บทความวิจัย

ปัจจัยที่มีความสัมพันธ์กับการเกิดวัณโรคในผู้ป่วยโรคไตเรื้อรัง: การศึกษาแบบเนสท์เตทเคสคอนโทรลของโรงพยาบาลเขตกรุงเทพมหานคร

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บทคัดย่อ

การศึกษานี้ มีวัตถุประสงค์เพื่อศึกษาปัจจัยที่มีความสัมพันธ์กับการเกิดวัณโรคในผู้ป่วยโรคไตเรื้อรัง รูปแบบการศึกษา Matched nested case-control เก็บข้อมูลจากโรงพยาบาลสังกัดสำนักการแพทย์ กรุงเทพมหานคร จำนวน 8 แห่ง จากทะเบียนผู้ป่วยโรคไตเรื้อรังอายุ 18 ปีขึ้นไป และไม่ได้เป็นวัณโรค โดยกลุ่มโรคที่เป็นกลุ่มศึกษา จำนวน 171 คน คือ ผู้ป่วยโรคไตเรื้อรังที่ได้รับการวินิจฉัยเป็นวัณโรคหลังจากขึ้นทะเบียนรักษา ไตเรื้อรัง และกลุ่มควบคุมคัดเลือกจาก Risk-set ของผู้ป่วยโรคไตเรื้อรังที่ขึ้นทะเบียนรักษาในปีเดียวกับกลุ่มศึกษาและมารับการตรวจรักษาในวันที่กลุ่มศึกษาได้รับการวินิจฉัย จับคู่ระหว่างคนที่เป็นโรคและกลุ่มควบคุมด้วยอายุและเพศ อัตราส่วน 1 ต่อ 1 เคส และคอนโทรล จำนวน 171 คู่ การวิเคราะห์สถิติเชิงพรรณนาด้วยความถี่ ร้อยละ Chi-square และวิเคราะห์ความสัมพันธ์ปัจจัยด้วย Conditional logistic regression นำเสนอด้วยค่า Adjusted Odds Ratio (ORadj) และช่วงความเชื่อมั่นที่ร้อยละ 95.0

ผลการศึกษา พบว่า ปัจจัยที่มีความสัมพันธ์กับการเกิดวัณโรคในผู้ป่วยโรคไตเรื้อรัง ได้แก่ ความรุนแรงของโรคไตเรื้อรังระยะที่ 3-5 (OR_{adj} = 8.40, 95% CI = 3.32-21.23) ระยะเวลาการป่วยโรคไตเรื้อรังจนถึงการวินิจฉัยวัณโรค 2-24 เดือน (OR_{adj} = 7.99, 95% CI = 3.85-16.61) และการฟอกไต (OR_{adj} = 5.08, 95% CI = 1.42-18.21) ดังนั้น ผู้ป่วยโรคไตเรื้อรังควรได้รับการตรวจคัดกรองวัณโรคอย่างสม่ำเสมอ โดยเฉพาะผู้ป่วยฟอกไตและผู้ป่วยโรคไตเรื้อรังที่ขึ้นทะเบียนรักษาในระยะ 1 ปี 6 เดือน เพื่อป้องกันการระบาดของวัณโรคในคลินิกโรคไตเรื้อรัง

คำสำคัญ: การฟอกไต โรคไตเรื้อรัง วัณโรค

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Risk factors associated with tuberculosis among patients with chronic kidney diseases: A hospital-based nested case-control study Bangkok Metropolitan, Thailand

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ABSTRACT

The study aimed to study tuberculosis-related factors among patients with chronic kidney disease (CKD). The matched nested case-control study was conducted in the cohort of chronic kidney disease patients from eight hospitals under the jurisdiction of the Medical Service Department, Bangkok. The CKD comprised CKD patients aged 18 and above, and free from tuberculosis. From the pool of CKD patients, 171 cases who developed tuberculosis after registration were selected. Controls were chosen from a risk-set of CKD patients who remained tuberculosis-free, registered in the same year, and visited the same hospital when a case was diagnosed. The 171 controls were matched one-to-one by sex and age. Descriptive statistics, namely frequency, percentage, and chi-square, were calculated. Conditional logistic regression was used to identify associated factors, and the results were presented in terms of adjusted odds ratio (OR_{adj}) and a 95% confidence interval (95% CI).

The study found that related factors for developing tuberculosis were CKD patients at stages 3-5 of severity (OR_{adj} = 8.40, 95% CI = 3.32-21.23) and the duration of CKD until tuberculosis diagnosis of 2-24 months (OR_{adj} = 7.99, 95% CI = 3.85-16.61), kidney dialysis (OR_{adj} = 5.08, 95% CI = 1.42-18.21). Patients with CKD should undergo regular screening for tuberculosis, especially those undergoing dialysis and patients who were registered not longer than 1 year and 6 months, to prevent the spread of tuberculosis in the kidney disease clinic.

Keywords: Dialysis, Chronic kidney disease, Tuberculosis

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Introduction

Chronic Kidney Disease (CKD) has become a major public health problem worldwide (Al-Efraij, Mota, Lunny, Schachter, Cook, & Johnston, 2015; Lv, & Zhang, 2019). In 2017, 697.5 million cases of all stages of CKD and 1.2 million deaths from CKD were reported globally that increased by 29.3% and 41.5% since 1990, respectively (Bikbov, Purcell, Levey, Smith, Abdoli, Abebe et al., 2020). The Thai Screening and Early Evaluation of Kidney Disease (SEEK) reported the prevalence of CKD in Thailand at 17.5% and the highest prevalence was in Bangkok (23.9%). Every year, 20,000 end-stage renal disease (ESRD) cases in Thailand require dialysis treatment. The incidence rate of hemodialysis was 187 permillion population/year and peritoneal dialysis was 159 per million population/year (Kanjanabuch & Takkavatakarn, 2020). It has widely known that CKD associated with human immunodeficiency frequently occurs among ESRD patients than in the general population (Pahl & Vaziri, 2015). Consequently, infections contribute significantly to co-morbidity and mortality in ESRD patients. Moreover, kidney dialysis induces inflammation and contributes to an altered immune system (Lamarche, Iliuta, & Kitzler, 2019). Tuberculosis is a common opportunistic disease among human immunodeficiency people in particular the high endemic area of tuberculosis (Castro, 1995; Ruangkanchanasetr et al., 2008)

In 2021, World Health Organization (WHO) reported 105,000 new tuberculosis cases and relapsed tuberculosis cases in Thailand (Ministry of Public Health, 2018). Several studied have confirmed that kidney dialysis is associated with an increased risk of tuberculosis and reported a greater risk than the general population (Al-Efraij et al., 2015; Min, Kwon, Jeong, Han, Kim et al., 2018; Yan, Puyat, Shulha, Clark, Levin, & Johnston, 2021). In United Kingdom study the overall incidence rate of tuberculosis in those without CKD and in those with CKD was 9.89 (7.96-2.30) and 14.63 (12.28-17.42) per 100,000-person-years, respectively (Ruzangi, Iwagami, Smeeth, Mangtani, & Nitsch, 2020). The factors related to tuberculosis in patients with CKD have been studied, but the findings have remained unclear (Cheng, Liao, Lin, Liu, & Lai, 2018). The treatment outcome of tuberculosis in CKD was poor in patients with a low estimated glomerular filtration rate (eGFR) of < 30 ml/min/1.73 m^2, as successful treatment was 20.0% and death was 50.0%. The treatment outcomes of CKD stages 4 and 5 were poor, with lower successful treatment and higher death rates (Igari, Imasawa, Noguchi, Nagayoshi, Mizuno, Ishikawa et al., 2015). In the country with high double burden of chronic diseases as CKD and infectious diseases as tuberculosis as Thailand, understanding the situation and related factors of tuberculosis would likely provide a crucial information for preventing and controlling tuberculosis among this immunity compromised CKD patients.

Although the association of risk factors in patients with CKD leading to tuberculosis had been studied, the findings remained unclear. Understanding the risk of infectious diseases such as tuberculosis among non-communicable chronic diseases such as CKD would have provided essential information for public health policy makers in the syndemic era.The results of this study provide valuable insights into the risk factors associated with tuberculosis development in patients with CKD. This information can be utilized to implement preventive measures and enhance

tuberculosis screening protocols specifically tailored for CKD patients. By identifying these risk factors, healthcare systems can expedite the process of admitting CKD patients into appropriate healthcare programs.

Objectives

To identify factors associated with tuberculosis among CKD patients in hospitals affiliated of Bangkok Metropolitan Administration.

Methods

This study applied a matched nested case-control design among the cohort of CKD patients aged 18 years old and above who were diagnosed with CKD stage 1-5 by physicians and registered in the hospital database of eight hospitals under jurisdiction of the Medical Service Department, Bangkok Metropolitan Administration from 1 January 2017 to 31 December 2021.

This research protocol was approved by the Ethical Review Committee for Human Research Faculty of Public Health, Mahidol University (Protocol no. MUPH 56/2022) and the Bangkok Metropolitan Administration Ethic Committee (Protocol no. U007h/65_EXP).

Population and sample

Cases were the CKD patients who were diagnosed with tuberculosis after the date of CKD diagnosis. Inclusion criteria of case were the CKD patients who diagnosed of tuberculosis either pulmonary or extrapulmonary tuberculosis from the eight study sites after date of CKD diagnosis and date of diagnosed of tuberculosis was available. Exclusion criteria were transferred-in and out tuberculosis cases were excluded. CKD-related variables are not recorded i.e. CKD treatment, stage of CKD. and the cases did not have matched controls.

Risk-set was the CKD patients registered in the same month, year, and hospital with the case and visited the clinic on the same date that the case was diagnosed with tuberculosis.

The inclusion criteria for controls were CKD patients in the same risk-set as the cases, who were not diagnosed with tuberculosis, and had the same age and sex as the corresponding case. The exclusion criteria included cases where CKD-related variables such as CKD treatment and stage of CKD were not recorded. One control was randomly selected from the risk-set and matched age and sex with cases in ratio of 1:1. In cases where more than one control was matched with a case, simple random sampling was used for control selection. Total of 171 case-control pairs were included and further analyzed. Sample Size (Fleiss, Levin, & Paik, 2013)

$$N = \frac{(M+1)[\frac{Z_{1-\alpha/2}(1+R)+2Z_{1-\beta}\sqrt{R}}{R-1}]^2}{2Mk(R+1)P(1-P)}$$

R = 2.47 (Odds ratio of dialysis exposure in cases relative to controls) (Shu, Hsu, Lee, Wang, Wu,Yang et al., 2015)

P = 0.10 (Probability of tuberculosis among non-dialysis patients)

M = 1 (Number of matched controls per case)

Z_{α} = 1.96 (Significance level 0.05)

Z_{β} = 1.28 (Power of test 0.80)

k = 1/[1+(R-1)P]

N = 152 + 10.0% of compensation for missing data

N case = 168 persons, N control = 168 person

The study included 171 participants per group as this was the number of cases that met the inclusion criteria when the data was exported. Therefore, the researcher selected all 171 cases to form the sample size.

Tools

Data of the patients who visited 8 selected hospitals during the study period were retrieved from the hospital information system called "E-PHIS" identified by ICD10. Case record forms were used to collect data of cases and controls from the E-PHIS. The data from the E-PHIS contained of personal characteristics, risk factors of CKD i.e. stage of CKD, comorbidity, and CKD treatment.

Data collection

The matched nested case-control study was conducted from July to December 2022. Data of cases and controls were recorded in the Hospital Information System called E-PHIS of all study sites. CKD cases by indicating ICD10 (N180-N184), pulmonary tuberculosis, ICD-10 (A15-A16), extrapulmonary tuberculosis ICD-10 (A17-A19), comorbidities i.e. diabetes ICD-10 (E10-E14), COPD, ICD-10 (J44-J449), HIV, ICD-10 (B20-B24), and types of CKD treatment were retrieved from the hospital information system. To retrieved data, we firstly selected tuberculosis cases among CKD cohort and then selected one CKD patient from risk-set with same age and sex with a case. Then we used the code of hospital number to retrieve study variables i.e. occupation, duration of CKD, stage of CKD, type of CKD treatment, and comorbidities.

Data analysis

Characteristics of cases and controls were described i.e. frequency, percentage, and mean (S.D.) The univariate analysis used for the differences of categorical data between case and control using Chi-square and 95% confidence interval were calculated using conditional logistic regression. p-value at < 0.05 considered statistically significant. The multiple conditional logistic regression was used to control other confounding factors as following steps: first step, only CKD-related factors were in the model. In the second step, we added personal characteristics, and in the final step added comorbidities. A p-value < 0.05 was considered statistically significant.

Comorbidities was categorized into 4 categories including: Tuberculosis-related disease means the CKD patients have a condition/preexisting disease related to tuberculosis, i.e. diabetes mellites (DM), chronic obstructive pulmonary disease (COPD) and human immunodeficiency virus. Non-tuberculosis-related disease means the CKD patients have the condition that is not related to tuberculosis, i.e. cardiovascular disease (CVD), hypertension (HT). and stroke. Combination group means the CKD patients have co-condition of illness related to Tuberculosis, i.e. DM, COPD. and HIV and not related to TB such as CVD, HT. and Stroke and no comorbidity means the CKD patients who did not have other preexisting diseases. Correlation matrix was used to check collinearity among independent factors, and found that strong correlation between "Stage of CKD" and "Dialysis" (Correlation = 0.587, p < 0.001). Then "Dialysis" was selected to add into the multiple conditional logistic regression.

Results

There were 7,058 CKD patient in the cohort met eligible criteria. Among this 7,058, 171 of cases and controls were selected matched by sex and age. Of 171 pair, 108 were males and mean age was 66.68 (S.D. = 13.56). Distribution of occupation between cases and control do not differ (p-value = 0.533). The findings revealed a higher percentage of CKD stages 3-5 among cases than controls (94.7% vs. 73.1%). (p-value < 0.001), a higher percentage of dialysis among cases than controls (24.6% vs. 12.3%). The difference was statistically

significant (p-value = 0.002). Higher percentage of cases among group of CKD duration 2-24 months than controls (69.0% vs. 26.9%). The difference was statistically significant (p-value < 0.001). The study results revealed a higher percentage of cases in the combination group compared to controls (46.1% vs. 36.4%) followed by not TB-related 46 cases and 56 controls (26.9% vs 32.6%, respectively) (p-value = 0.291) (Table 1).

Table1 Personal characteristics and CKD-related factors in case and control groups

Variable	Case (n = 171)		Control (n = 171)		p-value†
	n	%	n	%	
Sex					
Male	108	63.2	108	63.2	
Female	63	36.8	63	36.8	
Age (years)					
25-44	16	9.4	16	9.4	
45-64	52	30.4	52	30.4	
65 above	103	60.2	103	60.2	
Min-Max	28-93		28-93		
Mean ± S.D.	66.68 ± 13.56		66.68 ± 13.56		
Occupation					0.533
Housewives	33	19.3	39	22.8	
Government officer	11	6.5	11	6.5	
Merchant	13	7.6	12	7.1	
Employee	76	44.4	74	43.3	
No data	38	22.2	35	20.3	
Stage of CKD					< 0.001
Stage 1-2	9	5.3	46	26.9	
Stage 3-5	162	94.7	125	73.1	
Type of CKD treatment					0.002
Dialysis	42	24.6	21	12.3	
No dialysis	129	75.4	150	87.7	
Duration of CKD (month)					< 0.001
2-24 months	118	69.0	46	26.9	
25-60 months	53	30.1	125	73.1	
Min-Max	2-55	12-59			
Mean ± S.D.	18.35 ± 13.9		37.27 ± 14.6		

Table1 Personal characteristics and CKD-related factors in case and control groups (Continued)

Variable	Case (n = 171)		Control (n = 171)		p-value†
	n	%	n	%	
Comorbidity					0.291
No comorbidity	23	13.5	24	14.0	
No TB related	46	26.9	56	32.6	
TB related	23	13.5	29	17.0	
Combination	79	46.1	62	36.4	

Footnote: †p-value is calculated by Chi-square test and p-value < 0.05 is considered statistically significant.

The univariate analysis

There was a statistically significant association between the duration of CKD and tuberculosis (p-value < 0.001). Duration of CKD illness for 2-24 months has greater odds of tuberculosis (OR = 5.00, 95% CI = 3.01-8.29, p-value < 0.001). Similarly, CKD stage 3-5 has significantly greater odds of tuberculosis (OR = 8.40, 95% CI = 3.32-21.23, p-value < 0.001) than stage 1-2.CKD patients who under dialysis has greater odds of tuberculosis than non-dialysis patients (OR = 2.91, 95% CI = 1.47-5.78, p-value = 0.002). The association between occupation, comorbidity and tuberculosis was not statistically significant.

The multivariate analysis

In model 1, there was no statistically significant association observed between occupation and tuberculosis. In model 2, which added duration of 2-24 months and dialysis to the model, there was no statistically significant association observed between occupation and tuberculosis. In contrast, a significant association was observed for duration of 2-24 months (OR_{adj} = 7.45, 95% CI = 3.70-15.01, p-value < 0.001) and dialysis (OR_{adj} = 6.30, 95% CI =1.81-21.92, p-value = 0.004). In model 3, which added comorbidity to the model, the final model showed that duration of 2-24 months (OR_{adj} = 7.99, 95% CI = 3.85-16.61, p-value < 0.001) and dialysis (OR_{adj} = 5.08, 95% CI = 1.42-18.21, p-value = 0.013) were significant risk factors for tuberculosis. The combination group appeared to be not statistically significant (OR_{adj} = 1.98, 95% CI = 0.64-6.11, p-value = 0.236) (Table 2).

Table 2 The multivariate analysis for the association between risk factors and tuberculosis by controlling potential confounding factors

Variables	Model 1			Model 2			Model 3		
	OR_{adj}	95% CI	p-value	OR_{adj}	95% CI	p-value	OR_{adj}	95% CI	p-value
Occupation									
Housewives	1			1			1		
Government officer	1.32	0.39-4.48	0.651	1.31	0.26-6.62	0.746	1.39	0.26-7.42	0.698
Merchant	1.27	0.42-3.81	0.675	1.20	0.29-5.03	0.801	1.31	0.29-5.83	0.724
Employee	1.17	0.57-2.41	0.671	1.02	0.38-2.73	0.969	1.16	0.41-3.27	0.780
Duration of CKD									
2-24 months				7.45	3.70-15.01	< 0.001	7.99	3.85-16.61	< 0.001
Dialysis				6.30	1.81-21.92	0.004	5.08	1.42-18.21	0.013
Comorbidity									
No comorbidity							1		
No TB related							1.080	0.34-3.45	0.896
TB related							1.00	0.23-4.42	0.999
Combination							1.98	0.64-6.11	0.236

Footnote: Matched by age, sex, and time at risk. Occupation compared with housewives. Duration compared with 25-60 months. Dialysis compared with no dialysis. Comorbidity compared with no comorbidity.

†Model 1 contained of occupation.

‡Model 2 contained of occupation, duration of CKD, and dialysis.

††Model 3 contained of occupation, duration of CKD, dialysis, and comorbidity.

Discussion and Conclusion

Tuberculosis risk among CKD patients is more significant than normal kidney function. The coexistence of systemic inflammation and immunocompromised are the common implication of the uremic state (Bandiara, Indrasari, Dewi Rengganis, Sukesi, Afiatin, et al., 2022). Our study included housewives, government officers, merchants, and employees in both the case and control groups. We found no statistically significant difference in the incidence of tuberculosis between CKD patients (p-value = 0.533). In a study examining risk factors for tuberculosis infection among household contacts in Bangkok, occupation (unemployed, officer, laborer, and merchant) was not significantly associated with the presence of tuberculosis symptoms (Tornee, Kaewkungwal, Fungladda, Silachamroon, Akarasewi, & Sunakorn, 2004). However, a study in Saudi Arabia found that the incidence rate was highest among workers in basic engineering, followed by the agriculture, animal husbandry, fishing, and services. Certain occupations may be associated with exposure to silica dust, which can lead to the development of silicosis and silico-tuberculosis (Semilan, Abugad, Mashat, & Abdel Wahab, 2021). The findings of this study suggested that occupational exposure may not have been a significant risk factor for tuberculosis infection in CKD patients. However, the results of studies conducted in different regions and populations may have varied. Comorbidity was not associated with tuberculosis. In contrast, a previous study showed that diabetes is a common risk factor for acquiring LTBI or developing active tuberculosis (Moran, Baharani, Dedicoat, Robinson, Smith, Bhomra et al., 2018) COPD and HIV were found to have risk factor for developing tuberculosis (Park, Lee, Kim, Lee, Kang, Cho et al., 2019; Romanowski, Clark, Levin, Cook, & Johnston, 2016). DM is also an independent risk factor for lower respiratory tract infections and predisposes individuals to a higher risk of severe complications. Increased levels of pro-inflammatory cytokines are correlated with increased blood glucose levels, and a delayed adaptive immune response (Cheng, Wang, & Gong, 2022). Multiple diseases and frequent use of medication among patients with chronic diseases can result in lowered immunity and increased susceptibility to tuberculosis infection.

The average duration of tuberculosis development was 18.35 months after CKD diagnosed. In the previous study in England, the median time from diagnosis was 12 months (range 0-192 months) (Ostermann, Palchaudhuri, Riding, Begum, & Milburn, 2016). Most patients who contracted tuberculosis did so within the first year of dialysisinitiation (Ali, Dosani, Corbett, Johansson, Charif, Kon et al., 2022).

Stage CKD which had stage 3-5, had the highest risk compared to stage 1-2. It also reported that the risk of tuberculosis increased in patients with CKD stage 3 or above (Shu et al., 2015). Similarly, in the study in Taiwan. The incidence of tuberculosis development tends to increase in patients with a decline in kidney function of CKD stage 3 and beyond, possibly due to the impact on immune function, oxidative stress, and inflammation resulting from reduced renal clearance of toxins. Additionally, Vitamin D insufficiency, which is prevalent among CKD and dialysis patients, may lead to immune dysfunction. The attenuation of immune cells like T cells, B cells, and natural killer cells typically starts in stage 3 CKD, along with a significant buildup of waste products (Shu et al., 2015). Patients with stage 3 or above and dialysis are likely to

develop tuberculosis, mainly because of the impaired cellular immunity characteristic of this condition. Multiple diseases and the often-used drug among patients were the reason for low immunity, and they became susceptible to tuberculosis infection.

This study found higher risk of tuberculosis among dialysis CKD patients. From previous studies, dialysis has a high risk of increased rate ratio of 7.7 compared with the general population (Romanowski et al., 2016). South Africa showed a high incidence of 4.1 times that of the local population (Ndamase, Okpechi, Carrara, Black, Calligaro, & Freercks, 2020). Going in London, it was also found that the risk increased 85-fold in hemodialysis patients and 26-fold in peritoneal dialysis patients (Ostermann, Palchaudhuri, Riding, Begum, & Milburn, 2016). In our study, dialysis had the highest risk compared to no dialysis (OR_{adj} = 6.30, 95% CI = 1.81-21.92). The finding can likely be explained by the condition of impaired cellular immunity suppresses the mitogenic response of lymphocytes among the patients with ESRD. Protein malnutrition, zinc, and pyridoxine deficiency, and defects in leukocyte function following exposure to dialysis membranes increase the susceptibility of dialysis patients to tuberculosis (Vikrant, 2019).

Suggestions

Suggestions for applying the research results

The more effective surveillance system to have routine screening in the study suggested the need for aggressive and routine diagnostic measures, including Xpert MTB/RIF tests, among early CKD and those under dialysis. It was essential to make an early diagnosis for instituting timely and appropriate therapy and preventing TB transmission among this vulnerable group. The factors found to be associated with the occurrence of tuberculosis in patients with CKD can be utilized to develop guidelines for prevention and screening of tuberculosis in CKD patients. Additionally, these findings can be incorporated into collaborative programs with the results of other research studies to prevent tuberculosis infection in CKD patients.

Suggestions for future research

The future studies could be designed to include variables such as salary and living with tuberculosis patients to gain a more complete picture of the factors associated with the disease.

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