International Journal of Infectious Diseases 84 (2019) 127–130

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Post-tuberculosis incidence of diabetes, myocardial infarction, and stroke: Retrospective cohort analysis of patients formerly treated for tuberculosis in Taiwan, 2002–2013

Argita D. Salindri[a,*], Jann-Yuan Wang[b], Hsien-Ho Lin[c], Matthew J. Magee[a]

[a] Division of Epidemiology and Biostatistics, School of Public Health, Georgia State University, Atlanta, GA, USA
[b] Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[c] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 28 March 2019
Received in revised form 3 May 2019
Accepted 7 May 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Diabetes
Myocardial infarction
Stroke
Incidence

ABSTRACT

Objectives: To estimate the incidence of diabetes, acute myocardial infarction (AMI), and stroke; and to determine factors associated with diabetes, AMI, and stroke incidence among patients previously treated for tuberculosis (TB) disease.
Methods: A retrospective cohort study was conducted among non-pediatric TB patients registered in the Taiwan National Health Insurance Research Database (NHIRD) from 2002–2013. Diabetes, AMI, and stroke incidence were defined by International Classification of Diseases (ICD)-9 codes, drug prescriptions, and records of patient's clinic visits. Cox proportional hazard models were used to estimate the hazard rate ratio (HR) of incident diabetes, AMI, and stroke.
Results: From 2002–2013, there were 157,444 patients treated for TB registered in NHIRD. Among 129,453 patients with no prior history of diabetes, the age-adjusted incidence rate (IR) of diabetes was 3.85 (95%CI 3.70–4.01) per 1000 person-years. Among 143,646 patients with no prior history of AMI, the age-adjusted IR of AMI as 3.26 (95%CI 3.13–3.40). Among 118,774 patients with no prior history of stroke, the age-adjusted IR of stroke was 16.08 (95%CI 15.76–16.32).
Conclusions: Chronic non-communicable disease risk factors like dyslipidemia, hypertension, and chronic kidney disease diagnosed before time of TB diagnosis were predictive of diabetes, AMI, and stroke incidence.

Introduction

Increasing evidence suggest that tuberculosis (TB) disease may disrupt host metabolism and contribute to subsequent risks of chronic non-communicable diseases (NCDs) (Huaman et al., 2017, Kamper-Jorgensen et al., 2015, Sheu et al., 2010). Importantly, the majority of TB patients reside in low- and middle-income countries where chronic NCDs such as type-2 diabetes (diabetes), acute myocardial infarction (AMI), and stroke are increasingly threatening public health achievements (Gaziano et al., 2010).

Diabetes is a well-established risk factor for TB infection (Lee et al., 2017), TB disease, and poor TB treatment outcomes (Riza et al., 2014). However, epidemiologic data to support the relationship between TB and risk of NCDs are scarce. *Chlamydia pneumoniae*, *Helicobacter pylori*, influenza, and HIV are associated with cardiovascular disease risk, likely due to chronic systemic inflammation that can lead to atherosclerotic lesions (Huaman et al., 2015). However, whether individual-level TB risk factors (e.g., comorbidities, treatment duration, site of infection) increase the risk of post-infection incident NCDs is unknown. Therefore, among a large cohort of patients post-TB treatment, we aimed to estimate the incidence rates of diabetes, AMI, and stroke and to determine characteristics associated with these incident NCDs.

Methods

We conducted a cohort study among patients formerly treated for TB disease using data from the Taiwan National Health Insurance Research Database (NHIRD) during 2002–2013. NHIRD is maintained by the National Health Research Institute and contains original registration and insurance claim data from the single-payer national

* Corresponding author at: Division of Epidemiology and Biostatistics, Georgia State University School of Public Health, Urban Life Building Suite 433, 140 Decatur St SE, Atlanta, GA 30303, USA.
E-mail address: asalindri1@student.gsu.edu (A.D. Salindri).

https://doi.org/10.1016/j.ijid.2019.05.015

health insurance system which covers 99.9% of the Taiwanese population.

Eligible patients included those with non-pediatric active TB disease (≥15 years old for DM study; ≥25 years old for AMI and stroke studies) confirmed by ICD-9 codes (010-018) and prescriptions of anti-TB drugs for ≥28 days within a year. The earliest date of TB diagnosis indicated by ICD-9 codes was defined as the TB date. Patients with ICD-9 diagnoses of diabetes, AMI, or stroke on or before date of TB disease were excluded. Incident diabetes was defined as patients who received anti-diabetes drug prescriptions for ≥28 days within a year and a confirmed diabetes ICD-9 (250.X0 or 250.X2) first indicated ≥2 years after TB date. Incident AMI (ICD-9 410.XX) and stroke (ICD-9 430.XX - 438.XX) were defined by ICD-9 codes and ≥3 out-patient clinic visits or 1 hospitalization indicated ≥1 year after TB date. Other comorbidity characteristics including dyslipidemia, hypertension, overweight, HIV, and chronic kidney diseases (CKD) were determined by ICD-9 codes. We calculated incidence of diabetes, AMI, and stroke using Poisson regression, and proportional hazards regression was used to estimate relative hazards of NCDs incidence. Incidence rates (IR) were presented per 1000 person-years. Patients were censored if they left the insurance system or did not develop diabetes, AMI, or stroke by the end of follow-up (December 2013).

Results

During the study period, there were 157,444 patients treated for TB disease and 1315 were <15 years and excluded. Among adult TB cases, 82.9% (129,453/156,129) patients did not have prior diabetes diagnosis; 98.0% (143,678/146,646) did not have prior history of AMI; and 81.0% (118,774/146,646) did not have prior stroke diagnosis (Supplemental Material 1) and were included. Among those without preexisting diabetes, 2479 incident diabetes diagnoses occurred during 643,754 person-years (age-adjusted IR 3.85, 95%CI 3.70–4.01) (Table 1). The median time of incident diabetes post TB date was 7 years (IQR 5–9) (Supplemental

Table 1
Incidence rates of diabetes, acute myocardial infarction (AMI), and stroke among a cohort of patients formerly treated for tuberculosis, Taiwan National Health Insurance Research Database (NHIRD), 2002–2013.

Characteristics	Diabetes		AMI		Stroke	
	N (%) = 2479 (1.97%)		N (%) = 2287 (1.59%)		N (%) = 9539 (8.08%)	
	Total PTY = 643754		Total PTY = 700890		Total PTY = 596395	
	Overall IR = 3.85 (3.70–4.01)		Overall IR = 3.26 (3.13–3.40)		Overall IR = 15.99 (15.68–16.32)	
	N/PTY	IR (95% CI)	N/PTY	IR (95% CI)	N/PTY	IR (95% CI)
Age group						
15–24	14/55138	0.25 (0.15–0.43)	Excluded	N/A	Excluded	N/A
25–44	344/151792	2.27 (2.04–2.52)	68/162616	0.42 (0.33–0.53)	530/159684	3.32 (3.05–3.61)
45–64	959/179001	5.36 (5.03–5.71)	663/229965	2.88 (2.67–3.11)	2788/211591	13.18 (12.70–13.67)
≥65	1162/257823	4.51 (4.26–4.77)	1556/308309	5.05 (4.80–5.30)	6275/225120	27.87 (27.19–28.57)
Gender						
Female	639/217826	2.93 (2.72–3.17)	490/223450	2.19 (2.01–2.40)	2447/194418	12.59 (12.10–13.09)
Male	1840/422458	4.36 (4.16–4.56)	1797/474570	3.79 (3.62–3.97)	7146/399157	17.90 (17.49–18.32)
Unknown	0/3470	N/A	0/2870	N/A	0/2820	N/A
TB site						
Pulmonary	2145/547526	3.92 (3.76–4.09)	2001/600655	3.33 (3.19–3.48)	8331/512211	16.26 (15.92–16.62)
Extrapulmonary	320/91256	3.51 (3.14–3.91)	264/94947	2.78 (2.47–3.14)	1206/79812	15.11 (14.28–15.99)
Miliary	14/4972	2.82 (1.67–4.75)	22/5288	2.74 (2.74–6.32)	56/4372	12.81 (9.86–16.64)
TB treatment duration						
≤6 months	1749/469072	3.73 (3.56–3.91)	1564/504205	3.10 (2.95–3.26)	6698/428522	15.63 (15.26–16.01)
7–12 months	668/159157	4.20 (3.89–4.53)	656/178856	3.67 (3.40–3.96)	2633/152429	17.27 (16.63–17.95)
>12 months	62/15525	3.99 (3.11–5.12)	67/17829	3.76 (2.96–4.78)	262/15444	16.96 (15.03–19.15)
Dyslipidemia[a]						
No	2108/574547	3.67 (3.52–3.83)	1766/599014	2.95 (2.81–3.09)	7900/518986	15.22 (14.89–15.56)
Yes	371/69207	5.36 (4.84–5.94)	521/101876	5.11 (4.69–5.57)	1693/77409	21.87 (20.85–22.94)
Hypertension[a]						
No	1410/448700	3.14 (2.98–3.31)	917/444348	2.06 (1.93–2.20)	4795/415207	11.55 (11.23–11.88)
Yes	1069/195054	5.48 (5.16–5.82)	1370/256542	5.34 (5.07–5.63)	4798/181188	26.48 (25.74–27.24)
Overweight[a]						
No	2456/641308	3.83 (3.68–3.98)	2276/697646	3.26 (3.13–3.40)	9554/593576	16.10 (15.78–16.42)
Yes	23/2446	9.40 (6.25–14.15)	11/3244	3.39 (1.88–6.12)	39/2819	13.83 (10.11–18.94)
HIV[a]						
No	2474/639526	3.87 (3.72–4.02)	2276/696710	3.27 (3.14–3.41)	9579/592428	16.17 (15.85–16.50)
Yes	5/4228	1.18 (0.49–2.84)	8/4180	1.91 (0.96–3.83)	14/3967	3.53 (2.09–5.96)
CKD[a]						
No	2378/612063	3.89 (3.73–4.05)	1985/660103	3.01 (2.88–3.14)	8870/567777	15.62 (15.30–15.95)
Yes	101/31691	3.19 (2.62–3.87)	302/40787	7.40 (6.62–8.29)	723/28618	25.26 (23.49–27.17)
Diabetes[a]	Excluded					
No			1512/582699	2.60 (2.47–2.73)	7183/502688	14.29 (13.96–14.62)
Yes			775/118191	6.56 (6.11–7.04)	2410/93707	25.72 (24.71–26.77)
Myocardial infarction[a]			Excluded			
No	2457/637226	3.86 (3.71–4.01)			9453/590847	16.00 (15.68–16.32)
Yes	22/6528	3.37 (2.22–5.12)			140/5548	25.23 (21.38–29.78)
Stroke[a]						
No	2133/563277	3.79 (3.63–3.95)	1707/598831	2.85 (2.72–2.99)	Excluded	
Yes	346/80477	4.30 (3.87–4.78)	580/102059	5.68 (5.24–6.17)		

Notes:
Abbreviation: AMI – Acute Myocardial Infarction; IR – incidence rate; CI – Confidence Interval; PTY – person time in years.
[a] Comorbidities (i.e., dyslipidemia, hypertension, overweight, HIV, and chronic kidney disease) were diagnosed earlier or at the time of TB diagnosis.

Table 2
Adjusted Cox regression model[a] to predict post-tuberculosis incident diabetes, acute myocardial infarction (AMI), and stroke, Taiwan National Health Insurance Research Database (NHIRD), 2002–2013.

Characteristics	Diabetes aHR[c] (95% CI)	AMI aHR[c] (95% CI)	Stroke aHR[c] (95% CI)
Age group			
15–24	**0.11 (0.07–0.19)**	Excluded	Excluded
25–44	Ref	Ref	Ref
45–64	**1.96 (1.73–2.23)**	**4.72 (3.67–6.08)**	**3.11 (2.83–3.42)**
≥65	**1.66 (1.46–1.90)**	**8.01 (6.24–10.28)**	**6.57 (6.00–7.20)**
Gender			
Female	Ref	Ref	Ref
Male	**1.36 (1.24–1.49)**	**1.57 (1.42–1.74)**	**1.28 (1.22–1.34)**
TB site			
Pulmonary	Ref	Ref	Ref
Extrapulmonary	0.93 (0.82–1.04)	0.90 (0.79–1.02)	1.00 (0.94–1.07)
Miliary	0.82 (0.48–1.38)	1.30 (0.86–1.98)	0.82 (0.63–1.06)
TB treatment duration			
≤6 months	Ref	Ref	Ref
7–12 months	1.05 (0.96–1.14)	1.09 (0.99–1.19)	1.03 (0.99–1.08)
>12 months	0.78 (0.61 – 1.01)	1.03 (0.81 – 1.32)	0.89 (0.78 – 1.00)
Dyslipidemia[b]			
No	Ref	Ref	Ref
Yes	**1.41 (1.25–1.58)**	**1.29 (1.17–1.43)**	**1.20 (1.13–1.27)**
Hypertension[b]			
No	Ref	Ref	Ref
Yes	**1.78 (1.62–1.94)**	**1.70 (1.54–1.86)**	**1.67 (1.60–1.75)**
Overweight[b]			
No	Ref	Ref	Ref
Yes	**2.67 (1.76–4.03)**	1.08 (0.60–1.95)	0.98 (0.72–1.35)
HIV[b]			
No	Ref	Ref	Ref
Yes	0.44 (0.18–1.06)	1.81 (0.90–3.64)	0.62 (0.36–1.04)
CKD[b]			
No	Ref	Ref	Ref
Yes	**0.78 (0.64–0.96)**	**1.86 (1.65–2.11)**	**1.26 (1.17–1.36)**
Diabetes[b]	Excluded		
No		Ref	Ref
Yes		**1.96 (1.79–2.14)**	**1.47 (1.40–1.54)**
Myocardial infarction[b]		Excluded	
No	Ref		Ref
Yes	0.84 (0.55–1.28)		1.05 (0.89–1.24)
Stroke[b]			Excluded
No	Ref	Ref	
Yes	0.96 (0.85–1.08)	**1.24 (1.12–1.37)**	

Abbreviation: AMI – Acute Myocardial Infarction; IQR – interquartile range; CHR – Crude hazard ratio; AHR – Adjusted Hazard Ratio; CI – Confidence Interval; TB – Tuberculosis.
Bold indicates statistical significance (two-sided P-value <0.05).
[a] Proportional hazard assumption was assessed using Schoenfeld's residual and log of negative log curve.
[b] Comorbidities (i.e., dyslipidemia, hypertension, overweight, HIV, and chronic kidney disease) were diagnosed earlier or at the time of TB diagnosis.
[c] Hazard Ratios after adjusting for age, gender, type of TB, anti TB treatment duration, dyslipidemia, hypertension, and chronic kidney disease status.

Material 2). In the adjusted model, TB patients with pre-existing dyslipidemia (adjusted hazard ratio [aHR] 1.41; 95%CI 1.25–1.58), hypertension (aHR 1.78, 95%CI 1.62–1.94), and overweight (aHR 2.67, 95%CI 1.76–4.03) had increased risk of diabetes post-TB treatment (Table 2).

The age-adjusted IR of AMI was 3.26 (95%CI 3.13–3.40), and 16.08 (95%CI 15.76–16.32) for stroke. The median time of incident AMI and stroke post-TB date was 6 years (IQR 3–8) and 6 years (IQR 3–9), respectively. In the adjusted models, factors predictive of incident AMI and stroke included pre-existing dyslipidemia (aHR AMI 1.29, 95%CI 1.17–1.43; aHR stroke 1.20, 95%CI 1.13–1.27), hypertension (aHR AMI 1.70, 95%CI 1.54–1.86; aHR stroke 1.67, 95% CI 1.60–1.75), CKD (aHR AMI 1.86, 95%CI 1.65–2.11; aHR stroke 1.26, 95%CI 1.17–1.36), and diabetes (aHR AMI 1.96, 95%CI 1.79–2.14; aHR stroke 1.47, 95%CI 1.40–1.54).

Discussion

Our preliminary findings suggest that older age, male gender, and traditional pre-existing chronic NCDs are predictive of diabetes, AMI, and stroke incidence post-TB treatment. Although overall TB treatment duration was not predictive of diabetes, AMI, and stroke incidence, we found that patients treated for 7–12 months had higher incidence of NCDs compared to those treated for ≤6 months. Furthermore, our incidence estimation of diabetes, AMI, and stroke were higher when compared to previous Taiwanese national estimates using NHIRD database. For example, the annual age-standardized incidence rate of diabetes was <1% across Taiwanese population (Jiang et al., 2012). Additionally, the age and gender-adjusted incidence of AMI was 50.7/100,000 persons in 2015 (Lee et al., 2018) and the estimated stroke incidence was 12.3/1000 person-years (Chan et al., 2018). Our results highlight the need for studies to determine the impact of TB disease on risk of NCDs; such studies will require substantial follow-up time and a control group without TB disease.

Author contributions

ADS, MJM, and HHL conceived the study design. JYW obtained the data. ADS and MJM performed the analyses and wrote the

initial draft. All authors contributed to the interpretation of study findings and revised the manuscript. All authors approved of the final manuscript.

Conflict of interest

We have no conflict of interest to declare.

Acknowledgements

This work is supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health [grant number R03AI133172 to M.J.M]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We would like to thank Miss Chih-Hui Wang, MPH and Miss Chieh-Yin Wu, MPH (National Taiwan University College of Public Health) for their assistance in the data abstraction and feedback during the initial data analyses phase.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.05.015.

References

Chan PC, Chang WL, Hsu MH, Yeh CH, Muo CH, Chang KS, et al. Higher stroke incidence in the patients with pancreatic cancer: a nation-based cohort study in Taiwan. Medicine 2018;97(11):e0133.

Gaziano TA, Bitton A, Anand S, Abrahams-Gessel S, Murphy A. Growing epidemic of coronary heart disease in low- and middle-income countries. Curr Probl Cardiol 2010;35(2):72–115.

Huaman MA, Henson D, Ticona E, Sterling TR, Garvy BA. Tuberculosis and cardiovascular disease: linking the epidemics. Trop Dis Travel Med Vaccin 2015;1:.

Huaman MA, Kryscio RJ, Fichtenbaum CJ, Henson D, Salt E, Sterling TR, et al. Tuberculosis and risk of acute myocardial infarction: a propensity score-matched analysis. Epidemiol Infect 2017;145(7):1363–7.

Jiang YD, Chang CH, Tai TY, Chen JF, Chuang LM. Incidence and prevalence rates of diabetes mellitus in Taiwan: analysis of the 2000-2009 Nationwide Health Insurance database. J Formos Med Assoc 2012;111(11):599–604.

Kamper-Jorgensen Z, Carstensen B, Norredam M, Bygbjerg IC, Andersen PH, Jorgensen ME. Diabetes-related tuberculosis in Denmark: effect of ethnicity, diabetes duration and year of diagnosis. Int J Tuberc Lung Dis 2015;19(10):1169–75.

Lee CH, Fang CC, Tsai LM, Gan ST, Lin SH, Li YH. Patterns of acute myocardial infarction in Taiwan from 2009 to 2015. Am J Cardiol 2018;122(12):1996–2004.

Lee MR, Huang YP, Kuo YT, Luo CH, Shih YJ, Shu CC, et al. Diabetes mellitus and latent tuberculosis infection: a systemic review and metaanalysis. Clin Infect Dis 2017;64(6):719–27.

Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B, van de Vijver S, Panduru NM, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrinol 2014;2(9):740–53.

Sheu JJ, Chiou HY, Kang JH, Chen YH, Lin HC. Tuberculosis and the risk of ischemic stroke: a 3-year follow-up study. Stroke 2010;41(2):244–9.