Burden of Active Tuberculosis in an Integrated Health Care System, 1997–2016: Incidence, Mortality, and Excess Health Care Utilization

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Active tuberculosis (TB) is preventable. To quantify the potential value of prevention, we assessed active TB burden in a large health system from 1997 to 2016. Compared with a matched non-TB cohort, patients with active TB had higher mortality (8.4% vs 1.3%), mean number of hospitalizations (0.55 vs 0.10), emergency department visits (0.78 vs 0.28), and outpatient visits (14.6 vs 5.9) in the first year. TB-associated hospital use (mean number of hospitalizations and total length of stay) increased from 1997–2000 compared with 2013–2016 despite decreasing active TB incidence. Active TB is associated with high mortality and health care utilization and has remained stable or increased over time.

Keywords. health care utilization; tuberculosis.

Approximately one-quarter of the world population has latent tuberculosis infection (LTBI) [1], leading to significant morbidity and mortality, as 5%–10% of persons with untreated LTBI will reactivate and develop active tuberculosis (TB) disease [2]. In the United States, up to 80% of active TB disease is due to LTBI reactivation [3] and could have been prevented through LTBI screening and treatment, as recommended by national guidelines [2]. However, few persons with LTBI have been identified and treated [4]. For example, in California only 12% of >2 million non-US-born persons with LTBI have been treated [5]. As active TB incidence has declined in the United States, LTBI screening and treatment have become a less visible priority for clinicians and health systems. Thus, we set out to re-assess the burden of active TB disease on the health system to quantify the potential value of LTBI programs.

Few prior studies have comprehensively assessed incidence, mortality, and health care utilization by patients with active TB disease in a single health system. Mortality data are available through public health surveillance, and published estimates of hospital use have been based on the Nationwide Inpatient Sample using billing code diagnoses [6–8] or medical records from individual hospitals or health systems [9, 10]. No studies have looked at incidence, mortality, and health care utilization comprehensively or assessed emergency department and ambulatory care utilization. To add to this scant evidence base, we assessed microbiologically confirmed active TB incidence and mortality as well as health care utilization (inpatient, ambulatory, and emergency department use) in a large, integrated health system in Northern California from 1997 to 2016.

METHODS

In this retrospective cohort study, we included all patients diagnosed with microbiologically confirmed active TB in Kaiser Permanente Northern California (KPNC), a large integrated health system, between 1997 and 2016. Data were extracted from KPNC administrative databases and from an integrated electronic health record database (Epic, Verona, WI, USA). All patients with at least 1 culture or polymerase chain reaction test positive for *Mycobacterium tuberculosis* between January 1, 1997, and December 31, 2016, were identified and included in the study. Patients were excluded if they had active TB disease before 1997. In addition, patients were excluded if they had <2 years of KPNC membership after active TB diagnosis to exclude patients who received the majority of their care outside KPNC. Active TB disease incidence was assessed as the number of active TB cases per 100 000 active KPNC members per calendar year. We assessed the incidence of death as well as hospital, emergency department, and ambulatory clinic use within 1 year of active TB diagnosis. Ambulatory visits comprised both urgent care and routine outpatient clinic visits. Active TB utilization was compared with a 40:1 age-, sex-, and year of diagnosis–matched non-TB cohort, with data stratified by 4-year intervals. The 2-sample *t* test and chi-square test were conducted for comparing the health care utilization between the active TB and non-TB cohorts. The Wilcoxon-Mann-Whitney test was used for comparing hospital length of stay, and the Cochran-Armitage trend test was conducted for active TB incidence rates stratified by 4-year intervals. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Multivariate Poisson regression models were conducted to obtain adjusted utilization rates, and a multiple logistic regression model was conducted to obtain the predicted mortality rate within 1 year. All models were adjusted for patients’ age, sex, year of diagnosis, year of active TB diagnosis, and racial/ethnic group.
demographics, selected comorbidities (diabetes, end-stage renal disease, HIV infection, post–organ transplant, history of malignant cancer diagnosis) and time period in 4-year intervals. The study was approved by the KPNC Institutional Board Review with a waiver of the requirement for informed consent and was funded by the KPNC Graduate Medical Education Program, Kaiser Foundation Hospitals and was supported by a grant from the KPNC Community Benefit Program.

RESULTS

In all, we identified 1957 patients with active TB who met membership criteria between 1997 and 2016. Our active TB cohort was 55.7% male and 59.6% Asian or Pacific Islander race/ethnicity (Table 1), with a mean age of 52 years. The overall incidence of active TB was 3.4 cases per 100 000 person-years over the study period, with a gradual decrease from 4.3 cases per 100 000 person-years in 1997–2000 to 2.9 cases per 100 000 person-years in 2013–2016 (Table 2). Of our active TB cohort, 164 (8.4%) died and 603 (30.8%) had at least 1 hospitalization within 1 year of diagnosis. Our comparison group had 76 638 patients, among whom 1004 (1.3%) died and 5396 (7.0%) had at least 1 hospitalization.

KPNC active TB patients had higher hospital use (0.55 vs 0.10 hospitalizations per person per year) and longer mean length of stay per hospitalization (9.5 vs 4.6 days) than the matched cohort in the year after diagnosis. Overall, active TB patients used 10 114 hospital-days from 1997 to 2016, 505.7 hospital-days per year, or 5.2 hospital-days per active TB patient. In comparison, patients in the matched non-TB cohort used 0.46 hospital-days per person per year. KPNC active TB patients had more emergency department (0.78 vs 0.28 visits) and ambulatory care visits (14.6 vs 5.9) per year.

The mean number of hospitalizations per patient per year increased from 1997–2000 to 2013–2016 (range, 0.49–0.59 for active TB cohort and 0.09–0.11 for matched non-TB cohort). The length of stay per hospitalization increased by 4 days in the active TB cohort (7.3 days in 1997–2001 to 11.3 days in 2013–2016) compared with 0.9 days in the matched non-TB cohort (4.0 days in 1997–2001 to 4.9 days in 2013–2016). The mean number of hospital days per active TB patient increased from 3.6 in 1997–2000 to 6.5 in 2013–2016.

We used multivariable models to estimate health care utilization (hospital, emergency department, ambulatory care) and mortality rates among patients with active TB disease compared with the comparison cohort adjusted for patients’ demographics, selected comorbidities, and time period (Table 3). Patients in the active TB cohort had higher adjusted hospital (adjusted rate ratio, 5.0), emergency department (adjusted rate ratio, 2.7), and ambulatory care (adjusted rate ratio, 2.5) utilization compared with the comparison cohort. In addition, patients with active TB disease had substantially higher mortality (adjusted rate ratio, 6.8) compared with the comparison cohort. All of the differences in mortality and health care utilization between the 2 cohorts were still statistically significant after adjustment for covariates.

Table 1. Characteristics of Persons With Active TB Disease and a Matched Cohort of Patients Without Active TB Disease in a Large, Integrated Health System, Kaiser Permanente Northern California, 1997–2016

|                      | Active TB Cohort | Comparison Cohort | PValue |
|----------------------|------------------|-------------------|--------|
| Total                | 1957 (100)       | 76 638 (100)      | .83    |
| Sex                  |                  |                   |        |
| Male                 | 1090 (55.7)      | 42 496 (55.5)     | .83    |
| Female               | 867 (44.3)       | 34 142 (44.5)     |        |
| Age                  |                  |                   | .82    |
| 0–4 y                | 19 (1.0)         | 740 (1.0)         |        |
| 5–14 y               | 21 (1.1)         | 688 (0.9)         |        |
| 15–24 y              | 111 (5.7)        | 4489 (5.9)        |        |
| 25–44 y              | 589 (30.1)       | 22 129 (26.9)     |        |
| 45–64 y              | 683 (34.9)       | 27 294 (35.6)     |        |
| 65+ y                | 534 (27.3)       | 21 300 (27.3)     |        |
| Race/ethnicity       |                  |                   |        |
| White, not Hispanic  | 204 (10.4)       | 41 148 (53.7)     | <.0001 |
| Black, not Hispanic  | 135 (6.9)        | 5367 (7.0)        |        |
| Hispanic             | 266 (13.6)       | 11 425 (14.9)     |        |
| Asian/Pacific Islander| 1166 (59.6)     | 11 131 (14.5)     |        |
| American Indian/Alaska Native/other/mixed race | 186 (9.5) | 7567 (9.9) |        |
| Comorbidities        |                  |                   |        |
| Diabetes             | 519 (26.5)       | 7837 (10.2)       | <.0001 |
| End-stage renal disease | 52 (2.7)      | 218 (0.3)         | <.0001 |
| HIV infection        | 46 (2.4)         | 212 (0.3)         | <.0001 |
| Post–organ transplant| 19 (1.0)         | 70 (0.1)          | <.0001 |
| History of malignant cancer diagnosis | 164 (8.4) | 4020 (5.2) | <.0001 |

Abbreviation: TB, tuberculosis.
DISCUSSION

Active TB disease continues to be associated with substantial mortality and high health care utilization. In this analysis, we quantified the excess mortality and health care utilization among patients with active TB disease compared with a matched cohort of non-TB patients over a 20-year period in an integrated health system with >4.5 million members in Northern California. Much of this excess mortality and health care utilization is preventable, as most active TB cases are due to reactivation of LTBI, and thus we can begin to quantify the possible prevention benefit of improved LTBI programs.

This might be due to difference in underlying populations; KPNC members are insured and thus might have lower proportion of persons with known risk factors for active TB disease (e.g., fewer recent immigrants, homeless persons). The mortality rate among TB patients has been well described; the mortality rate in our study (8.4%) was similar to reported estimates for California (9%) [5] and the United States (5.7%) [3] and has not changed substantially from 1997 to 2016. Older estimates of hospital use from Montreal, Canada, from January 1997 to May 2007 (0.65 hospitalizations per TB case, 17.8 hospital-days per TB case, and a mean length of stay of 27.2 days) [10] and 10 large health departments in the United States in 1995 (0.55 hospitalizations per TB case) [9] can be compared with our estimates using data from KPNC from 1997 to 2016 (0.55 hospitalizations per TB case, 17.8 hospital-days per TB case, and a mean length of stay of 27.2 days).

Table 2. Health Care Utilization and Mortality Among Patients With Active TB Disease Compared With an Age-, Sex-, and Year of Diagnosis–Matched Comparison Cohort Without Active TB Disease in Kaiser Permanente Northern California, Stratified by 4-Year Intervals, 1997–2016

| 1997–2000 | 2001–2004 | 2005–2008 | 2009–2012 | 2013–2016 | 1997–2016 | P Value |
|-----------|-----------|-----------|-----------|-----------|-----------|---------|
| No. of patients | Active TB 438 | 406 | 343 | 377 | 393 | 1957 |
| Comparison | 16,312 | 15,997 | 14,072 | 14,759 | 15,498 | 76,638 |
| Active TB incidence per 100,000 member-years | 4.3 | 3.7 | 3.1 | 3.1 | 2.9 | 3.4 | <.01* |
| Mean hospitalizations per patient per year | Active TB 0.49 | 0.59 | 0.49 | 0.58 | 0.57 | 0.55 | <.01* |
| Comparison | 0.10 | 0.10 | 0.11 | 0.10 | 0.09 | 0.10 |
| Total hospital-days | Active TB 1572 | 2349 | 1813 | 1828 | 2552 | 10,114 |
| Comparison | 6412 | 7961 | 7380 | 6161 | 7049 | 34,963 |
| Mean (median) LOS per hospitalization | Active TB 7.3 (5.0) | 9.8 (6.0) | 10.7 (6.0) | 8.3 (5.0) | 11.3 (6.0) | 9.5 (6.0) | <.01* |
| Comparison | 4.0 (3.0) | 4.9 (3.0) | 4.8 (3.0) | 4.2 (3.0) | 4.9 (3.0) | 4.6 (3.0) |
| Mean ED visits per patient per year | Active TB 0.72 | 0.67 | 0.66 | 0.84 | 1.00 | 0.78 | <.01* |
| Comparison | 0.27 | 0.25 | 0.26 | 0.30 | 0.33 | 0.28 |
| Mean ambulatory visits per patient per year | Active TB 13.7 | 16.4 | 14.4 | 14.6 | 14.0 | 14.6 | <.01* |
| Comparison | 6.0 | 6.2 | 6.0 | 5.7 | 5.8 | 5.9 |
| Mortality rate, % | Active TB 10.0 | 7.4 | 7.3 | 8.0 | 8.9 | 8.4 | <.01* |
| Comparison | 1.2 | 1.4 | 1.3 | 1.1 | 1.5 | 1.3 |

Utilization and mortality among patients with active TB disease within 1 year of TB diagnosis and among patients in the comparison cohort within 1 year of sex, age, and year of diagnosis match date. Rates are adjusted for patients’ demographics, selected comorbidities (diabetes, end-stage renal disease, HIV infection, post–organ transplant, history of malignant cancer diagnosis), and time period in 4-year intervals (1997–2000, 2001–2004, 2005–2008, 2009–2012, 2013–2016). Multivariate Poisson regression models were used for utilization analyses, and a multiple logistic regression model was used for mortality analysis.

Table 3. Adjusted Health Care Utilization and Mortality Among Patients With Active TB Disease Compared With an Age-, Sex-, and Year of Diagnosis–Matched Comparison Cohort Without Active TB Disease in Kaiser Permanente Northern California, 1997–2016

|     | Active TB (Adjusted Rate) | Comparison (Adjusted Rate) | Adjusted Rate Ratio (95% CI) | P Value |
|-----|--------------------------|---------------------------|-----------------------------|---------|
| No. of patients | 1957 | 76,638 |
| Mean hospitalizations per patient per year | 0.45 | 0.09 | 5.00 (4.64–5.37) | <.001 |
| Mean LOS per hospitalization per year | 9.04 | 4.54 | 1.99 (1.94–2.04) | <.001 |
| Mean ED visits per patient per year | 0.71 | 0.26 | 2.73 (2.58–2.89) | <.001 |
| Mean ambulatory visits per patient per year | 14.28 | 5.70 | 2.51 (2.47–2.54) | <.001 |
| Mortality rate, % | 6.80 | 1.00 | 6.80 (6.79–6.81) | <.001 |

Utilization and mortality among patients with active TB disease within 1 year of TB diagnosis and among patients in the comparison cohort within 1 year of sex, age, and year of diagnosis match date. Rates are adjusted for patients’ demographics, selected comorbidities (diabetes, end-stage renal disease, HIV infection, post–organ transplant, history of malignant cancer diagnosis), and time period in 4-year intervals (1997–2000, 2001–2004, 2005–2008, 2009–2012, 2013–2016). Multivariate Poisson regression models were used for utilization analyses, and a multiple logistic regression model was used for mortality analysis.

Abbreviations: CI, confidence interval; ED, emergency department; LOS, length of stay; TB, tuberculosis.
hospitalizations per TB case, 5.2 hospital-days per TB case, and mean length of stay of 9.5 days). In addition, hospital use by TB patients has been assessed using the nationally representative Nationwide Inpatient Sample in 2000 [8], 2000–2010 [6], and 2014 [7], but these estimates do not reflect microbiologically confirmed TB cases and exclude TB patients who were not hospitalized and thus cannot be directly compared with this study. However, allowing for these differences and comparing the burden of TB-related hospitalizations (96,431) [6] with the reported number of active TB cases in the United States from 2000 to 2010 (153,217) [3], the mean number of hospitalizations per TB case was 0.63, with 9.3 hospital-days per TB case and a mean length of stay of 14.7 days. It is unclear if the noted differences are due to differences in the underlying TB epidemiology, TB case definitions, local practice patterns, or temporal differences. However, the estimates provided in this manuscript provide the most recent estimates of hospital use among TB patients in the United States. Moreover, our assessment of hospital use includes a matched non-TB cohort of KPNC members who have hospital use similar to that of overall utilization in the United States (0.11 hospitalizations annually with an average length-of-stay of 4.6 days.) [11] In addition, it is notable that the overall mean number of hospitalizations per patient per year for patients with active TB disease increased from 0.49 in 1997–2000 to 0.57 in 2013–2016, and the mean length of stay per hospitalization for patients with active TB disease increased from 7.3 days in 1997–2000 to 11.3 days in 2013–2016; overall hospital use increased from 3.6 hospital-days per patient with active TB disease in 1997–2000 to 6.5 hospital-days in 2013–2016. Both the increased number of hospitalizations and the number of hospital-days per stay have led to an increase in overall number of hospital-days due to active TB disease despite the decrease in active TB incidence over time. No prior studies have assessed emergency department and ambulatory clinic utilization among TB patients, and thus our study is the first to highlight high utilization by TB patients in both settings.

This comparison allows health system planners to estimate the excess utilization by TB patients compared with patients without TB. Health care utilization and mortality are significantly higher among patients with active TB disease compared with a non-TB comparison cohort. Even after adjusting for differences in demographic characteristics, presence of comorbidities, and time period, patients with active TB disease have significantly higher health care utilization and mortality. Both the unadjusted and adjusted results can be used to better understand the burden of active TB disease on the health system. Our study had a few limitations. First, KPNC members belong to a large, integrated health system and are thus insured; previous analyses comparing KPNC members with the general adult population of Northern California have suggested that the 2 populations are similar but have some differences in socioeconomic status [12]. These differences could impact the generalizability of these results to all of California or other regions of the United States. Second, health care utilization is dependent on health system and population factors, and thus overall utilization estimates might vary depending on the setting. Third, active TB incidence in KPNC was lower than in all California and might reflect a lower proportion of incarcerated, homeless, and foreign-born persons with limited access to care [5]. Fourth, data on country of birth are not systematically captured in our electronic medical record and could not be extracted to be used as an analytic variable.

In summary, although active TB disease incidence has declined over the past 20 years, patients with TB disease continue to experience high mortality and health care utilization. As most active TB disease can be prevented with screening for and treatment of LTBI, these data provide critical estimates to appropriately “value” LTBI programs. By improving screening practices and early treatment of LTBI, we may be able to reduce much of the mortality and health care utilization associated with active TB.

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References

1. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med 2016; 13:e1002152.
2. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for latent tuberculosis infection in adults: US Preventive Services Task Force recommendation statement. JAMA 2016; 316:962–9.
3. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2017. Atlanta: Centers for Disease Control and Prevention; 2019. Available at: https://www.cdc.gov/tb/statistics/reports/2017/default.htm. Accessed September 10, 2019.
4. Alsdurf H, Hill PC, Matteelli A, et al. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis 2016; 16:1269–78.
5. Tuberculosis Control Branch. Report on Tuberculosis in California, 2018. Richmond, CA: California Department of Public Health, Tuberculosis Control Branch; 2019. Available at: https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TB-Disease-Data.aspx. Accessed September 10, 2019.
6. Allareddy V, Rampa S, Allareddy V, Nalliah RP. Tuberculosis management continues to utilize a large amount of hospital resources in the United States. Clin Respir J 2017; 11:21–7.
7. Aslam MV, Owusu-Edusei K, Marks SM, et al. Number and cost of hospitalizations with principal and secondary diagnoses of tuberculosis, United States. Int J Tuberc Lung Dis 2018; 22:1495–504.
8. Hansel NN, Merriman B, Haponik EF, Diette GB. Hospitalization for tuberculosis in the United States in 2000: predictors of in-hospital mortality. Chest 2004; 126(4):1079–86.
9. Taylor Z, Marks SM, Rios Burrows NM, Weiss SE, Stricof RL, Miller B. Causes and costs of hospitalization of tuberculosis patients in the United States. Int J Tuberc Lung Dis 2000; 4(10):931–9.
10. Ronald LA, FitzGerald JM, Benedetti A, et al. Predictors of hospitalization of tuberculosis patients in Montreal, Canada: a retrospective cohort study. BMC Infect Dis 2016; 16:679.

11. Healthcare Cost and Utilization Project (HCUP). Trends in hospital costs/utilization - HCUP fast stats. Available at: https://www.hcup-us.ahrq.gov/faststats/NationalTrendsServlet. Accessed September 10, 2019.

12. Gordon N. Similarity of the Adult Kaiser Permanente membership in Northern California to the insured and general population in Northern California: statistics from the 2011 California Health Interview Survey. 2015. Available at: https://divisionofresearch.kaiserpermanente.org/projects/memberhealthsurvey/SiteCollectionDocuments/chis_non_kp_2011.pdf. Accessed September 10, 2019.