Journal of Microbiology, Immunology and Infection 55 (2022) 926–934

Available online at www.sciencedirect.com

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Original Article

Tuberculosis treatment delay and nosocomial exposure remain important risks for patients undergoing regular hemodialysis

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Received 5 April 2021; received in revised form 7 July 2021; accepted 5 August 2021
Available online 1 September 2021

KEYWORDS
End-stage renal disease;
Hemodialysis;
Infection control;
Tuberculosis;
Nosocomial transmission

Abstract *Background and objective:* Studies have reported an increased tuberculosis (TB) incidence among patients with end-stage renal disease (ESRD). This nationwide nested Case–control study investigated the risk of active TB due to nosocomial exposure and its correlation with the delay in TB treatment in hemodialysis patients.
Methods: Adult (aged ≥20 years) patients with incident ESRD over 2000–2010 were identified from Taiwan National Health Insurance Research Database; 2331 patients with incident active TB (Case) were matched with 11,655 patients without TB (control) by age, sex, year of ESRD onset, Charlson comorbidity index, chronic obstructive pulmonary disease, and diabetes mellitus, at a 1:5 case-to-control ratio.

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https://doi.org/10.1016/j.jmii.2021.08.011

Results: Compared with the control group, the Case group had greater nosocomial exposure to index patients with pulmonary TB (2.36 vs. 0.11 month of exposure, $p < 0.001$). Nosocomial exposure increased active TB risk (adjusted odds ratio [OR; 95% confidence interval, CI]: 1.60 [1.55—1.66] per month of exposure), particularly when the exposure time was either within 6 months before the index case was diagnosed or 6—15 months before the ESRD patient became an incident active TB case. For patients with active TB, cough-related medication prescriptions (proxy for cough symptoms) exponentially increased over 6 months before TB treatment.

Conclusion: Nosocomial exposure attributed to delay in the diagnosis of index pulmonary TB is important in TB transmission among patients undergoing regular hemodialysis. Additional studies investigating how TB can be diagnosed and treated early are warranted.

Summary at a glance: Our study revealed that nosocomial exposure, attributed to delay in pulmonary TB diagnosis, is important in TB transmission among patients undergoing regular hemodialysis. Strategies to diagnose and treat TB early are crucial to infection control, and they warrant further investigations.

Introduction

Tuberculosis (TB) is a main cause of death from an infectious disease, with an estimated 10.0 million new diagnoses and 1.4 million deaths globally in 2019.[1] Patients with end-stage renal disease (ESRD) have immunodeficiency,[2] making them more susceptible to infectious diseases[3]: these patients are 6.9—8.6 times more likely to develop active TB. Among the patients with ESRD, the 1-year mortality rate for those with active TB is 3.3 times higher than those without TB,[4] and a higher risk of mortality was associated with active TB even after multivariate adjustment (hazard ratio: 1.48; 95% confidence interval, CI: 1.36—1.60).[5] Minimizing TB transmission among patients with ESRD and investigating potential modifiable factors that improve their outcome are crucial.

In patients with ESRD, active TB is a result of a complex interplay of uremia-associated immunosuppression, underlying comorbidities, and nosocomial exposure to other patients with undiagnosed infectious pulmonary TB. Patients with ESRD with uremia have impaired innate and adaptive immunity, leading to a decreased phagocytic activity of monocytes, neutrophils, and dendritic cells and decreased toll-like receptor activity.[6,7] Patients with ESRD are more likely to have associated comorbidities, such as diabetes mellitus, organ transplantation, and human immunodeficiency virus infection, which all have been linked to increased risk of active TB.[8] Patients with ESRD who harbor latent infection are at a 10—25 times greater risk to develop active TB than the general population.[9,10]

Patients with ESRD rely on long-term peritoneal or hemodialysis to remove waste products, with hemodialysis requiring a patient to visit a hemodialysis center two to three times a week for 4 h per session. Taiwan has the highest rate of dialysis globally,[11] and >93.2% of patients select hemodialysis over peritoneal dialysis.[12] The median delay in TB treatment is 92 days for patients with ESRD because they demonstrated a myriad of clinical presentations and their radiological findings are easily masked by their underlying comorbidities.[13,14] During this time gap, vulnerable patients with ESRD in contact with patients with untreated pulmonary TB may have an increased risk of TB infection through exposure to the nuclei of infectious respiratory droplets in hemodialysis facilities. Healthcare workers, who have been shown to have increased incidence of TB in high TB burden countries,[15] may also facilitate TB transmission.

Large cohort studies in Taiwan and Korea have reported an increased incidence of active TB in patients with ESRD.[8,16] A study indicated that increased regional TB prevalence also increased the risk of nosocomial exposure to TB.[17] However, no study has quantitated active TB risk in relation to the extent of nosocomial exposure in hemodialysis centers or correlated this risk with TB treatment delay. Thus, in this population-based study, the risk of active TB due to effective nosocomial exposure was quantitated based on the length of time spent in a hemodialysis center with patients with index pulmonary TB and the association of this risk with TB treatment delay was investigated.

Materials and methods

Ethics statement

The Institutional Review Board of Taipei Medical University approved the study (N201712019) and waived the need for informed consent because this retrospective study used deidentified data and presented no risk to participants.

Study design and cohort selection

National Health Insurance (NHI), the universal healthcare system in Taiwan, covers >96% of the approximately 23 million Taiwan residents. The NHI Research Database is a comprehensive database suitable for biomedical studies.[18] The working dataset used in this study, including inpatient and outpatient records between 1997 and 2013, was extracted from the full population dataset of NHI claims data.[19]

In this nested case-control study on ESRD patients, the case group included individuals who developed active TB 6

months or later after the commencement of long-term hemodialysis. During the study period, 2331 patients with incident active TB were identified and selected as case group. For each of them, 5 patients who did not develop active TB during study period and matched by age, sex, year of ESRD onset, Charlson comorbidity index,[20] presence of chronic obstructive pulmonary disease, and presence of diabetes mellitus were selected as the control group (n = 11,655). For each case and its matched control subjects, the event date was defined as the incident date of active TB.

Definitions of ESRD

A patient was defined as having ESRD if they underwent regular hemodialysis at least two times a week for ≥90 days.[5,21] The study cohort comprised patients with incident ESRD at any period between 2000 and 2010. Patients aged <20 years, with a history of kidney transplant before ESRD, or with incomplete data were excluded.

Definitions of TB

A previous study validated the diagnostic criteria of TB[17] against clinical data in a tertiary medical center.[22] In this study, patients with active TB were identified by corresponding diagnoses, prescriptions of anti-TB agents, and records of positive *Mycobacterium tuberculosis* drug susceptibility testing results. Incident pulmonary TB was identified if a patient fulfilled abovementioned criteria for having active TB and had compatible diagnoses (ICD-9-CM 010–012 and 018) suggesting pulmonary involvement. The incident date was defined as the start date of taking anti-TB agents or the date of death for those without taking anti-TB agents.

Definition of nosocomial TB exposure

The NHI Research Database provided systemic records of when and where each patient underwent hemodialysis. To stay in a shared indoor ventilation circumstance can contribute to significant TB transmission.[23] Nosocomial TB exposure was defined as if an ESRD patient without active TB underwent hemodialysis with a pulmonary TB patient within the infectious period at the same hemodialysis center. The infectious period was defined as the last 6 months before the incident date.[24]

Quantification of nosocomial TB exposure

When calculating the risk of being infected and developing active TB, the exposure period for a non-TB ESRD contact was defined as the 6–24-month period before the event date. The length of the overlapping intervals between the infectious period of the ESRD patients with pulmonary TB and the exposure period of the non-TB ESRD contacts were calculated to quantify the effective nosocomial exposure (Fig. 1A). If exposure to multiple patients with pulmonary TB was recorded, the effective nosocomial exposure periods were summed together. The robustness of the Definition on effective nosocomial exposure was tested in the sensitivity analyses.

Comorbidities and other variables

The comorbidities and clinical characteristics of patients with ESRD were extracted from the working dataset. Steroid users received a cumulative dose of systemic corticosteroids equivalent to prednisolone ≥700 mg. Those who received immunosuppressant drugs (anatomical therapeutic chemical codes L01 and L04) during the last 2 years before the event date were identified as immunosuppressant users.[25] The Definitions of comorbidities are summarized in Appendix Table 1.

Prescriptions of cough-related medications (days per month) were aggregated every 3 months as a surrogate for the evolution of cough symptoms. Cough-related medications included oral antitussives, mucolytic agents, and sympathomimetics (e.g., oral methylphedrine).[26]

Statistical analysis

The chi-square test, Fisher exact test, and paired-samples *t* test were used to compare the distributions of demographic characteristics between the case and control groups. Multivariate conditional logistic regression was used to identify the independent factors, including those pertaining to clinical demographics, comorbidities, steroid users, immunosuppressant users, and nosocomial exposure, which were associated with developing active TB. All analyses were performed using R (2016, version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at a two-tailed p of <0.05.

Sensitivity analysis

The assessment of susceptibility of patients with ESRD and infectiousness of patients with incident pulmonary TB was performed by specifying different combinations of the time intervals of the exposure and the infectious periods as illustrated in Fig. 1B and C. The 6–36 month period before the event date of the susceptible subjects was divided into independent 3-month exposure periods. During each 3-month period of interest, the susceptibility (effect of nosocomial exposure on active TB risk) was expressed in terms of adjusted odds ratio (aOR) obtained from the multivariate conditional logistic regression. The process was independently iterated for the 6–36-month period before the event date to define the susceptibility of each 3-month period of interest (Fig. 1B). Similarly, the 18-month period before the incident date of pulmonary TB was divided into independent 3-month infectious periods and screened for infectiousness. The infectiousness expressed in terms of aOR during each 3-month period of interest was determined sequentially (Fig. 1C).

Results

Case selection and clinical characteristics

Of the 144,067 patients with ESRD undergoing hemodialysis, recorded in the NHI Research Database, 112,131 were

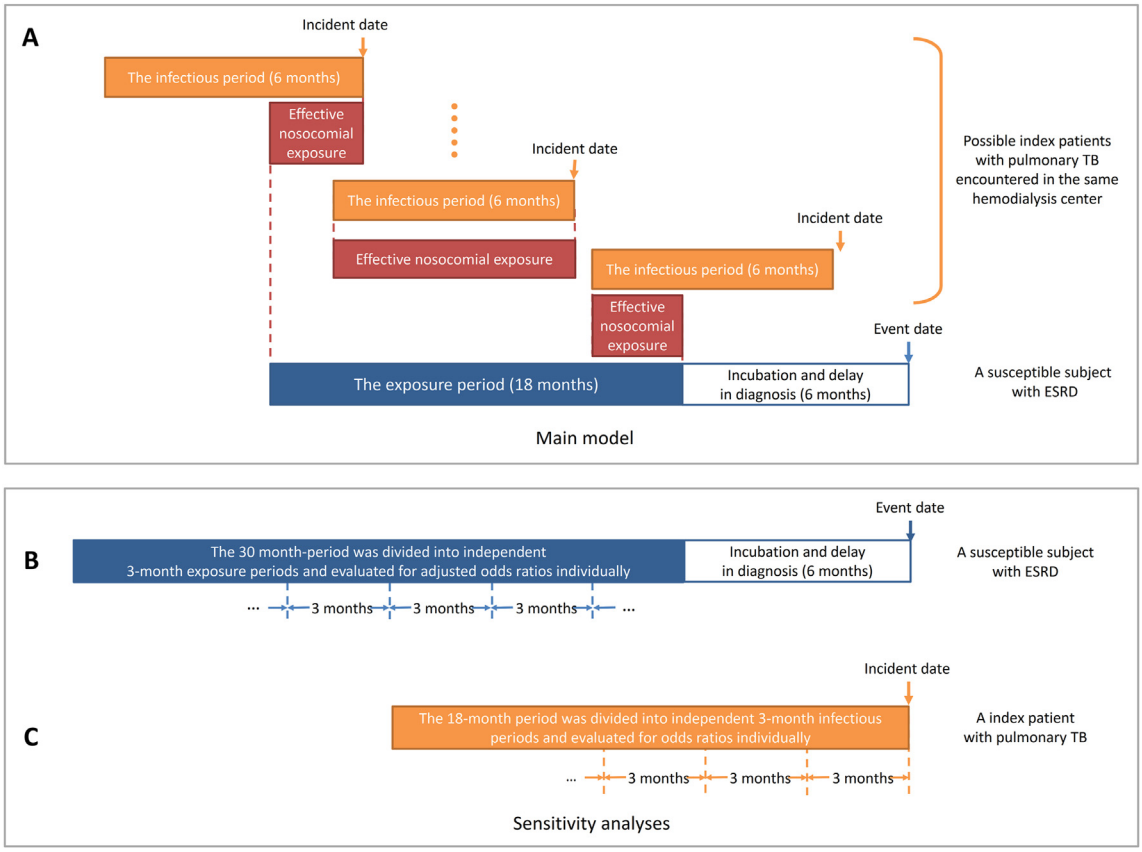

Figure 1. **(A)** In the main analysis, nosocomial exposure of a susceptible contact (patient with ESRD) and index patients with pulmonary TB in the same institute was shown. Three different possible overlapping patterns (effective exposure) between the infectious period of index patients with pulmonary TB and exposure periods of a susceptible contact are illustrated. The blue block represents a contact with the filled segment representing the exposure period and the empty segment representing the period before the diagnosis of active TB (assumed 6 months), if it occurs. The orange blocks represent the infectious periods and the red blocks represent effective exposures **(B)** In the sensitivity analysis, for the exposure period of a contact, the 6–36 months before the event date was divided into 10 independent 3-month exposure periods. For each segment, effect of exposure on risk (adjusted odds ratio) of developing active TB was calculated using a multivariate conditional logistic regression. **(C)** In the sensitivity analysis, for infectious period of index patients with pulmonary TB, the 18 months before the TB diagnosis was divided into 6 independent 3-month infectious periods. For each segment, the effect of exposure on risk (adjusted odds ratio) of developing active TB was calculated using a multivariate conditional logistic regression.

enrolled in the study cohort. Of these patients, 2331 patients who developed active TB (case group) after ESRD onset were matched with 11,655 patients with ESRD without active TB (control group), at a 1:5 case-to-control ratio (Fig. 2). Their clinical characteristics are summarized in Table 1.

The baseline characteristics were balanced between the case and control groups. Both groups had more men than women, and approximately 70% of the patients were aged >60 years. The average Charlson comorbidity indexes were 3.95 ± 2.08 and 4.00 ± 2.20 ($p = 0.353$) for the control and case groups, respectively. The two most common comorbidities were diabetes mellitus and chronic obstructive pulmonary disease, comprising 47.7% and 38.4% of all participants, respectively (Table 1).

Risk factors for TB in hemodialysis patients with ESRD

Compared with the control group, the case group was more likely to have liver cirrhosis (1.9% vs. 1.3%, $p = 0.044$), use steroids (2.4% vs. 1.4%, $p < 0.001$), and have greater nosocomial exposure to index patients with pulmonary TB (2.36 vs. 0.11 month of exposure, $p < 0.001$; Table 1). The multivariate conditional logistic regression indicated that having liver cirrhosis, using immunosuppressants, using steroids, and having had nosocomial exposure were independently associated with an increased risk of developing active TB (adjusted ORs [CI]: 1.63 [1.10–2.42], 2.24 [1.54–3.25], 1.22 [1.03–1.44], and 1.60 [1.55–1.66] per month of exposure, respectively; Table 2).

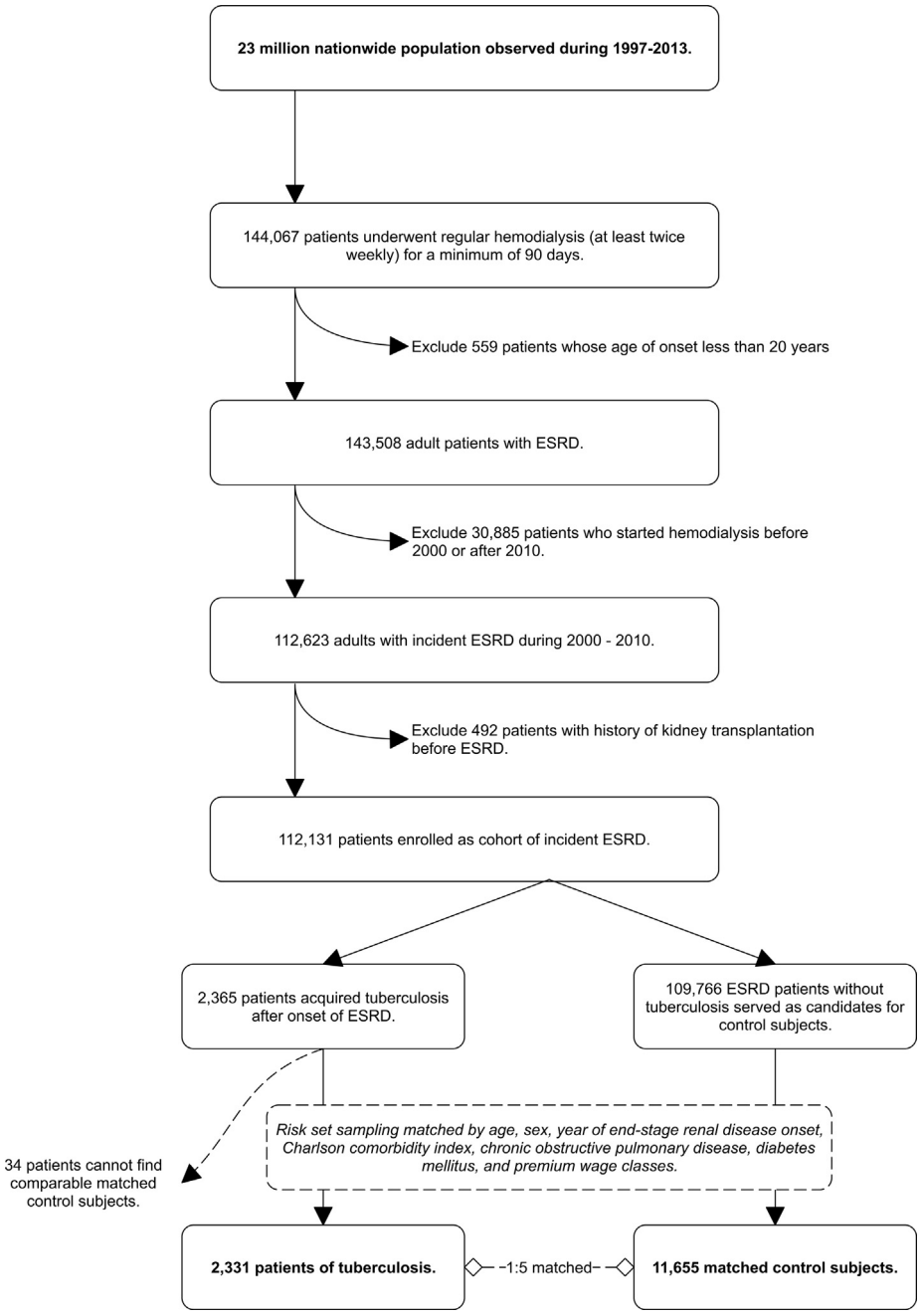

Figure 2. Enrollment of 2331 patients who developed active tuberculosis and 11,655 control participants without active tuberculosis. All participants were patients undergoing long-term hemodialysis for incident ESRD during at any period during 2000—2010.

Validation for the sensitivity of nosocomial effective exposure period

The stepwise verification for susceptibility of ESRD contacts indicated a significant risk of developing active TB if exposed 6—30 months before the event date (Fig. 3A), particularly during the 6—15 months before the event date. The adjusted ORs (95% CIs) of nosocomial exposure during 6—9-, 9—12-, and 12—15-month intervals before the date of incident active TB were 1.73 (1.67—1.81), 1.97 (1.90—2.04), and 1.84 (1.77—1.92) per month of exposure, respectively. Our sensitivity analysis indicated significant infectiousness for the index patients with pulmonary TB during the last 6 months before the incident date of pulmonary TB (Fig. 3B). The adjusted ORs of nosocomial exposure during the 0—3- and 3—6-month intervals before the incident date of pulmonary TB were 1.77 (1.71—1.81) and 1.30 (1.13—1.52) per month of exposure, respectively. During the three years before the event date, more cough-related medications were prescribed to patients who developed active TB than to those in the control group. The prescription of cough-related medications for patients who

Table 1 Characteristics of 13,986 patients with ESRD who underwent long-term hemodialysis stratified by development of tuberculosis.

Tuberculosis	No (n = 11,655)	Yes (n = 2331)	p
Age (year)			0.587[a]
≤40	289 (2.5%)	58 (2.5%)	
40–50 (inclusive)	1054 (9.0%)	216 (9.3%)	
50–60 (inclusive)	2109 (18.1%)	407 (17.5%)	
60–70 (inclusive)	3289 (28.2%)	629 (27.0%)	
>70	4914 (42.2%)	1021 (43.8%)	
Sex			1[a]
Female	4765 (40.9%)	953 (40.9%)	
Male	6890 (59.1%)	1378 (59.1%)	
Charlson comorbidity index	3.95 ± 2.08	4.00 ± 2.20	0.353[b]
Comorbidities			
Diabetes mellitus	5565 (47.7%)	1113 (47.7%)	1[a]
COPD	4475 (38.4%)	895 (38.4%)	1[a]
Cerebrovascular disease	1584 (13.6%)	301 (12.9%)	0.400[a]
Congestive heart failure	1110 (9.5%)	225 (9.7%)	0.877[a]
Malignancy	845 (7.3%)	163 (7.0%)	0.693[a]
Myocardial infarction	444 (3.8%)	88 (3.8%)	0.984[a]
Liver cirrhosis	154 (1.3%)	44 (1.9%)	0.044[a]
Immunosuppressant user	68 (0.6%)	16 (0.7%)	0.660[a]
Systemic steroid user	166 (1.4%)	56 (2.4%)	<0.001[a]
Nosocomial tuberculosis exposure (month)	0.11 ± 1.10	2.36 ± 3.53	<0.001[b]

[a] Comparisons in the chi-square test.
[b] Comparisons in paired-samples t test.
COPD, chronic obstructive pulmonary disease.

Table 2 Conditional logistic regression analysis for risk factors for developing tuberculosis among 13,986 patients with ESRD who underwent long-term hemodialysis.

	Adjusted OR (95% CI)	p
Liver cirrhosis	1.63 (1.10, 2.42)	0.014
Immunosuppressant use	2.24 (1.54, 3.25)	<0.001
Systemic steroid use	1.22 (1.03, 1.44)	0.019
Effective nosocomial tuberculosis exposure (month)	1.60 (1.55, 1.66)	<0.001

OR, odds ratio; CI, confidence interval.

developed active TB exponentially increased in the immediate 6 months before the initiation of TB medications, whereas that of the control group remained constant (Fig. 4). The increased prescription of cough-related medications for the case group was also significantly higher than that of the control group during the last 6 months.

Discussion

This population-based study demonstrated that for patients with ESRD, the risk of developing active TB increased with greater nosocomial exposure to other index patients with pulmonary TB in hemodialysis centers (2.36 vs. 0.11 month of exposure). The infectiousness of index patients with pulmonary TB was greatest during the last 6 months immediately before diagnosis and the commencement of TB medications; this trend matched that of increased cough-related medication prescriptions for patients who developed active TB during the same period. These findings support previous studies which reported a 92-day median delay in receiving TB treatment.[13] Index patients with pulmonary TB during this time gap presented active TB symptoms but had not yet been given TB medications, and the progression of cough could lead to greater infectiousness. Thus, the delay in initiating TB medications was associated with increased nosocomial exposure and transmission risk of TB in hemodialysis centers.

With an insidious onset and slow progression, patients may neglect the cough as a warning sign and fail to seek medical help timely. TB treatment may be delayed because the clinician is unaware of the association between cough symptoms and the underlying pulmonary TB disease and because some time is required to gather confirmative microbiological evidence from valid sputum samples and screening tests.[13] Nucleic acid amplification test for *M. tuberculosis* and fluorescence microscopy have been shown to substantially improving diagnostic yield and shorten diagnosis delay, leading to early and proper respiratory isolation.[17,27]

The two groups were matched for clinical diagnosis of COPD during cohort selection, but patients who developed TB were found to be prescribed with more cough-related medications way before the diagnosis of TB. The actual causes for such association are not clear and it is hard to tell whether cough-related medications to suppress airway clearance could directly contribute to the risk of developing TB. Possible mechanisms underlying this phenomenon may be chronic airway inflammation from smoking-associated subclinical bronchitis; or cough induced by exposures to occupational particulates and air pollution.[28,29]

Recent studies and guidelines have suggested that the screening and treatment of latent TB infection (LTBI) may benefit patients with chronic kidney disease, regardless of their TB epidemiology.[30,31] At present, in Taiwan, all individuals with a TB contact history must undergo a chest X-ray. LTBI screening using interferon-gamma release assay (IGRA), shown to be helpful in controlling and monitoring both active and latent TB in patients during TB outbreaks,[32] is required for those whose index case have culture-confirmed pulmonary TB.[33] However, during the study period, contact screening included only chest X-rays, and LTBI screening was not performed, either for contact screening or as a routine procedure for patients with ESRD.

The delay described in this report focused on healthcare system delay, i.e.; from a patient with TB-associated symptoms managed in the healthcare system to the commencement of anti-TB treatment. Specifically, airway symptoms were investigated because the aim of the study was to investigate the impact of nosocomial (airborne) TB

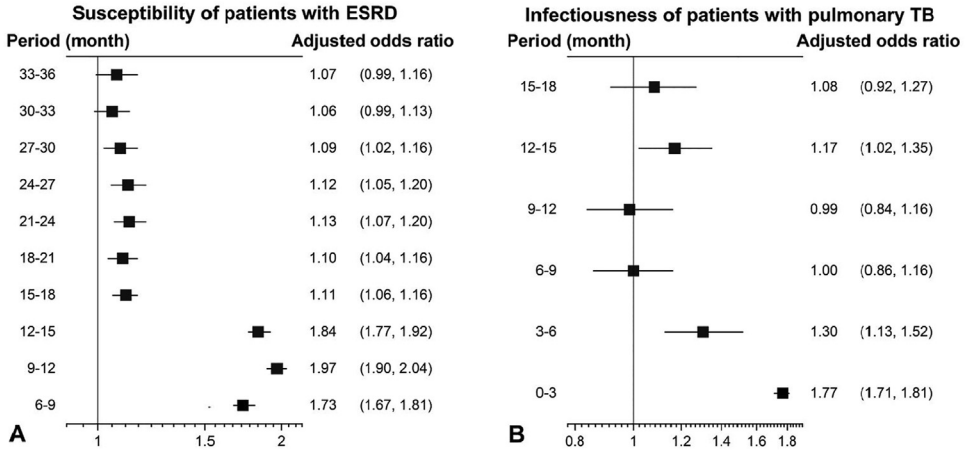

Figure 3. (A) Forest plot illustrating the susceptibility of contacts with ESRD during specific periods on nosocomial exposure to index patients with pulmonary tuberculosis. This figure correlates with Fig. 1B of the sensitivity analysis (B) Forest plot illustrating the infectiousness of index patients with pulmonary tuberculosis in relation to other susceptible contacts during specific periods before the diagnosis of pulmonary tuberculosis. This figure correlates with Fig. 1C of the sensitivity analysis.

transmission. As demonstrated in the present study, isolation and TB treatment cannot completely eliminate nosocomial transmission due to extended delays in diagnosing active TB, and LTBI intervention can prevent TB from activating and further spreading to other patients.[34] Both the tuberculin skin and IGRA tests are less sensitive in patients with ESRD than in those without ESRD.[35] Thus, a negative test result does not definitively indicate the absence of LTBI. As demonstrated in the present study, the delay in TB diagnosis is about 6 months, which is shown to be the most infectious period. Prospective interventional study to test whether biannually routine screening using chest radiography and IGRA can reduce subsequent incident TB cases in this vulnerable population is indicated. Household TB exposure may also contribute to the development of TB in our study cohort. Since the health insurance reimbursement dataset contains only events in the healthcare system, the disclosed association between the nosocomial TB exposure and risk of developing active TB does not imply to negate the possible contribution of household contact.

In a previous report following 9332 subjects with documented history of TB contact for up to ten years, the risk of developing TB after exposure was found to be highest during the first six month and 97.2% of the coprevalent and incident TB occurred within two years.[36] Taking account for the 6-month delay in diagnosis of TB, the result of the sensitivity analysis for exposure period in the present study fairly reflected this time-relationship coupling the exposure and subsequent development of TB. An incident TB is most likely resulted from a prior exposure 6—12 months ago and less likely due to remote exposure apart from more than two years.

This study has several limitations. First, it was conducted using the NHI Research Database, which captures only the regional nosocomial risk of TB in Taiwan. However, the risk of nosocomial exposure depends on local TB prevalence[17]; thus, our results reflect only the relative, rather than absolute, risks of active TB in patients with ESRD, which must be considered when our findings are extrapolated to other countries. Second, this database does not include information on ventilation condition of the hemodialysis centers, genotyping, smear positivity, and imaging studies of the active TB cases; instead, we only used TB selection criteria. However, these criteria were validated in a tertiary medical center to have high sensitivity, specificity, positive predictiveness, and negative predictiveness.[17,22] Third, we did not match index patients with pulmonary TB and their susceptible contacts by their exact (or hour-level) hemodialysis schedules. Therefore, the proposed nosocomial exposure may overestimate the extent of direct close contact, and our analyses likely underestimated the actual risk of nosocomial exposure on subsequent TB development, with a bias toward no effect. Furthermore, although alcohol use was a predisposing factor for TB, alcohol consumption is not systematically recorded in the NHI Research Database and we did not further determine the causes of cirrhosis.

In conclusion, our findings suggest that delayed TB treatment remains the principal gap in halting nosocomial TB transmission in hemodialysis centers. This is the first study to provide epidemiological evidence that the extent of risk considerably increases with the extent of nosocomial exposure to other patients on hemodialysis with untreated pulmonary TB. To protect patients and healthcare workers in hemodialysis centers, further studies should investigate the effectiveness of infection control policies, such as routine radiological screening, LTBI screening and treatment, and programmed cough monitoring, to minimize delay in TB diagnosis and treatment.

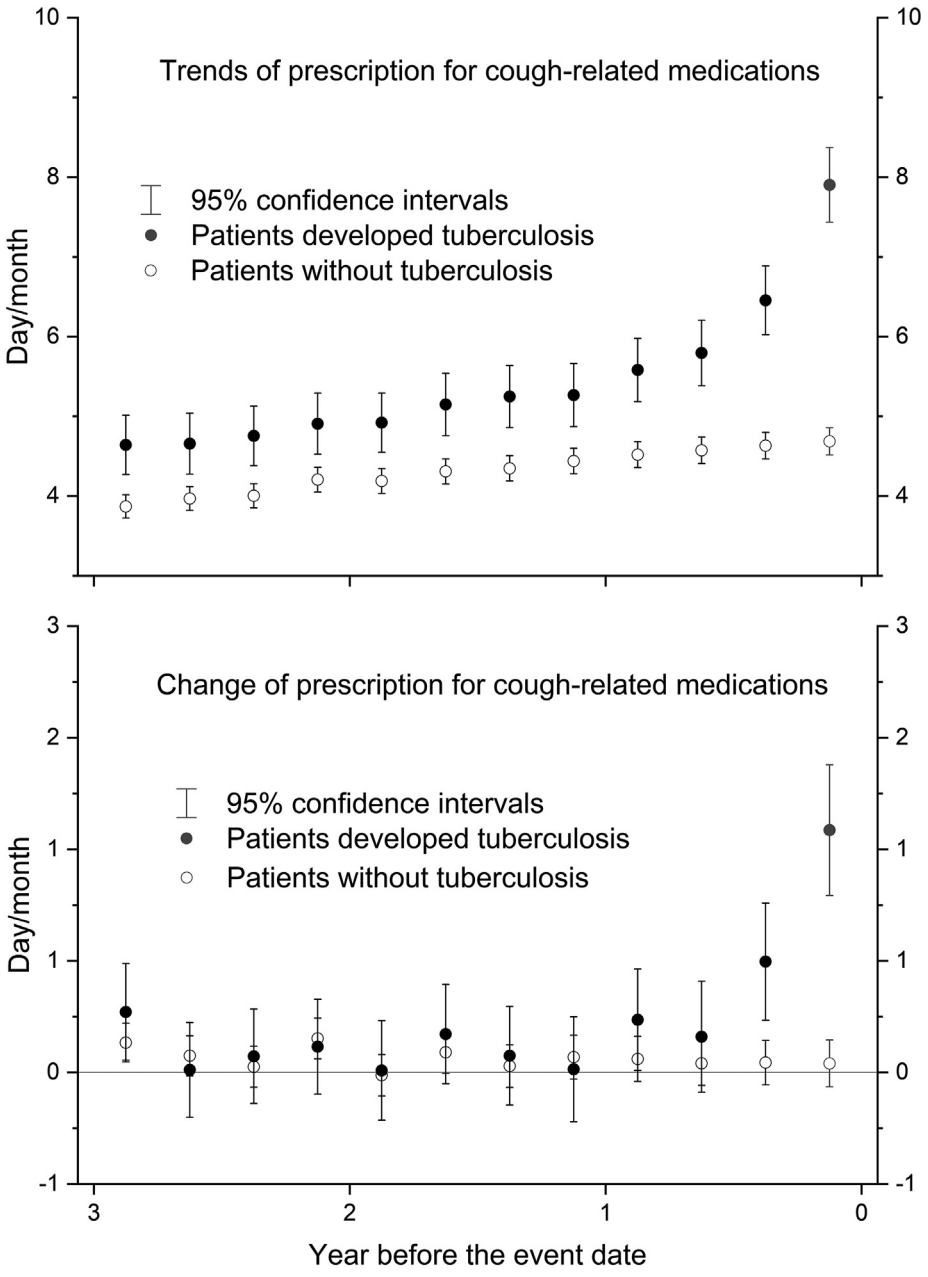

Figure 4. Trends of prescription for cough-related medications before the event date among patients with ESRD stratified by development of tuberculosis. Prescription of cough-related medications as a surrogate for the evolution of cough symptoms was aggregated every three months; the mean and 95% CI (days per month) are shown.

Declaration of competing interest

The authors declare no conflicts of interest, financial or otherwise.

Acknowledgements

The authors thank the National Health Research Institutes of Taiwan for granting us access to the National Health Insurance Research Database. This manuscript was edited by Wallace Academic Editing.

References

1. *Global tuberculosis report 2020*. Geneva: World Health Organization; 2020.
2. Vaziri ND, Pahl MV, Crum A, Norris K. Effect of uremia on structure and function of immune system. *J Ren Nutr* 2012;**22**:149—56.
3. Syed-Ahmed M, Narayanan M. Immune dysfunction and risk of infection in chronic kidney disease. *Adv Chron Kidney Dis* 2019; **26**:8—15.
4. Chou KJ, Fang HC, Bai KJ, Hwang SJ, Yang WC, Chung HM. Tuberculosis in maintenance dialysis patients. *Nephron* 2001; **88**:138—43.

5. Bai KJ, Huang KC, Lee CH, Tang CH, Yu MC, Sue YM. Effect of pulmonary tuberculosis on clinical outcomes of long-term dialysis patients: pre- and post-DOTS implementation in Taiwan. *Respirology* 2017;**22**:991—9.
6. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008;**3**:1526—33.
7. Ong CW, Elkington PT, Brilha S, Ugarte-Gil C, Tome-Esteban MT, Tezera LB, et al. Neutrophil-derived MMP-8 drives AMPK-dependent matrix destruction in human pulmonary tuberculosis. *PLoS Pathog* 2015;**11**:e1004917.
8. Min J, Kwon SK, Jeong HW, Han JH, Kim YJ, Kang M, et al. End-stage renal disease and risk of active tuberculosis: a nation-wide population-based cohort study. *J Kor Med Sci* 2018;**33**: e341.
9. Lin SY, Chiu YW, Yang HR, Chen TC, Hsieh MH, Wang WH, et al. Association of vitamin D levels and risk of latent tuberculosis in the hemodialysis population. *J Microbiol Immunol Infect* 2020; **54**(4):680—6. https://doi.org/10.1016/j.jmii.2020.06.001.
10. Passalent L, Khan K, Richardson R, Wang J, Dedier H, Gardam M. Detecting latent tuberculosis infection in hemodialysis patients: a head-to-head comparison of the T-SPOT.TB test, tuberculin skin test, and an expert physician panel. *Clin J Am Soc Nephrol* 2007;**2**:68—73.
11. Prasad N, Jha V. Hemodialysis in asia. *Kidney Dis* 2015;**1**: 165—77.
12. Chang YT, Hwang JS, Hung SY, Tsai MS, Wu JL, Sung JM, et al. Cost-effectiveness of hemodialysis and peritoneal dialysis: a national cohort study with 14 years follow-up and matched for comorbidities and propensity score. *Sci Rep* 2016;**6**:30266.
13. Lee CH, Wang JY, Lin HC, Lin PY, Chang JH, Suk CW, et al. Treatment delay and fatal outcomes of pulmonary tuberculosis in advanced age: a retrospective nationwide cohort study. *BMC Infect Dis* 2017;**17**:449.
14. Segall L, Covic A. Diagnosis of tuberculosis in dialysis patients: current strategy. *Clin J Am Soc Nephrol* 2010;**5**:1114—22.
15. Hung WT, Lee SS, Sy CL, Wu KS, Chen JK, Tsai HC, et al. Prevalence of latent tuberculosis infection in BCG-vaccinated healthcare workers by using an interferon-gamma release assay and the tuberculin skin test in an intermediate tuberculosis burden country. *J Microbiol Immunol Infect* 2015;**48**: 147—52.
16. Hu HY, Wu CY, Huang N, Chou YJ, Chang YC, Chu D. Increased risk of tuberculosis in patients with end-stage renal disease: a population-based cohort study in Taiwan, a country of high incidence of end-stage renal disease. *Epidemiol Infect* 2014; **142**:191—9.
17. Wang JY, Lee MC, Chang JH, Yu MC, Wu VC, Huang KL, et al. Mycobacterium tuberculosis nucleic acid amplification tests reduce nosocomial tuberculosis exposure in intensive care units: a nationwide cohort study. *Respirology* 2015;**20**:1233—40.
18. Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the national health insurance Research database (NHIRD). *Epidemiol Health* 2018;**40**:e2018062.
19. Hsing AW, Ioannidis JP. Nationwide population science: lessons from the taiwan national health insurance Research database. *JAMA Intern Med* 2015;**175**:1527—9.
20. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;**45**:613—9.
21. Tang CH, Wang CC, Chen TH, Hong CY, Sue YM. Prognostic benefits of carvedilol, bisoprolol, and metoprolol controlled release/extended release in hemodialysis patients with heart failure: a 10-year cohort. *J Am Heart Assoc* 2016;**5**.
22. Lee MC, Chiang CY, Lee CH, Ho CM, Chang CH, Wang JY, et al. Metformin use is associated with a low risk of tuberculosis among newly diagnosed diabetes mellitus patients with normal renal function: a nationwide cohort study with validated diagnostic criteria. *PloS One* 2018;**13**:e0205807.
23. Du CR, Wang SC, Yu MC, Chiu TF, Wang JY, Chuang PC, et al. Effect of ventilation improvement during a tuberculosis outbreak in underventilated university buildings. *Indoor Air* 2020;**30**:422—32.
24. Sreeramareddy CT, Panduru KV, Menten J, Van den Ende J. Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature. *BMC Infect Dis* 2009;**9**:91.
25. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989;**11**: 954—63.
26. Lee CH, Lee MC, Lin HH, Shu CC, Wang JY, Lee LN, et al. Pulmonary tuberculosis and delay in anti-tuberculous treatment are important risk factors for chronic obstructive pulmonary disease. *PloS One* 2012;**7**:e37978.
27. Sun HY, Wang JY, Chen YC, Hsueh PR, Chen YH, Chuang YC, et al. Impact of introducing fluorescent microscopy on hospital tuberculosis control: a before-after study at a high caseload medical center in Taiwan. *PloS One* 2020;**15**:e0230067.
28. Lin YJ, Lin HC, Yang YF, Chen CY, Ling MP, Chen SC, et al. Association between ambient air pollution and elevated risk of tuberculosis development. *Infect Drug Resist* 2019;**12**: 3835—47.
29. Lin HH, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. *Lancet* 2008;**372**:1473—83.
30. Campbell JR, Johnston JC, Ronald LA, Sadatsafavi M, Balshaw RF, Cook VJ, et al. Screening for latent tuberculosis infection in migrants with ckd: a cost-effectiveness analysis. *Am J Kidney Dis* 2019;**73**:39—50.
31. Ostermann M, Palchaudhuri P, Riding A, Begum P, Milburn HJ. Incidence of tuberculosis is high in chronic kidney disease patients in South East England and drug resistance common. *Ren Fail* 2016;**38**:256—61.
32. Li CY, Chen HC, Cheng HY, Chian CF, Chang FY, Chen HI, et al. Role of QuantiFERON-TB-Gold in Tube assay for active and latent tuberculosis infection in investigation of tuberculosis outbreak in a university. *J Microbiol Immunol Infect* 2015;**48**: 263—8.
33. Chiang C-Y. *Taiwan guidelines for TB diagnosis & treatment*. 6 ed. Taipei, Taiwan: Taiwan Centers for Disease Control; 2017.
34. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clin Microbiol Rev* 2018;**31**.
35. Moran E, Baharani J, Dedicoat M, Robinson E, Smith G, Bhomra P, et al. Risk factors associated with the development of active tuberculosis among patients with advanced chronic kidney disease. *J Infect* 2018;**77**:291—5.
36. Sloot R, Schim van der Loeff MF, Kouw PM, Borgdorff MW. Risk of tuberculosis after recent exposure. A 10-year follow-up study of contacts in Amsterdam. *Am J Respir Crit Care Med* 2014;**190**:1044—52.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.08.011.