were old age (odds ratio [OR]: 1.03 [1.01–1.04] per year increment), prior TB lesion on chest radiograph (OR: 2.90 [1.45–5.83]), serum albumin (OR: 2.59 [1.63–4.11] per 1 g/dl increment), and...
need for dialysis (OR: 2.47, [1.02–5.95]). The QFT-GIT response was similar among the three groups. Malignancy (OR: 4.91 [1.84–13.10]) and low serum albumin level (OR: 0.22 [0.10–0.51], per 1 g/dl decrease) were associated with indeterminate IGRA results.

Conclusions

More patients on dialysis have LTBI compared to those with severe CKD and the dialysis-unit staff. Old age, prior radiographic TB lesion, high serum albumin, and need for dialysis are predictors of LTBI in patients with renal failure. Patients with severe CKD are a lower priority for LTBI screening. The hemodialysis environment is not a risk for LTBI and dialysis-unit staff may be treated as general healthcare workers.

Introduction

Tuberculosis (TB) remains one of the most important infectious diseases in the world. According to estimates by the World Health Organization (WHO), there were 5.7 million new cases in 2012 [1]. Future control strategies include early treatment to prevent transmission and treatment of latent TB infection (LTBI) to reduce reactivation [2]. Patients with severe chronic kidney disease (CKD) or those undergoing dialysis have increased risk of TB due to their attenuated cellular immunity [3, 4]. For instance, the risk of developing active TB in the dialysis population is 7.8 times higher compared to that of the general population [5]. However, the diagnosis of TB is usually delayed because of frequent extra-pulmonary manifestations [6, 7]. Thus, early LTBI detection is important [2].

Currently, interferon-gamma release assay (IGRA) is used as a diagnostic tool for LTBI. Although positive IGRA results cannot be 100% specific for LTBI and there are problems of inter-experiment variation [8, 9], IGRA has several advantages, including convenience [10–12] and application in an immuno-compromised population [13], BCG-vaccinated population [14], and high non-tuberculous mycobacteria (NTM) prevalent area [15]. The IGRA-positive proportion is around 21–40% in patients undergoing hemodialysis [16–19]. Nonetheless, there is a paucity of data on other subgroups associated with dialysis group, e.g. severe CKD patients not receiving dialysis or the dialysis-unit staff.

In non-dialysis patients, those with severe CKD have higher prevalence of infections compared to those with mild or moderate CKD because the former have poorer host immunity [20]. However, there is insufficient data on the prevalence of LTBI in patients with severe CKD and whether or not LTBI screening should include them. On the other hand, dialysis-unit staff who care for hemodialysis patients may also have high LTBI/TB prevalence. Whether the exposure in a closed space of hemodialysis environment increases the risk of LTBI of health care workers is unclear. Understanding the risk of LTBI in severe CKD and the dialysis environment is important for determining the priority groups for LTBI screening because the population is enlarging [21, 22].

This cross-sectional study was conducted to analyze the prevalence of LTBI in severe CKD patients, in those receiving long-term dialysis, and in dialysis-unit staff. The study also examined predictors of LTBI.
Methods

This cross-sectional study was conducted at National Taiwan University Hospital, a tertiary referral center, and its branches, regional teaching hospitals, and a local hemodialysis clinic. Except for one in southern Taiwan, all of the study sites were located in northern Taiwan. The institutional review board of National Taiwan University Hospital approved the study (201110013RC and 201009061R). All of the study participants provided written informed consent.

Between January 2012 and June 2013, adult patients (age ≥ 20 years) with severe CKD (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73 m²) who received long-term (>3 months) hemodialysis and the staff members working in the hemodialysis units were prospectively identified. The eGFR was calculated for the severe CKD group using the equation developed by the Modification of Diet in Renal Disease Study Group [23]. The participant’s clinical history and chest x-rays were reviewed to exclude active TB. Mycobacterial study of three sputum samples were arranged if active TB could not be excluded. Those with human immuno-deficiency virus (HIV) infection, liver cirrhosis of Child-Pugh class C [24], cancer or autoimmune disease receiving chemotherapy within the last three months, or treatment history of active TB were excluded.

The participant’s peripheral blood were collected and the LTBI status was determined by IGRA using the QuantiFERON-TB Gold In-tube assay (QFT-GIT) (Celestis, Australia) according to the manufacturer’s instructions [25]. A three-tube kit of QFT-GIT was used for patients with severe CKD or dialysis, whereas the two-tube kit was used for dialysis-unit staff. Interferon-γ level was measured in the reaction supernatants and the results were interpreted as positive, negative, or indeterminate [26, 27]. In this study, LTBI was defined as a positive IGRA result.

Data collection

Demographic and clinical data, including age, sex, underlying co-morbidities, prior TB history, respiratory and constitutional symptoms, smoking status, and blood albumin levels were collected and recorded in standardized case report forms. Every HD session lasted for 4 hours according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) [28], with two-to-three regular sessions per week depending on the patient’s residual renal function and adequacy of dialysis. Cough ≥ 3 weeks was defined as chronic cough. Current smoker was defined as those who smoked > 100 cigarettes, with the latest time of smoking within one month prior to the study [29].

Chest radiography was interpreted independently by one radiologist and one pulmonologist. Both were blind to the participant groupings. If there was a discrepancy, a final decision was made by consensus. The radiographic findings were classified into “no lung parenchymal lesion”; “lung lesion not compatible with TB”; “lung lesion compatible with prior TB”, or “lung lesion, cannot be excluded for TB” [30]. Prior TB-like radiographic lung lesion was defined as fibrotic infiltrates with pleural thickening or calcified nodules over the upper lung fields, or other fibrotic lesions documented from previous TB.

Statistical analysis

Inter-group differences were analyzed using the student t test or Mann-Whitney U test for numerical variables, as appropriate, and chi-square test for categorical variables. Multivariate logistic regression analysis was used to identify factors associated with LTBI. All potential predictors were included in the stepwise variable selection procedure. Statistical significance
was set at a two-sided $p<0.05$. All analyses were performed using the SPSS (Version 19.0, Chicago, IL).

**Results**

A total of 425 subjects (mean age, 60.4 years; male, 51%) with long-term dialysis (mean length of dialysis use, 6.5 years) were enrolled, together with 63 patients with severe CKD (mean age, 61.8 years; male, 75%) and 111 dialysis-unit staff (mean age, 41.3 years; male, 6%) (Table 1). Among patients with long-term dialysis, 391 (92%) had three sessions per week while 34 (8%) had two sessions per week. In the severe CKD group, the average eGFR was $18.4\pm11.3$ ml/min/1.73 m$^2$. The dialysis-unit staff had worked in the dialysis unit for a mean of $8.5\pm5.8$ years. Among them, five (4%) were nephrologists and the rest were nursing staff.

Compared to dialysis patients (Table 1), patients with severe CKD had similar age and a higher proportion of males, whereas the dialysis-unit staff members were significantly younger and predominantly female. Underlying co-morbidity was higher in the severe CKD group than that in dialysis group although smoking was similar in both groups. By radiographic findings, “lesion compatible with prior TB” was higher in the dialysis group than in the severe CKD group. Respiratory and constitutional symptoms were more common in the dialysis group than in the dialysis-unit staff.

The IGRA result was “positive” in seven (11%) patients with severe CKD, 106 (25%) dialysis patients, and 12 (11%) dialysis-unit staff, but “indeterminate” in two (3%) severe CKD and 15 (4%) dialysis patients. Positive QFT-GIT results were higher in the dialysis group than in either the severe CKD group or dialysis-unit staff ($p = 0.015$ and $0.001$, respectively) (Fig 1). Among the participants with positive IGRA, the dialysis and severe CKD groups were older than dialysis-unit staff, which was predominantly female. Diabetes mellitus was higher in the severe CKD group than in the dialysis group. Otherwise, other clinical variables were insignificant between the dialysis group and either the severe CKD group or the dialysis-unit staff. The

### Table 1. Baseline clinical characteristics of the different study groups.

|                                | Dialysis patients (n = 425) | Severe CKD patients (n = 63) | Dialysis-unit staff (n = 111) |
|--------------------------------|-----------------------------|-----------------------------|-------------------------------|
| **Age, year**                  | 60.4 [13.0]                 | 61.8 [12.7]                 | 41.3 [13.7]*                  |
| **Male sex**                   | 218 (51)                    | 47 (75)*                    | 7 (6)*                        |
| **Current smoker**             | 41 (10)                     | 2 (3)                       | 0*                            |
| **Dialysis age, year**         | 6.5 [6.0]                   | -                           | -                             |
| **Malignancy**                 | 21 (5)                      | 8 (13)*                     | 0*                            |
| **Diabetes mellitus**          | 54 (13)                     | 31 (49)*                    | 0*                            |
| **Autoimmune disease**         | 10 (2)                      | 3 (5)                       | 0                             |
| **Any radiological lesion**    |                             |                             |                               |
| Not compatible with TB         | 50 (12)                     | 3 (5)                       | 15 (14)                       |
| Compatible with prior TB       | 34 (8)                      | 0*                          | 4 (4)                         |
| TB cannot be excluded          | 1 (1)                       | 0                           | 1 (2)                         |
| **Presence of symptoms**       | 92 (22)                     | 7 (11)                      | 3 (3)*                        |
| **Serum albumin, g/dL**        | 4.0 [0.33]                  | 3.9 [0.57]                  | -                             |

Data were number (%) or mean [standard deviation].
Abbreviations: CKD, chronic kidney disease; TB, tuberculosis.
*Statistical significance ($p<0.05$) between indicated group and dialysis group.
†Indicated chronic cough, dyspnea, fever, and other constitutional symptoms.
QFT-GIT response was similar among the three groups with positive IGRA ($p = 0.814$ by One Way ANOVA) (Fig 2).

By multivariate logistic regression, independent predictors of LTBI among patients with severe CKD or those undergoing dialysis included age (O.R. 1.03, 95% C.I. 1.01–1.04, per year increment), presence of dialysis (O.R. 2.47, 95% C.I. 1.02–5.95, vs. presence of severe CKD), serum albumin (OR: 2.59, 95% C.I. 1.63–4.11, per 1 g/dl increment), and presence of radiographic finding compatible with prior TB (O.R. 2.90, 95% C.I. 1.45–5.83) (Table 2). The independent predictor of “indeterminate” results of QFT-GIT was the presence of underlying
malignancy (O.R. 4.91, 95% C.I. 1.84–13.10) and serum albumin level (OR 0.22, 95% C.I. 0.10–0.51, per 1 g/dl increment).

Discussion

The present study investigated the prevalence of LTBI in patients with renal dysfunction and in dialysis-unit staff using IGRA. The LTBI status was higher in dialysis patients (25%) than in those with severe CKD (11%) and the dialysis unit staff (11%). Independent predictors of LTBI were old age, long-term dialysis (versus severe CKD), increased serum albumin, and presence of radiographic lesion of prior TB. In patients with renal dysfunction, indeterminate QFT-GIT results accounted for 3–4%, especially in patients with malignancy or low serum albumin level.

Previous studies using IGRA report an LTBI prevalence of 21–40% in dialysis patients [16–19]. The IGRA-positive rate in the present study is within this range. This study shows that patients with severe CKD who are not undergoing dialysis have relatively lower LTBI prevalence than those on dialysis, even if the former has higher underlying co-morbidities. In multivariate analysis, dialysis, rather than severe CKD, is an independent factor associated with LTBI. Non-dialysis severe CKD patients are not similarly weak as those on dialysis [31] and their LTBI is only 11%, even with an average age of 60 years [19, 32]. This suggests that patients on dialysis, not those with severe CKD, should be the priority group for LTBI screening, especially when resources are limited.

As regards dialysis-unit staff, their LTBI prevalence (11%) is similar to that of dialysis patients aged 40–50 years (14%) [19] and that of general healthcare workers (10%) [33]. Although there is no other literature on LTBI prevalence of local, healthy, middle-aged adults, the risk of LTBI among the dialysis-unit staff can be considered comparable to those of other healthcare workers and is not affected by the closed environment of the hemodialysis unit. Furthermore,

| Characteristics                          | Multivariate p value | OR (95% C.I.) |
|-----------------------------------------|----------------------|--------------|
| Age, year                               | <0.001               | 1.03 (1.01–1.04) |
| Sex, male vs. female                    | 0.710                |              |
| Current smoker vs. non-smoker            | 0.065                |              |
| Malignancy, presence vs. none            | 0.793                |              |
| Diabetes mellitus, presence vs. none     | 0.405                |              |
| Serum albumin level, per 1 g/dl increment| <0.001               | 2.59 (1.63–4.11) |
| Renal function                           |                      |              |
| Severe CKD                               | reference            | 1            |
| Dialysis                                | 0.044                | 2.47 (1.02–5.95) |
| Symptoms¶, presence vs. none             | 0.810                |              |
| Radiologic lesion                        |                      |              |
| None                                    | reference            | 1            |
| Not compatible with TB                   | 0.690                |              |
| Compatible with prior TB lesion          | 0.008                | 2.90 (1.45–5.83) |
| TB, not excluded                         | 0.504                |              |

Abbreviations: TB, tuberculosis; CKD, chronic kidney disease.

¶Indicated chronic cough, dyspnea, fever, and other constitutional symptom.

doi:10.1371/journal.pone.0124104.t002
the risk of LTBI may be similar between patients receiving peritoneal dialysis and those on hemodialysis [19].

Focusing on severe CKD and dialysis patients, the risk factors for LTBI aside from dialysis are old age, high serum albumin, and radiographic lesions compatible with prior TB. Old age has been reported in another LTBI study [34] and is also a risk factor in a previous study on the dialysis population [19]. This further suggests that the incidence of active TB is also higher in the elderly. High serum albumin level is considered a good nutritional status that can provide good immune reactivity for LTBI assay [35, 36]. In the present study, although those with past treatment history of active TB have been excluded, chest radiographs of prior TB lesions are still a significant factor, possibly because radiography is more reliable. Moreover, some radiographic lesions can be tuberculoma formed during LTBI and is not detected at all [37].

The IGRA is reportedly sensitive in patients with HIV infection [38]. However, reports on other populations are lacking. Interferon-γ response in dialysis patients with LTBI is as good as those of severe CKD patients or dialysis-unit staff with LTBI. Indeterminate QFT-GIT result is based on the manufacturer’s protocol and is similar between the severe CKD and dialysis groups, suggesting that the dialysis population is not a contra-indicated group for IGRA.

The present study has several limitations. First, the participants were voluntarily enrolled, so their demographics were heterogeneous across different groups. Second, without detailed contact records, the use of TB exposure history for analysis of QFT-positivity cannot be confirmed. Lastly, this is a small cross-sectional study, especially for the severe CKD group. A long-term cohort study focusing on the occurrence of active TB is required.

In conclusion, patients receiving dialysis have a higher prevalence of LTBI than those with severe CKD and the dialysis-unit staff (25%, 11%, and 11%, respectively). Old age, prior TB lesion by radiography, increased serum albumin level, and long-term dialysis are predictors of LTBI. Severe CKD patients may not be the priority group for LTBI screening if resources are limited. The hemodialysis environment is also not a significant risk for LTBI and dialysis-unit staff members may be considered a risk group similar to general healthcare workers.

Supporting Information
S1 Dataset. Dataset of patient’s delinked information. Dataset file includes detail delinked information which is collected and analyzed in this study.

(XLS)

Acknowledgments
The authors thank the staff of the Eighth Core Lab of the Department of Medical Research of National Taiwan University Hospital for their technical support. The authors also thank the Department of Medical Research of National Taiwan University Hospital.

Disclosures
Parts of the study results have been presented as a poster discussion in the 2014 International Conference of the American Thoracic Society.

Author Contributions
Conceived and designed the experiments: CCS LNL CJY. Performed the experiments: CLH CYL JYW CCS VCW FJY JTW. Analyzed the data: CCS JYW. Wrote the paper: CCS JYW LNL CJY.
References
1. Global Tuberculosis Report, 2013: World Health Organization 2013.
2. Rose DN. Benefits of screening for latent Mycobacterium tuberculosis infection. Arch Intern Med. 2000; 160(10):1513–21. PMID: 10826467
3. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med. 2004; 350(20):2060–7. PMID: 15141044
4. Li SY, Chen TJ, Chung KW, Tsai LW, Yang WC, Chen JY, et al. Mycobacterium tuberculosis infection of end-stage renal disease patients in Taiwan: a nationwide longitudinal study. Clin Microbiol Infect. 2011; 17(11):1646–52. doi: 10.1111/j.1469-0691.2011.03473.x PMID: 21375664
5. Dobler CC, McDonald SP, Marks GB. Risk of tuberculosis in dialysis patients: a nationwide cohort study. PloS one. 2011; 6(12):e29563. doi: 10.1371/journal.pone.0029563 PMID: 22216316
6. Venkata RK, Kumar S, Krishna RP, Kumar SB, Padmanabhan S. Tuberculosis in chronic kidney disease. Clin Nephrol. 2007; 67(4):217–20. PMID: 17474557
7. Fang HC, Lee PT, Chen CL, Wu MJ, Chou KJ, Chung HM. Tuberculosis in patients with end-stage renal disease. Int J Tuberc Lung Dis. 2004; 8(1):92–7. PMID: 14974751
8. Metcalfe JZ, Cattamanchi A, McCulloch CE, Lew JD, Ha NP, Gaviss EA. Test variability of the QuantiFERON-TB gold in-tube assay in clinical practice. Am J Respir Crit Care Med. 2013; 187(2):206–11. doi: 10.1164/rccm.201203-043OC PMID: 23103734
9. Shu CC, Wu VC, Yang FJ, Hsu CL, Pan SC, Wang JY, et al. Dynamic changes in positive interferon-gamma release assay in a dialysis population: An observational cohort study. J Infect. 2013; 67(6):529–35. doi: 10.1016/j.jinf.2013.07.029 PMID: 23933475
10. Simsek H, Alpar S, Ucar N, Aksu F, Ceyhan I, Gozalan A, et al. Comparison of tuberculin skin testing and T-SPOT.TB for diagnosis of latent and active tuberculosis. Jpn J Infect Dis. 2010; 63(2):99–102. PMID: 20332570
11. Brock I, Weldingh K, Lillebaek T, Follmann F, Andersen P. Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts. Am J Respir Crit Care Med. 2004; 170(1):65–9. PMID: 15087297
12. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with Mycobacterium tuberculosis. Am J Respir Crit Care Med. 2008; 177(10):1164–70. doi: 10.1164/rccm.200711-1613OC PMID: 18276940
13. Mazurek GH, Jereb J, Vernom A, LoBue P, Goldberg S, Castro K, et al. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection—United States, 2010. MMWR Recomm Rep. 2010; 59(RR-5):1–25. PMID: 20577159
14. Yu MC, Suo J, Huang C, Bai KJ, Lin TP, Luh KT. Annual risk of tuberculous infection in Taiwan, 1996–1998. J Formos Med Assoc. 1999; 98(7):496–9. PMID: 10462999
15. Lai CC, Tan CK, Chou CH, Hsu HL, Liao CH, Huang YT, et al. Increasing incidence of nontuberculous mycobacteria, Taiwan, 2000–2008. Emerg Infect Dis. 2010; 16(2):294–6. doi: 10.3201/eid1602.090675 PMID: 20113563
16. Triverio PA, Bridevaux PO, Roux-Lombard P, Niksic L, Rochat T, Martin PY, et al. Interferon-gamma release assays versus tuberculin skin testing for detection of latent tuberculosis in chronic haemodialysis patients. Nephrol Dial Transplant. 2009; 24(6):1525–6. doi: 10.1093/ndt/gfn748 PMID: 19164327
17. Lee SS, Chou KJ, Su IJ, Chen YS, Fang HC, Huang TS, et al. High prevalence of latent tuberculosis infection in patients in end-stage renal disease on hemodialysis: Comparison of Quantiferon-TB Gold, ELISPOT, and tuberculin skin test. Infection. 2009; 37(2):96–102. doi: 10.1007/s15010-008-0802-3 PMID: 19139810
18. Lee SS, Chou KJ, Dou HY, Huang TS, Ni YY, Fang HC, et al. High prevalence of latent tuberculosis infection in dialysis patients using the interferon-gamma release assay and tuberculin skin test. Clin J Am Soc Nephrol. 2010; 5(8):1451–7. doi: 10.2215/CJN.01792010 PMID: 20538837
19. Shu CC, Wu VC, Yang FJ, Pan SC, Lai TS, Wang JY, et al. Predictors and prevalence of latent tuberculosis infection in patients receiving long-term hemodialysis and peritoneal dialysis. PloS one. 2012; 7(8):e42592. doi: 10.1371/journal.pone.0042592 PMID: 22916137
20. James MT, Quan H, Tonelli M, Manns BJ, Faris P, Laupland KB, et al. CKD and risk of hospitalization and death with pneumonia. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2009; 54(1):24–32.
21. Stevens LA, Viswanathan G, Weiner DE. Chronic kidney disease and end-stage renal disease in the elderly population: current prevalence, future projections, and clinical significance. Adv Chronic Kidney Dis. 2010; 17(4):293–301. doi: 10.1053/j.ackd.2010.03.010 PMID: 20610356
22. Hill CJ, Fogarty DG. Changing trends in end-stage renal disease due to diabetes in the United Kingdom. J Ren Care. 2012; 38 Suppl 1:12–22. doi: 10.1111/j.1755-6686.2012.00273.x PMID: 22348360

23. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130(6):461–70. PMID: 10075613

24. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973; 60(8):646–9. PMID: 4541913

25. Lalvani A, Pathan AA, McShane H, Wilkinson RJ, Latif M, Conlon CP, et al. Rapid detection of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. Am J Respir Crit Care Med. 2001; 163(4):824–8. PMID: 11282752

26. Dyrhol-Riise AM, Gran G, Wentzel-Larsen T, Blomberg B, Haanshuus CG, Morkve O. Diagnosis and follow-up of treatment of latent tuberculosis; the utility of the QuantIFERON-TB Gold In-tube assay in outpatients from a tuberculosis low-endemic country. BMC Infect Dis. 2010; 10:57. doi: 10.1186/1471-2334-10-57 PMID: 20210999

27. Banach DB, Harris TG. Indeterminate QuantiFERON(R)-TB Gold results in a public health clinic setting. Int J Tuberc Lung Dis. 2011; 15(12):1623–30. doi: 10.5588/ijtld.11.0017 PMID: 22181689

28. National Kidney Foundation. NKF-DOQI clinical practice guidelines for hemodialysis adequacy. American journal of kidney diseases: the official journal of the National Kidney Foundation. 1997; 30(Suppl 2):S15–66. PMID: 9293257

29. Shin JH, Ezzati M, Chang HY, Murray M. Association between tobacco smoking and active tuberculosis in Taiwan: prospective cohort study. Am J Respir Crit Care Med. 2009; 180(5):475–80. doi: 10.1164/rccm.200904-0549OC PMID: 19542475

30. Jeong YJ, Lee KS. Pulmonary tuberculosis: up-to-date imaging and management. AJR Am J Roentgenol. 2008; 191(3):834–44. doi: 10.2214/AJR.07.3896 PMID: 18716117

31. Mansouri L, Paulsson JM, Moshfegh A, Jacobson SH, Lundahl J. Leukocyte proliferation and immune modulator production in patients with chronic kidney disease. PloS one. 2013; 8(8):e73141. doi: 10.1371/journal.pone.0073141 PMID: 23951343

32. Centers for Disease Control MoHaW, R.O.C. (Taiwan). Taiwan Tuberculosis Control Report 2013. Taiwan: Centers of Disease Control, Department of Health, R.O.C. (Taiwan); 2014.

33. Ringshausen FC, Nienhaus A, Schablon A, Schlosser S, Schultzze-Werninghaus G, Rohde G. Predictors of persistently positive Mycobacterium-tuberculosis-specific interferon-gamma responses in the serial testing of health care workers. BMC Infect Dis. 2010; 10:220. doi: 10.1186/1471-2334-10-220 PMID: 20653946

34. Martinez L, Arman A, Haveman N, Lundgren A, Cabrera L, Evans CA, et al. Changes in tuberculin skin test positivity over 20 years in periurban shantytowns in Lima, Peru. Am J Trop Med Hyg. 2013; 89(3):507–15. doi: 10.4269/ajtmh.13-0005 PMID: 23878185

35. Shankar MS, Aravindan AN, Sohal PM, Kohli HS, Sud K, Gupta KL, et al. The prevalence of tuberculin sensitivity and anergy in chronic renal failure in an endemic area: tuberculin test and the risk of post-transplant tuberculosis. Nephrol Dial Transplant. 2005; 20(12):2720–4. PMID: 16188895

36. Altunoren O, Kahraman H, Sayarlioglu H, Yavuz YC, Dogan E, Koksal N. The affecting factors and comparison of tuberculin skin test in peritoneal dialysis and hemodialysis patients. Ren Fail. 2012; 34(3):304–7. doi: 10.3109/0886022X.2011.647299 PMID: 22260191

37. Barry CE 3rd, Boshoff HI, Dartois V, Dick T, Ehr T, Flynn J, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nature reviews Microbiology. 2009; 7(12):845–55. doi: 10.1038/nrmicro2236 PMID: 19855401

38. Aichelburg MC, Rieger A, Breitenecker F, Pfistershammer K, Tittes J, Eltz S, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. Clin Infect Dis. 2009; 48(7):954–62. doi: 10.1086/597351 PMID: 19245343