Exploring the risk of cardiovascular disease due to latent tuberculosis infection in a low tuberculosis incidence setting: a population-based cohort study

Md. Belal Hossain *, James C. Johnston, Hubert Wong, Mohsen Sadatsafavi, Victoria J. Cook, Mohammad Ehsanul Karim

*Correspondence to: Md. Belal Hossain; Email: belal.hossain@ubc.ca

Abstract

Background: We investigated the risk of cardiovascular disease (CVD) associated with latent tuberculosis infection (LTBI) (Aim 1) and LTBI therapy (Aim 2) in British Columbia, where tuberculosis (TB) incidence is low, and 86% of people with TB are born outside of Canada.

Methods: Using linked immigration, public health surveillance, and health administrative databases, we developed a population-based retrospective cohort of immigrants between 1985 and 2019. A total of 49,197 participants had valid LTBI test results. The Cox proportional hazards model was fitted, adjusting for potential confounders.

Results: Compared to the participants who tested LTBI negative, LTBI positive was associated with an 11% higher CVD risk (adjusted hazard ratio [aHR]: 1.11, 95% CI: 1.02-1.20). A significant 10% higher CVD risk was also observed when additional proxy variables supplementing known unmeasured confounders were incorporated in the high-dimensional disease risk score technique to reduce residual confounding (aHR: 1.10, 95% CI: 1.01-1.20). In Aim 2, compared to participants who tested negative, CVD risk was 27% higher among people who were LTBI positive but did not complete LTBI therapy (aHR: 1.27, 95% CI: 1.04-1.55), while the risk was similar in people who completed LTBI therapy (aHR: 1.04, 95% CI: 0.87-1.24). Findings were consistent in different sensitivity analyses.

Conclusion: LTBI is associated with an increased CVD risk in a low-tuberculosis-incidence setting, with a higher risk associated with incomplete LTBI therapy and attenuated risk when therapy is completed.

Summary of the poster

Aims

The aims of this study were two-fold. First, we explored whether LTBI is associated with an increased risk of CVD among people who immigrated to British Columbia, Canada. Second, we investigated the risk of CVD associated with the completion of LTBI therapy.

Study setting

This study is part of a larger project describing TB among foreign-born people immigrating to British Columbia [1]. For the present study, we developed a retrospective cohort of immigrants in British Columbia between 1 January 1985 and 31 December 2019. The cohort was developed based on linked immigration, public health surveillance, and health administrative databases that consist of approximately 1.4 million individuals. Data elements include immigration information, demographics, Vital Statistics (deaths in BC), Medical Services Plan (registration and physician billings), Hospital Discharge Abstract Database (inpatients and day surgeries), Statistics Canada Census (neighbourhood income quintiles), and provincial disease registries, including the Provincial TB Registry [2–10]. The setting, cohort construction, and data linkage have been described elsewhere [1].

Participants

The participants in this study were foreign-born people tested for LTBI using a tuberculin skin test (TST) or interferon-gamma release assay (IGRA), as coded in the provincial TB registry. We excluded participants without valid TST or IGRA test results (Figure 1). The cohort entry date was set to one year after the date of residency in British Columbia was established. The date of residency was defined as 90 days before provincial health insurance coverage started or the first contact with the healthcare system [1].

Exposures

The binary LTBI status (positive/negative) is the exposure of interest for Aim 1. Participants were classified as LTBI positive if they tested positive on TST alone or IGRA. Participants were classified as LTBI negative if they were negative on both TST and IGRA, negative on TST alone, negative on IGRA alone, and positive on TST but negative on IGRA [11]. We considered induration size ≥10 mm as TST positive and TB antigen ≥0.35 IU/ml as IGRA positive [11,12].

The exposure variable for Aim 2 was LTBI therapy, classified as LTBI negative, LTBI positive with incomplete LTBI therapy, and LTBI positive with completed LTBI therapy. A participant would have been classified as completed LTBI therapy if they received an adequate regimen of LTBI treatment as defined by the provincial TB registry [13].

Outcome

The outcome variable was the time from cohort entry date to the first occurrence of a CVD event (either ischemic heart disease or stroke). The follow-up was censored at emigration, death, or study end (31 December 2019). The CVD events were identified from hospital separations, outpatient physician claims, and vital statistics deaths databases [14].

Confounders

All covariates were defined using a one-year covariate assessment window, which began on the date residency in British Columbia was established and ended 365 days later. The following covariates were identified as potential confounders: age at immigration, sex, income, education, World Health Organization (WHO) region of birth, immigration class, smoking, alcohol use disorder, substance use disorder, hypertension, diabetes, chronic kidney disease, obesity, HIV/AIDS, and dyslipidemia [15–20].

References

1. Ronald LA, Campbell JR, Balshaw RF, et al. Predicting tuberculosis risk in the foreign-born population of British Columbia, Canada: Study protocol for a retrospective population-based cohort study. BMJ Open **2016**; 6:1–8.
2. British Columbia Ministry of Health [creator]. Vital Events Deaths. V2. Population Data BC [publisher]. Data Extract. MOH(2015). 2017. Available at: https://www.popdata.bc.ca/data. Accessed 22 October 2021.
3. British Columbia Ministry of Health [creator]. Consolidation File (MSP Registration & Premium Billing). V2. Population Data BC [publisher]. Data Extract. MOH(2015). 2017. Available at: https://www.popdata.bc.ca/data. Accessed 22 October 2021.
4. Canadian Institute for Health Information [creator]. Discharge Abstract Database (Hospital Separations). V2. Population Data BC [publisher]. Data Extract. MOH(2015). 2017. Available at: https://www.popdata.bc.ca/data. Accessed 22 October 2021.
5. BC Ministry of Health [creator]. PharmaNet. BC Ministry of Health [publisher]. Data Extract. Data Stewardship Committee (2014). 2015. Available at: http://www.popdata.bc.ca/data.
6. Statistics Canada. Statistics Canada Income Band Data. Catalogue Number: 13C0016. V2. Population Data BC. Data Extract. Population Data BC(2015). 2009. Available at:

https://www.popdata.bc.ca/data. Accessed 22 October 2021.

7. BC Cancer. BC Cancer Registry Data. V2. Population Data BC. Data Extract. BC Cancer(2015). 2017. Available at: http://www.popdata.bc.ca/data. Accessed 22 October 2021.
8. BC Centre for Disease Control [creator]. BC Provincial HIV/AIDS Surveillance Database (BCCDC-HAISIS). Population Data BC [publisher]. Data Extract. BCCDC (2014). 2015. Available at: http://www.popdata.bc.ca/data. Accessed 22 October 2021.
9. BC Renal Agency [creator]. BC Provincial Renal Agency Database (PROMIS). Population Data BC [publisher]. Data Extract. PROMIS(2014). 2015. Available at: http://www.popdata.bc.ca/data. Accessed 22 October 2021.
10. BC Centre for Disease Control [creator]. BC Provincial TB Registry (BCCDC-iPHIS). Population Data BC [publisher]. Data Extract. BCCDC (2014). 2015. Available at: http://www.popdata.bc.ca/data. Accessed 22 October 2021.
11. Campbell JR, Pease C, Daley P, Pai M, Menzies D. Chapter 4: Diagnosis of tuberculosis infection. Can J Respir Crit Care, Sleep Med **2022**; 6:49–65.
12. Campbell JR, Chen W, Johnston J, et al. Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. Mol Diagn Ther **2015**; 19:107–117.
13. BC Centre for Disease Control. Section 6 - Treatment of Latent TB Infection (LTBI). In: Communicable Disease Control Manual - Chapter 4: Tuberculosis. Vancouver, BC: Provincial Health Services Authority, 2019: 1–20.
14. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak **2016**; 15:1–11.
15. Basham CA, Smith SJ, Romanowski K, Johnston JC. Cardiovascular morbidity and mortality among persons diagnosed with tuberculosis: A systematic review and meta-analysis. PLoS One **2020**; 15:e0235821.
16. Wongtrakul W, Charoenngam N, Ungprasert P. Tuberculosis and risk of coronary heart disease: A systematic review and meta-analysis. Indian J Tuberc **2020**; 67:182–188.
17. Huaman MA, Ticona E, Miranda G, et al. The relationship between latent tuberculosis infection and acute myocardial infarction. Clin Infect Dis **2018**; 66:886–892.
18. Hasanain AFA, El-Maghraby KM, Zayed AAH, Nafee AMA, Abdel-Aal SM, Bakkar SM. Latent tuberculosis infection among patients with coronary artery stenosis: A case–Control study. Int J Mycobacteriology **2018**; 7:143.
19. Huaman MA, De Cecco CN, Bittencourt MS, et al. Latent Tuberculosis Infection and Subclinical Coronary Atherosclerosis in Peru and Uganda. Clin Infect Dis **2021**;
20. Al Khoufi EA. Association between latent tuberculosis and ischemic heart disease: a hospital-based cross-sectional study from Saudi Arabia. Pan Afr Med J **2021**; 38:362.