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Trends in mortality, length of stay, and inpatient charges among tuberculosis hospitalizations with and without coexisting diabetes, US, 2000 – 2011
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By

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Bachelor of Science
Washington College
2011

Thesis Committee Chair: Dr. John McGowan, MD

An abstract of
A thesis submitted to the Faculty of the
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Abstract

Trends in mortality, length of stay, and inpatient charges among tuberculosis hospitalizations with and without coexisting diabetes, US, 2000 – 2011
By Catherine Alicia Rappole

Background: Tuberculosis (TB) patients with diabetes mellitus (DM) may have poorer outcomes and a higher risk of death than those without DM. This study used a national sample to investigate trends in and compare inpatient mortality and healthcare utilization among hospitalized TB patients with and without DM.
Methods: A cohort of TB hospitalizations was constructed using data from the Nationwide Inpatient Sample during the years 2000 through 2011. Differences in the proportion of all-cause inpatient deaths, average length of stay (LOS), and average inpatient charges between primary TB hospitalizations with and without DM were compared using the *t* test. Trends in TB-DM hospitalizations, mortality, LOS, and charges were analyzed by the Cochran-Armitage test for trend. Bivariate analysis was done to identify crude predictors of mortality among primary TB hospitalizations.
Results: There was a total of 102,072 primary TB hospitalizations during the study period; 16,796 (16.5%) had comorbid DM. The rate of primary TB hospitalizations without DM decreased by 50% over the study period, whereas the rate of primary TB hospitalizations with DM increased by 27.6% ($p < 0.001$). TB hospitalizations with DM were an average of 1.5 days longer than those without DM ($p = 0.003$). There was a positive trend in mean charges incurred among TB hospitalizations with DM, from $53,460 to $84,338 ($p < 0.001$). On average, 3.8% of TB hospitalizations without DM died per year, compared with 4.08% of TB hospitalizations with DM per year ($p = 0.49$). There was no significant trend in average LOS ($p = 0.44$) or average mortality ($p = 0.49$) per year. In bivariate analyses, DM was not associated with an increased risk of inpatient death among hospitalized TB patients ($p = 0.57$).
Conclusions: The findings suggest that coexisting DM among hospitalized TB patients is not associated with increased mortality, but may result in increased healthcare utilization as measured by LOS and inpatient charges. Inpatient charges among TB patients hospitalized with DM increased 5.2% annually, illustrating the potential economic burden placed on the US healthcare system when the two conditions coexist.

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Chapter I: Literature Review

Introduction

In the US, tuberculosis (TB) incidence and mortality among TB patients have declined in the last two decades. However TB patients with comorbidities such as human immunodeficiency virus (HIV) and diabetes mellitus (DM) remain at a higher risk of poor outcomes, including death [1]. In the 22 countries that account for 80% of the global TB burden, an estimated 7.5% of the TB burden is attributable to DM [2].

Regional studies done in the US suggest that the prevalence of DM among adults with TB ranges from 14% and 28%, but these studies did not address the attributable burden of TB due to DM [1, 3-5]. A 1991 study among Hispanics in California determined that the estimated risk of TB attributable to DM was 25.2% and equivalent to that attributable to HIV infection [6]. A more recent analysis of DM and TB in South Texas determined that 63% of TB cases were attributable to DM across all age groups studied [7].

Studies examining the impact of DM on TB mortality have shown conflicting results [1, 3, 4, 8]. In one study, 11.5% of TB patients had coexisting DM and odds of death was similar among TB patients with and without DM [1]. Whereas, in another study of TB cases from three counties in Maryland, TB patients with DM had 6.5 (95% CI: 1.1 – 38.0) times the odds of death compared to TB patients without DM [3]. Similarly, a study by Fielder *et al.* in Maryland determined that the age-adjusted odds of death among TB patients with DM was 3.80 (95% CI: 1.42 – 10.16) times that of TB patients without DM [8]. Oursler *et al.* found that the age-adjusted mortality hazard ratio for TB-DM patients was 6.7 (95% CI: 1.6 – 29.3) times that of TB patients without DM [4]. In each of these studies the estimates were adjusted for a variety of potential confounders.

In contrast to some other comorbid conditions such as HIV, there is limited data on the attributable healthcare utilization and costs due to DM among TB patients [9-12]. For example, Rosenblum *et al.* used data from 1985 – 1990 to conclude that TB-HIV hospitalization costs accounted for between $2.5 and $3.1 billion of the total TB costs among all ages in the US [10]. Taylor *et al.* conducted a study in 2000 to determine the causes and costs of TB hospitalizations in ten US locations, but did not include data on DM [12]. In that study, the median length of stay per TB hospitalization was 11 days, with a median cost of $644 per day and a mean cost of $7,288 per case [12]. Importantly, these data were not based on national sample, as study participants were recruited and were mostly from urban locations [12]. Length of stay estimates were determined in one study after controlling for comorbidities such as HIV, but not DM [13].

To date there have been no national estimates of the US TB burden that is attributable to DM or nationwide studies that assess mortality, healthcare utilization, or healthcare costs associated with DM among TB patients. This thesis used data from the Health Cost and Utilization Project's Nationwide Inpatient Sample (NIS), during years 2000 through 2011, to describe and assess temporal trends in the proportion of hospitalized TB patients who had coexisting DM and to compare mortality, length of stay (LOS), and inpatient charges among hospitalized TB patients with and without DM.

Background

Tuberculosis (TB) and Diabetes Mellitus (DM)

Previous studies have demonstrated that DM is associated with an increased risk of TB [14]. A systematic review of 13 cohort studies found that DM patients had approximately three times the risk of developing TB compared to those without diabetes [15, 16]. This effect was consistent among people with DM regardless of background incidence of TB in the study, study region, or underlying medical conditions in the cohort [15]. A Taiwanese prospective cohort study of TB among people with DM concluded that DM (treated or untreated) increased the hazard of developing TB when controlling for factors such as age, sex, smoking, crowding, and socioeconomic status [17]. Another longitudinal cohort study using Taiwan's National Insurance Research Database concluded that DM was significantly associated with incident TB after controlling for age, sex, bronchiectasis, chronic obstructive pulmonary disease, and asthma [18]. In a study using the tuberculosis case-notification system in India, it was estimated that DM accounted for 7.1% to 23.8% of all incident pulmonary TB [19]. Stevenson *et al.* conducted a systematic review which determined that all studies, despite type, found a statistically significant association between DM and TB, varying from a 1.5 times to a 7.8 times increase [20]. It has also been found that incident TB is higher in insulin-dependent DM than in non-insulin dependent DM [3].

TB and DM Outcomes

Multiple studies in high- and low-income countries have suggested that treatment failure and death from TB are more frequent in DM patients [21]. A systematic review of four studies determined that the pooled risk of death among TB patients with DM was almost five times greater than among TB patients without DM, after adjusting for age and other potential confounders [16, 22]. Dooley *et al.* conducted a retrospective study using data from culture-confirmed tuberculosis in Maryland to determine the prevalence of DM among TB patients and their treatment outcomes [3]. After adjusting for HIV status, age, weight, and foreign birth, the odds of death was 6.5 (95% CI: 1.1 – 38.0) times higher in TB patients with DM than in those without DM [3]. A non-significant association was also shown between treatment failure and DM, with the odds of treatment failure reported as 59% higher among tuberculosis patients with DM than patients without DM, after adjusting for cavitary status, ethnicity, and age [3].

There may be multiple biologic reasons that explain the differences in outcomes among TB patients with and without DM. TB patients with DM tend to have higher sputum bacterial concentrations than those without DM, which may lead to increased time to sputum culture conversion among diabetic TB patients [14, 20, 21]. Some studies have also suggested that TB patients with DM present differently than those without DM; they may be more likely to have infection in multiple lung lobes and involvement in the lower lung field rather than the usual site of infection in the apex of the lung, which may lead to misdiagnosis [20, 21]. It has been reported that DM may reduce the efficacy of TB drugs by altering their pharmacokinetics, and DM may increase the risk of relapse after treatment conclusion; this has implications for treatment outcomes of TB patients [3, 20, 21].

Previous Studies

TB and TB-DM Mortality

There is an array of estimates of inpatient TB mortality and the impact of comorbidities such as DM on inpatient TB morbidity. Three of such studies only use data from specific areas in the state of Maryland, while the fourth uses data from the state of Georgia.

Dooley *et al.* studied TB patients in Montgomery, Baltimore, and Prince George's county Maryland between 2004 to 2005 and determined that TB patients with DM had 6.5 times (95% CI: 1.1 – 38.0) the odds of death as those without DM, after adjusting for HIV status, age, weight, and foreign birth [3]. Forty-four of the 297 TB patients in the study did not have an HIV status recorded; as HIV is a strong risk factor for death, this limited the multivariable model to a sample size of only 253 patients [3]. In addition, only twenty-six (9%) of the total 297 patients died of TB or other causes while undergoing TB treatment; therefore there is low power to detect differences in odds of death among TB patients with and without DM [3]. Estimates were also imprecise due to the small sample size [3]. Additionally, the relationship between the severity of DM and TB was not able to be determined because glycemic control was not systematically assessed due to the retrospective nature of the study [3]. Glycemic control may have an effect on treatment outcomes, and it is unknown whether increased mortality in TB patients with DM is secondary to DM-related comorbidities or to increased TB severity [3].

Another study in Baltimore, MD also found an association between DM and death during TB treatment. Fielder *et al.* studied the case-fatality rate of smear-positive TB among patients in Baltimore between January 1993 and June 1998 [8]. Their study included only 174 patients, of which 42 (24%) died while receiving TB treatment [8]. After adjusting for age, Fielder *et al.* concluded that DM and renal failure remained independent predictors of death [8]. Fielder *et al.* also concluded that TB patients with DM had 3.8 times (95% CI: 1.4 – 10.3) the risk of death compared to those without DM, after adjusting for age, but that HIV infection was not significantly associated with an increased risk of death [8]. It was hypothesized that much of the mortality was attributable to comorbid illness [8]. The sample size of this study was also small and the estimates were imprecise, suggesting the power may have been too low to detect meaningful differences in outcomes [8].

A second study utilizing Baltimore, MD, TB cases determined an association of DM and TB mortality about equal to that of Dooley *et al*. Oursler *et al.* conducted a prospective study in Baltimore from January 1994 to June 1996 that followed 139 TB patients whose isolates were in a restriction fragment-length polymorphism library [4]. The main outcome of interest was death due to any cause while in TB treatment [4]. Eighteen patients (14%) had comorbid DM [4]. Twenty-nine patients (21%) died during treatment, and it was determined that those with TB and DM had 6.7 (95% CI: 1.6 – 29.3) times the hazard of death as those without DM, after controlling for age and demographic variables [4]. The lack of precision in this estimate is likely due to the low sample size of the study. This study also excluded patients with extra-pulmonary TB.

In contrast, a study in Georgia determined there was no significant effect of DM on TB mortality. Magee *et al.* conducted a retrospective cohort study of all pulmonary or extra-pulmonary TB patients reported to the Georgia Department of Public Health between January 2009 and September 2012 [1]. The primary outcome of interest was time until death, measured among patients who died from any cause during TB treatment, among those with DM and/or HIV [1]. DM status was self-reported as having ever been diagnosed with DM, which may have added measurement error to the estimates [1]. Among the 1,325 TB patients included at baseline, 166 (8.8%) died [1]. Among the 151 TB patients with DM, 16 (10.8%) died [1]. Magee *et al.* found no difference in the odds of death among TB patients with and without DM, after controlling for age, socioeconomic, and behavioral characteristics (adjusted odds ratio [aOR]: 1.05, 95% CI: 0.60 – 1.84) [1]. The authors believed that potential misclassification of DM status due to self-report was non-differential with respect to mortality, therefore the estimated effect may be an underestimate of the true effect [1]. Also, although all-cause mortality was documented during TB treatment, the study was unable to determine if the cause of death was specific to TB disease [1].

TB and TB-DM length of stay and total inpatient charges

There are a variety of estimates regarding LOS and inpatient charges due to TB, but limited estimates available on the effect of DM comorbidity on TB LOS and inpatient charges. The majority of research on TB total inpatient charges occurred during the resurgence of TB with the rise of the HIV-epidemic in the early 1990s. Length of stay estimates for TB hospitalization range from a mean of 11 days to 24 days, dependent upon year, location, and dataset [11, 12, 23-25]. Estimates of total inpatient charges per TB hospitalization range from a median of $7,000 – $8,000 to a mean of $14,000 – $20,000 [11, 12, 23, 25].

The resurgence of TB between 1985 and 1992 in the US prompted research on the direct costs associated with medical resource use and expenditures due to TB [23]. Brown *et al.* conducted a study with data on TB inpatient hospitalizations from 16 states (representing

45% of the total US population) obtained from the Codman Research Group, NH [23]. This data included all 1990 TB hospitalizations recorded as the principal diagnosis according to the International Classification of Diseases, Ninth Revision, (ICD-9) codes [23]. The rate of hospitalization in the states was then applied to the TB cases reported nationally to gain a nationally representative estimate [23]. The charges in the dataset reflected the actual charges reported at discharge [23]. An estimated 20,803 hospitalizations with TB as the primary diagnosis occurred in 1991; the mean LOS was estimated at 19.9 days, and the median charges estimated at $18,588 (1991 dollars) [23]. This led to total hospital charges estimated to be $386.7 million; when added to the $37.1 million physician charges associated with those hospital stays, the total cost of TB inpatient treatment was estimated to be $423.8 million in 1991 [23]. Overall medical expenditures for TB were estimated at $703.1 million, 60% of which was attributable to inpatient charges [23]. It was also estimated that the shortest length of hospitalization was 11.1 days, and the longest LOS was 27.4 days [23]. Brown *et al.* also estimated that if hospital costs at $12,369 per discharge had been employed instead of charges, the total TB expenditures would have been lowered to $573.8 million [23]. As with the NIS, this dataset is based on hospital discharge records, therefore individuals with multiple hospitalizations will be represented in the data multiple times [23]. This study did not control for the effects of confounders such as HIV co-infection or drug-resistant TB infection on hospitalization, which may have caused an overestimate in the expenditure attributable to TB [23]. Another limitation of this study is that it did not reflect hospitalizations for which TB was listed as the secondary diagnosis; even as a secondary reason for hospitalization, the authors noted that the "charges related to the presence of

TB … appear to be considerable," further suggesting their analysis resulted in an underestimate of the true impact of TB on hospitalization costs [23].

Rosenblum *et al.* employed data from the National Hospital Discharge Survey (NHDS) for years 1985 through 1990 to estimate the effect of HIV and TB on hospitalizations and costs [10]. The NHDS is "a nationally representative probability survey of hospitalizations from nonfederal short-stay general and specialty hospitals in fifty states and the District of Columbia" [10]. A sample of about 500 hospitals, out of a total 6,000 US short-stay hospitals, was obtained for each year of analysis, and ICD-9 codes were used to define TB and HIV hospitalizations [10]. Data on hospital daily charges were obtained from statewide hospital billing records for HIV infection and TB from eighteen states, which accounted for 72% of TB cases among adults 15 – 44 years old within the NHDS jurisdiction during 1985 to 1990 [10]. It was estimated that hospitalizations related to TB increased twofold between 1988 and 1990 [10]. In addition, it was estimated that inpatient care costs increased 3.2-fold for TB hospitalizations during the study period [10]. It was also found that TB hospitalizations resulted 1,107,900 days of care, with an estimated direct cost of $0.89 to $1.07 billion [10]. As with the NIS, the unit of analysis is "hospitalization," therefore one person may have multiple hospitalizations represented in the dataset [10]. Importantly, this study examined data from 1985 through 1990, during the resurgence of TB concurrent with the HIV/AIDS epidemic, therefore it may not represent current hospitalizations and costs due to TB [10].

Taylor *et al.* also examined a prospective cohort from ten health departments reporting cases of active TB to the CDC from 1995 – 1996 to determine costs and LOS due to TB [12]. The calculated median LOS was 11 days, with a median cost per day of hospitalization at $644, and a median cost per hospitalization episode of $7,545 [12]. It was concluded that hospitalization costs were higher at sites with a higher number of hospitalizations and were also greater for homeless people and substance abusers [12]. This study was unable to control for severity of disease therefore it is unknown whether the variations in hospitalization was caused by differences in the presenting conditions of the patients upon hospitalization [12]. Also, patients volunteered to participate in the study, so estimates may not be representative of all US TB patients [12].

Prior research has also examined which institutions bear the cost of TB healthcare utilization. Marks, Taylor, & Miller conducted a study to determine who pays for TB hospitalization [11]. They followed a prospective cohort of active TB patients reported to CDC during 1995 to 1996 and examined costs associated with TB hospitalizations just prior to TB diagnosis or during the whole period of TB treatment [11]. Only ten sites were studied, eight major cities and two southern states, which lead to a convenience sample of 6.5% of all reported US TB cases in 1995 [11]. The authors obtained hospitalization charges from standard hospital billing forms (excluding physician charges) and converted the charges to costs using the Health Care Financing Administration cost-to-charge ratios specific to each hospital [11]. Three multivariate logistic regression models were employed to identify factors associated with having government, private, or no/unknown insurance [11]. They also estimated the direct and indirect costs of eliminating TB hospitalization with the estimated costs of preventing TB hospitalization in high-risk people; high-risk people included: homeless, HIV-positive, non-Hispanic blacks, substance abusers, correctional facility residents, MRD-TB patients, long-term care residents, and uninsured patients cared for in public hospitals [11].

Government insurance paid for 57% of TB hospitalization costs, and those with government insurance had disproportionally higher costs compared with others: median LOS of 13 days (mean 24 days) and median cost per episode $8,972 (mean $14,518) [11]. The median cost of TB hospitalization for a patient with no/unknown insurance status was $7,027 (mean $14,689) [11]. One limitation of this study is that the demographics of the cohort are more representative of urban populations than all of US TB patients [11]. It was concluded that taxpayers paid for 85% of TB hospitalization costs during this time period, because patients were covered by Medicaid, Medicare, Veteran's Affairs (VA), state, or local government sources, and uninsured patients were admitted to public hospitals [11]. This study did not control for diabetes status among the cohort; as mentioned above, TB patients with DM have a longer time to culture conversion than those without DM, suggesting hospitalization LOS and thus charges will also be higher than found in this study.

Two papers have previously been published examining TB hospitalizations in the NIS. Hansel *et al.* employed the 2000 NIS to characterize patients with TB and identify characteristics associated with in-hospital mortality [24]. There were 2,279 (un-weighted) hospitalizations with a primary TB discharge International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 010.xx to 018.xx [24]. The mean length of stay was 14.2 days (standard error (se): 18.8 days) and the median length of stay was 9 days; both of these were statistically different from other hospital admissions [24]. It was also found that total charges were almost 2.5 times higher for TB admissions than all other hospital admissions, with the mean total charges for TB at $33,985 (se: $52,414) [24]. Additionally, it was concluded that the in-hospital mortality rate of TB hospitalizations was 4.9%, more than double the mortality rate for all other hospital admissions [24].

Holmquist *et al.* also examined the characteristics of TB hospitalizations using the 2006 NIS [25]. This paper employed the HCUP free query website http://hcupnet.ahrq.gov/ to complete their statistical analyses [25]. The case definition of TB was a Clinical Classification Software (CCS) value of 1, which categorizes all ICD-9-CM codes for TB into one category [25]. It was determined that TB was listed as the primary diagnosis for 8,800 stays (15% of all TB-related stays) in 2006 [25]. It was also calculated that lengths of stays for TB as the primary diagnosis was 15.0 days, while length of stay for TB as a secondary diagnosis was only 6.6 days [25]. The average cost for a hospital stay principally for TB was $20,100, partly due to the long length of stay [25]. Of those with a primary or secondary diagnosis of TB, 3.6% died in the hospital, compared with 2.6% mortality among all conditions [25].

Nationwide Inpatient Sample (NIS)

The NIS retains all-payer data on hospital inpatient stays from states participating in the Healthcare Cost and Utilization Project (HCUP) [26]. Each year of the NIS provides information on approximately 8 million total inpatient stays from about 1,000 hospitals [26]. The NIS is designed to approximate a 20% sample of US community hospitals, defined by the American Hospital Association (AHA) to be “all non-Federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions” [26]. Veterans Hospitals and other federal hospitals are excluded [27]. The number of hospitals increased from 17 in 1993 to 46 in 2011, which increased the sample hospitalizations from about 6.5 million to about 8 million [26].

The NIS is a stratified sample of hospitals drawn from the subset of hospitals in the US that are open during any part of the year that provide data to HCUP and can be matched to AHA survey data [26, 27]. There are 60 strata, in which hospitals are stratified by five hospital characteristics: region, location/teaching status (within region), bed size category (within region and location/teaching status), and ownership (within region, location/teaching, and bed size categories) [26, 27]. Practice patterns vary substantially by region; therefore hospitals are stratified by census region of Northeast, Midwest, South, and West [26, 27]. Urban/rural designation is defined by the AHA, and rural hospitals are generally smaller and offer fewer services than urban [26, 27]. Teaching hospitals differ from non-teaching hospitals in terms of mission and finances [26]. Teaching status is defined by those hospitals with Council of Teaching Hospitals membership, with an American Medical Association-approved residency program, or with an intern-to-bed ratio of 25% or higher [27]. Bed size categories are specific to a hospital’s region, location, and teaching status [27, 28]. Thus HCUP designated bed size category cut-points to approximate one-third of the hospitals in a given region, teaching status, and location in each category [27, 28]. Hospitals may also have different missions and responses to government regulations and policies based on their ownership [26]. Ownership is broken down based on the degree of observed ownership variation within each region across bed size categories and includes government nonfederal (public), private not-for-profit (voluntary), and private investor-owned (proprietary) [26, 27, 29]. Sampling probabilities of hospitals in the frame are proportional to the number of US community hospitals in each stratum [26]. HCUP sorts hospitals by the first three digits of their zip code and then draws a systematic random sample of hospitals equal in size to

20% of the universe for that stratum [27]. All of the hospitalizations from the sampled hospitals are included in the NIS [27]. The discharge weights within each stratum are the ratio of hospitalizations in the universe to hospitalizations in the sample; therefore the sum of the sample weights in each stratum represents the total number of hospitalizations reported in the AHA survey for a given year [27]. Use of these weights produces unbiased estimates of the attributable mortality, length of stay, and total inpatient charges due to DM among hospitalized TB patients in the US [27].

Methods

Nationwide Inpatient Sample Database

The Nationwide Inpatient Sample (NIS), a database of hospital inpatient stays, was developed by the Healthcare Cost and Utilization Project. Each year the NIS collects information on approximately 8 million total inpatient stays from about 1,000 hospitals [26]. The NIS contains uniform inpatient stay data collected from existing hospital discharge databases maintained by state agencies, hospital associations, and other private data organizations. Each year, the NIS collects information on approximately 8 million inpatient stays from about 1,000 hospitals in the U.S. [26]. The NIS is designed to approximate a 20% sample of US community hospitals, defined by the American Hospital Association (AHA) to be "all non-Federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions" [26]. Veterans and other federal hospitals are excluded [27].

Study Design and Population

A cohort of all hospitalizations with a primary diagnosis of TB (ICD-9-CM codes 010.xx - 018.xx) was constructed for the years 2000 through 2011. These 12 years of data were concatenated to determine inpatient all-cause mortality, length of stay (LOS), and total inpatient charges among TB hospitalizations with and without coexisting DM.

Temporal Trends

The rate of primary TB hospitalizations per 10,000 all-cause admissions was computed. The rates of primary TB hospitalizations with type 1 DM and type 2 DM per 10,000 primary TB hospitalizations were also examined. The unit of analysis was an admission/discharge, rather than a patient. Trends in the mean proportion of deaths among TB hospitalizations with and without coexisting DM, as well as the mean LOS and mean inpatient charges among these groups, were examined.

Predictor Variables

The primary exposure for this study was DM, as classified by ICD-9-CM codes (Appendix 1). Type 1 DM was inclusive of ICD-9-CM codes 250.x1 and 250.x3. Type 2 DM was inclusive of ICD-9-CM codes 250.x0 and 250.x2. Additional independent variables examined included patient demographic characteristics (i.e. age, sex, race, median household income of zip code of residence, health insurance status, and hospital admission source), other comorbid conditions, and hospital characteristics (i.e. ownership, region, location, and teaching status). All independent variables were examined as categorical variables.

Years 2000 through 2008 of the NIS included 14 potential comorbidities, and years 2009 through 2011 included 24 potential comorbidities. The AHRQ Clinical Classification Software (CCS) was utilized to determine all comorbidities except for tobacco dependency, history of tobacco use, chronic kidney disease, and drug dependency (Appendix 1). The AHRQ CCS consolidates pertinent ICD-9-CM codes into one code for given diagnoses. The CCS code for HIV is 5, which is inclusive of the following ICD-9-CM codes for HIV diagnosis: 042, 0420 – 0422, 0429 – 0433, 0439 – 0440, 0449, 07953, 27910, 27919, 79571, 7958, and V08. The CCS code for chronic obstructive pulmonary disorder (COPD) is 127, which is inclusive of the following ICD-9-CM codes: 490, 4910 – 4912, 49120 – 49122, 4918 – 4920, 4928, 494, 4940, 4941, and 496. The indicator variable for cancer included multiple CCS codes for the following types of cancers: head and neck, esophagus, stomach, colon, rectum and anus, liver and intrahepatic bile duct, pancreas, other GI organs (and peritoneum), bronchus and lungs, other respiratory and intrathoracic, bone and connective tissue, melanomas of skin, other non-epithelial cancer of skin, breast, uterus, cervix, ovary, other female genital organs, prostate, testis, other male genital organs, bladder, kidney and renal pelvis, other urinary organs, brain and nervous system, thyroid, Hodgkin`s disease, non-Hodgkin`s lymphoma, leukemias, multiple myeloma, secondary malignancies, and malignant neoplasm without specification of site. Tobacco dependency was specified by ICD-9-CM code 305.1, and history of tobacco use was specified as ICD-9-CM code V15.82. Chronic kidney disease was specified as ICD-9-CM code 585.9. Drug dependency was specified as ICD-9-CM codes 30400 – 30403, 30410 – 30413, 30420 – 30423, 30430 – 30433, 30440 – 30443, 30450 – 30453, 30460 – 30463, 30470 – 30473, 30480 – 30483, and 30490 – 30493.

Age was categorized into three groups: < 44 years of age, 45 – 64 years, and > 65 years. This categorization was chosen to provide sufficient data in each age group when examining deaths by type of DM. The variables race/ethnicity, median household income at the ZIP code level, expected first payer, hospital admission source, hospital bed size, hospital ownership, hospital region, and hospital location and teaching status were provided by the NIS. The NIS categorized median household income quartiles for years 2000 to 2002 as: first quartile, $1–$24,999; second quartile, $25,000–$34,999; third quartile, $35,000–$44,999; fourth quartile, $45,000+. The NIS categorized median household income quartiles for years 2003 to 2011 as: first quartile, $1–$38,999; second quartile, $39,000–$47,999; third quartile, $48,000–$62,999; fourth quartile, $63,000+.

Outcome Variables

The primary outcome for this study was in-hospital mortality due to all causes during a primary hospitalization for TB. Trends in the proportion of TB hospitalizations with type 1 and type 2 DM resulting in death are compared with proportion of deaths among TB hospitalizations without DM through the Cochran-Armitage test for trend. Trends in the secondary outcomes included length of stay (LOS) (days) and total inpatient charges (US dollars) were also analyzed. Total inpatient charges reflect the amount the hospital is billed for each TB hospitalization and do not include physician fees. Total inpatient charges were adjusted to 2011 US dollars using the Bureau of Labor Statistics' Consumer Price Index Inflation Calculator, found here: http://www.bls.gov/data/inflation_calculator.htm.

Statistical Analysis

Weighted descriptive statistics were used to characterize the discharge sample, using proportion or means with standard deviations (SDs) where appropriate. Baseline differences for categorical variables were evaluated by χ^2 test. Differences in the overall proportion of deaths, overall average LOS, and overall average inpatient charges between TB hospitalizations with and without DM were determined by *t* test. Means were assumed normal due to the large cohort size. The Cochran-Armitage test for trend was utilized to test for significance of changes of TB hospitalizations with and without comorbid DM. Weighted values were used to calculate yearly average deaths, yearly average LOS, and yearly inpatient charges among TB hospitalizations with and without DM. Averages were used to account for the differences in size of the TB hospitalizations with and without DM. Then the proportion of average deaths, average LOS, and average charges that occurred among those with coexisting DM were calculated for each year. These yearly proportions were then analyzed for significant changes over the study period using the Cochran-Armitage test for trend. Bivariate analysis was used to examine predictors of death among TB hospitalizations; associations were presented as crude risk ratios (RR), with corresponding 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Chapter II: Manuscript

Trends in mortality, length of stay, and inpatient charges among tuberculosis hospitalizations with and without coexisting diabetes, US, 2000 – 2011

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Abstract

Background: Tuberculosis (TB) patients with diabetes mellitus (DM) may have poorer outcomes and a higher risk of death than those without DM. This study used a national sample to investigate trends in and compare inpatient mortality and healthcare utilization among hospitalized TB patients with and without DM.

Methods: A cohort of TB hospitalizations was constructed using data from the Nationwide Inpatient Sample during the years 2000 through 2011. Differences in the proportion of all-cause inpatient deaths, average length of stay (LOS), and average inpatient charges between primary TB hospitalizations with and without DM were compared using the *t* test. Trends in TB-DM hospitalizations, mortality, LOS, and charges were analyzed by the Cochran-Armitage test for trend. Bivariate analysis was done to identify crude predictors of mortality among primary TB hospitalizations.

Results: There was a total of 102,072 primary TB hospitalizations during the study period; 16,796 (16.5%) had comorbid DM. The rate of primary TB hospitalizations without DM decreased by 50% over the study period, whereas the rate of primary TB hospitalizations with DM increased by 27.6% ($p < 0.001$). TB hospitalizations with DM were an average of 1.5 days longer than those without DM ($p = 0.003$). There was a positive trend in mean charges incurred among TB hospitalizations with DM, from $53,460 to $84,338 ($p < 0.001$). On average, 3.8% of TB hospitalizations without DM died per year, compared with 4.08% of TB hospitalizations with DM per year ($p = 0.49$). There was no significant trend in average LOS ($p = 0.44$) or average mortality ($p = 0.49$) per year. In bivariate analyses, DM was not associated with an increased risk of inpatient death among hospitalized TB patients ($p = 0.57$).

Conclusions: The findings suggest that coexisting DM among hospitalized TB patients is not associated with increased mortality, but may result in increased healthcare utilization as measured by LOS and inpatient charges. Inpatient charges among TB patients hospitalized with DM increased 5.2% annually, illustrating the potential economic burden placed on the US healthcare system when the two conditions coexist.

Introduction

In the US, tuberculosis (TB) incidence and TB-related mortality have declined steadily over the last two decades. However, TB patients with comorbidities such as human immunodeficiency virus (HIV) and diabetes mellitus (DM) remain at a higher risk of death [1]. In the 22 countries that account for 80% of the global TB burden, an estimated 7.5% of the TB burden has been attributed to DM [2].

Regional studies done in the US suggest that the prevalence of DM among adults with TB ranges from 14% to 28%, but these studies do not address the attributable burden of TB due to DM [1, 3-5]. A 1991 study among Hispanics in California determined that the estimated risk of TB attributable to DM was 25.2%, equivalent to that of attributable to HIV infection [6]. A more recent analysis of DM and TB in South Texas determined that 63% of TB cases were attributable to DM across all age groups studied [7]. Studies examining the impact of DM on TB mortality have shown conflicting results [1, 3, 4, 8]. In a 3-year study in the state of Georgia where 11.5% of TB patients had coexisting DM, the odds of death was similar among TB patients with and without DM [1]. By contrast, in another study of TB cases in Maryland from 2004 through 2005, TB patients with DM had 6.5 (95% CI: 1.1 – 38.0) times the odds of death compared with TB patients without DM [3]. Similarly, a study by Fielder *et al.* using data from 1993 through 1998 in Maryland determined that the age-adjusted odds of death among TB patients with DM was 3.80 (95% CI: 1.42 – 10.16) times that of TB patients without DM [8]. Oursler *et al.* studied TB cases from 1994 through 1996 and found that the age-adjusted mortality hazard ratio for TB patients with DM was 6.7 (95% CI: 1.6 – 29.3) times that of TB patients without DM [4]. Other predictors of death determined by these studies included being US-born (odds ratio = 7.50), above 60 years old (hazard ratio [HR] = 5.2), male sex (HR = 2.55), being unemployed (HR = 3.17) or retired (HR = 9.87), renal failure (HR = 4.21), HIV co-infection (HR = 4.7), and chronic obstructive pulmonary disorder (COPD) (HR = 2.6) [1, 3, 4, 8].

HIV comorbidity has been shown to increase healthcare utilization and costs among patients with TB [9-12]. For example, Rosenblum *et al.* used data from 1985 – 1990 to conclude that TB-HIV hospitalization costs accounted for between $2.5 and $3.1 billion, or 35%, of the total TB costs among all ages in the US [10]. Taylor *et al.* conducted a study in 2000 to determine the causes and costs of TB hospitalizations in 10 US locations, but did not include data on DM [12]. In that study, the median length of stay per TB hospitalization was 11 days, with a median cost of $644 per day and a mean cost of $7,288 per case [12]. Importantly, these data were not based on a national sample, as study participants were recruited and were mostly from urban locations [12]. A study by Kaufman *et al.* using data from New York State from 1987 through 1992 determined that TB-HIV patients were hospitalized more frequently for lengthier stays (LOS > 21 days) compared with TB patients without comorbid HIV [13]. There have been no similar studies examining healthcare utilization and costs due to DM among patients with TB.

This study used data from the Nationwide Inpatient Sample (NIS) during the years 2000 through 2011 to assess temporal trends in the proportion of hospitalized TB patients who had coexisting DM and to determine and compare inpatient mortality, length of stay, and total inpatient charges among hospitalized TB patients with and without DM.

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Methods

Nationwide Inpatient Sample Database

The Nationwide Inpatient Sample (NIS) was established by the Agency for Healthcare Research and Quality in 1988 as part of the Healthcare Cost and Utilization Project (HCUP). The NIS retains all-payer data on hospital inpatient stays from HCUP participating states. The NIS collects uniform data from existing hospital discharge databases maintained by state agencies, hospital associations, and other private data organizations. Each year, the NIS collects information on approximately 8 million inpatient stays from about 1,000 hospitals in the U.S. [26]. The NIS is designed to approximate a 20% sample of US community hospitals, defined by the American Hospital Association (AHA) to be “all non-Federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions” [26]. Veterans and other federal hospitals are excluded [27].

Study Design and Population

A cohort of all hospitalizations with a primary diagnosis of TB (ICD-9-CM codes 010.xx - 018.xx) was constructed for the years 2000 through 2011. The unit of analysis was admission/discharge. These 12 years of data were concatenated to determine all-cause mortality, length of stay, and inpatient charges among TB hospitalizations with and without coexisting DM. This study was deemed exempt from Investigational Review Board (IRB) review by the Emory University IRB.

Outcome and Predictor Variables

The primary outcome for this study was in-hospital mortality due to all causes while hospitalized for TB. Secondary outcomes included length of stay (days) and total inpatient charges (2011 US dollars) for TB hospitalizations. Total inpatient charges reflected the amount the hospital is billed for each TB hospitalization and did not include physician fees. Total inpatient charges were adjusted to 2011 US dollars using the Bureau of Labor Statistics' Consumer Price Index Inflation Calculator, located here: http://www.bls.gov/data/inflation_calculator.htm. Trends in proportion of deaths, mean LOS, and mean inpatient charges were examined to control for differences in size of the TB hospitalizations cohorts with and without DM.

The primary exposure for this study was DM, as classified by ICD-9-CM codes (Appendix 1). Type 1 DM was defined as ICD-9-CM codes 250.x1 and 250.x3. Type 2 DM was defined as ICD-9-CM codes 250.x0 and 250.x2. Additional independent variables examined included patient demographic characteristics (i.e. age, sex, race, median household income of zip code of residence, health insurance status, and hospital admission source), other comorbid conditions, and hospital characteristics (i.e. ownership, region, location, and teaching status). Other comorbid conditions examined included: HIV, tobacco dependency, history of tobacco use, chronic obstructive pulmonary disorder, cancer, drug dependency, and chronic kidney disease (Appendix 1). All independent variables were examined as categorical variables.

Statistical Analysis

Weighted descriptive statistics were used to characterize the discharge sample, using proportion or means with standard deviations (SDs) where appropriate. Baseline differences for categorical variables were evaluated by χ^2 test. Differences in the overall proportion of deaths, overall average LOS, and overall average inpatient charges between TB hospitalizations with and without DM were determined by *t* test. Means were assumed normal due to the large cohort size. The Cochran-Armitage test for trend was utilized to test for significance of changes of TB hospitalizations with and without comorbid DM. Weighted values were used to calculate yearly average deaths, yearly average LOS, and yearly inpatient charges among TB hospitalizations with and without DM. Averages were used to account for the differences in size of the TB hospitalizations with and without DM. The proportion of average deaths, average LOS, and average charges that occurred among those with coexisting DM were calculated for each year. These yearly proportions were then analyzed for significant changes over the study period using the Cochran-Armitage test for trend. Bivariate analysis was used to examine predictors of death among TB hospitalizations; associations were presented as crude risk ratios (RR), with corresponding 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Socio-demographic Characteristics of Hospitalized TB Patients

From 2000 through 2011, there were a total of 102,072 (44.9%) hospitalizations with a primary diagnosis of TB; 16,796 (16.5%) had coexisting DM. Socio-demographic comparisons of TB hospitalizations with and without DM are shown in Table 1. Compared with TB hospitalizations without DM, those with comorbid DM were older, were more likely to be Hispanic or Asian Pacific Islanders or to have missing race/ethnicity, more likely to have Medicare as payer, more likely to have chronic kidney disease, more likely to be in private, non-profit or voluntary hospitals, and more likely to be in the western US but less likely to have to have HIV and to be located in urban teaching hospitals (Table 1). TB hospitalization with and with DM were similar in median household income of zip code of residence, and hospital bed-size (Table 1).
As trends were analyzed using yearly data, socio-demographic characteristics of TB hospitalizations for the years 2000, 2005, and 2011 are shown in Table 2. The number of participating states significantly increased from 28 states in 2000 to 46 states in 2011 (Table 2). The proportion of TB hospitalizations with type 1 DM decreased from 2.54% of the 11,231 TB hospitalizations in 2000 to 0.64% of the 5,972 TB hospitalizations in 2011 (Table). However, 19.47% of TB hospitalizations in 2011 had comorbid type 2 DM, compared with 13.28% of TB hospitalizations in 2000 (Table 2). The proportion of males, as well as the distributions of age, expected first payer, hospital bed size, hospital control, hospital region, and hospital location and teaching status did not significantly

change when examining years 2000, 2005, and 2011 (Table 2). It appeared that the percentage of the cohort that were White, Hispanic, Asian or Pacific Islander, Native American, and "other" race increased (Table 2). The percentage of TB hospitalizations in the first income quartile steadily increased from 2000 to 2005 to 2011, though this may be due to the change in the definition of "first quartile" in 2003 (Table 2). Hospital admission source was determined as missing in 71% of 2011 TB hospitalizations, compared with 2.77% in 2000 and 0.06% in 2005 (Table 2). The comorbidities tobacco dependency and history of tobacco use both increased (Table 2).

TB Hospitalizations With and Without DM

The rate of primary TB hospitalizations significantly decreased from 3.1 per 10,000 all-cause hospitalizations in 2000 to 1.5 per 10,000 all-cause hospitalizations in 2011 (p-value < 0.001) (Figure 1). However, the overall rate of primary TB hospitalizations with coexisting DM significantly increased from 1,576 per 10,000 primary TB hospitalizations in 2000 to 2,012 per 10,000 primary TB hospitalizations in 2011 (p-value < 0.001). There also were differences in hospitalization trends when analyzed by type of DM. The rate of primary TB hospitalizations with comorbid type 1 DM significantly decreased from 254 per 10,000 primary TB hospitalizations in 2000 to 64 per 10,000 primary TB hospitalizations in 2011 (p-value < 0.001) (Figure 2). Whereas, the rate of primary TB hospitalizations with comorbid type 2 DM significantly increased from 1,328 per 10,000 primary TB hospitalizations in 2000 to 1,947 per 10,000 primary TB hospitalizations in 2011 (p-value < 0.001) (Figure 2).

All-Cause Inpatient Mortality

Overall, 4,004 (3.9%) of the 102,072 primary TB hospitalizations died during the hospital stay. On average, 3.8% (95% CI: 3.30% – 4.30%) of TB hospitalizations without DM died per year, compared to 4.08% (95% CI: 3.37% – 4.79%) of TB hospitalizations with DM per year (p-value = 0.49). Among TB hospitalizations with type 1 DM, an average of 4.22% (95% CI: 1.64% – 6.81%) died per year (p-value = 0.73), and TB hospitalizations with type 2 DM an average of 4.09% (95% CI: 3.35% – 4.82%) died per year (p-value = 0.49).

There was a decreasing trend in the rate of in-hospital deaths among those hospitalized with primary TB from 1.5 to 0.5 deaths per 100,000 all-cause admissions. There was no significant change in the mean percentage of deaths per year among TB hospitalizations with and without DM over the study period (p-value = 0.42) or when DM was examined by type over the study period (p-value = 0.49).

Length of Stay

A total of 1,501,212 hospital inpatient days were attributable to a primary diagnosis of TB from 2000 through 2011. TB hospitalizations without DM had a mean LOS of 14.4 days (95% CI: 13.70 – 15.17 days), while TB hospitalizations with coexisting DM had a mean LOS of 15.9 days (95% CI: 15.25 – 16.58 days) (p-value = 0.003) (Table 3). When examined by type, TB hospitalizations with type 1 DM had a similar mean LOS of 17.8 days (95% CI: 13.76 – 21.77 days) as those without DM (p-value = 0.086), but those with

Type 2 DM had a higher mean LOS than those without DM (15.7 days, 95% CI: 15.16 – 16.31 days) (p-value = 0.005) (Table 3).

The average LOS for TB hospitalizations with and without DM did not significantly change over the study period (p-value = 0.44). There were also no significant changes in average LOS by DM type (Figure 3).

Inpatient Charges

After adjustment to 2011 US dollars, primary TB hospitalizations accounted for a total of $6.1 billion in hospital charges during the study period. There were no significant differences in the overall mean charges among TB hospitalizations with and without DM (Table 3). The overall mean charges among TB hospitalizations without DM were $60,981.60 (95% CI: $54,306.20 – $67,657.00) as compared with $71,996.40 (95% CI: $63,023.70 – $80,969.10) for those with DM (Table 3). The overall average inpatient charges for TB hospitalizations with type 1 DM was $89,244.80 (95% CI: $57,267.60 – $121,222.00) whereas TB hospitalizations with type 2 DM had overall average charges of $70,779.80 (95% CI: $61,702.40 – $79,857.20) over the study period (Table 3).

When examining trends in average charges, the mean charges among TB hospitalizations without comorbid DM increased from $41,898 in 2000 to $69,819 in 2011 (Figure 4). Mean charges incurred among TB hospitalizations with DM significantly increased over the study period, from $53,460 in 2000 to $84,338 in 2011 (p-value < 0.001). This increase was observed when DM was examined by type as well; inpatient charges for TB hospitalizations with type 1 DM increased nearly 4-fold from $54,753 in 2000 to $208,236 in 2011 (p-value < 0.001) (Figure 4). Inpatient charges for TB hospitalizations with type 2 DM also increased, albeit less dramatically, from $53,109 in 2000 to $80,196 in 2011 (p-value < 0.001) (Figure 4).

Crude Predictors of Inpatient All-Cause Mortality

Among those hospitalized with TB, crude predictors of death included expected first payer of Medicare (risk ratio (RR) = 1.10) and Medicaid (RR = 1.11), hospital admission source of emergency room (RR = 1.59), another hospital (RR = 3.39), and another facility (RR = 2.40), chronic obstructive pulmonary disease (RR = 1.99), cancer (RR = 2.44), and chronic kidney disease (RR = 2.28) (Table 4). Crude protectors against death included Black (RR = 0.71), Hispanic (RR = 0.52), Asian or Pacific Islander (RR = 0.74), "other" (RR = 0.60) or missing (RR = 0.55) race, and tobacco dependency (RR = 0.39) (Table 4). DM was not a crude significant predictor of death, as those with DM had 1.04 (95% CI: 0.88 – 1.27) times the risk of death as those without DM (p-value = 0.57) (Table 4).

Discussion

This study investigated the trends TB hospitalizations with coexisting DM and the all-cause inpatient mortality, hospital LOS, and charges among TB patients with and without DM from 2000 through 2011. During the 12-year study period, the rate of primary TB hospitalizations (per 10,000 all-cause hospitalizations) decreased by 50%. Whereas, the rate of primary TB hospitalizations with coexisting DM (per 10,000 primary TB hospitalizations) increased by 27.6%, which was largely due to the increased number of TB admissions with type 2 DM. The observed increase in comorbid DM among TB patients was not surprising given the increasing prevalence of DM in the US, which the CDC estimated changed from a median prevalence of 4.5% in 1995 to 8.2% in 2011 [30]. The observed rate of TB hospitalizations with type 2 DM was 2 to 19-fold higher than the rate of TB hospitalizations with type 1 DM.

In this cohort, the demographic features of the TB patients who were admitted with DM were consistent with those of the larger population of diabetics in the US (i.e., more likely to be Asian Pacific islanders or Hispanics). Also, the Centers for Disease Control and Prevention (CDC) reported that Hispanics represented the largest percentage of total TB cases in the US from 2004 through 2010, and the second largest racial or ethnic group in 2011 [31]. Additionally, the rate of DM among Hispanics increased from 6.3% in 1997 to 9.2% in 2011 [32]. This suggests that the observed high proportion of Hispanics within the TB hospitalizations with DM, compared to without DM, is likely due to the higher burden of both TB and DM among Hispanic populations. Low socioeconomic status of the TB hospitalizations in this study may be characterized by approximately 20% of the TB hospitalizations' stays expected to be paid by Medicaid.

Among this cohort, all-cause inpatient mortality did not change significantly during the study period, irrespective of DM status. National statistics on TB deaths also suggest a stable rate of TB deaths over the 12 year period ranging from 0.3 TB deaths per 100,000 population in 2000 through 2002 to 0.2 TB deaths per 100,000 population during 2003 through 2011 [33]. However, the average percentage of in-hospital deaths among TB hospitalizations (3.9%) was nearly double that for all-cause hospital admissions excluding TB (2.1%). The average percentage of in-hospital deaths among TB hospitalizations without coexisting DM was 3.8% per year, and among those with coexisting DM it was 4.08% per year.

The average LOS for TB hospitalizations with and without DM, as well as by type of DM, did not significantly change over the study period. However, TB hospitalizations with DM had a significantly longer mean LOS compared to those without DM, with TB patients with DM averaging an additional 1.5 days of hospitalization per year.

Total inpatient charges among patients with and without DM were similar, irrespective of type of DM (Type 1 versus Type 2). TB hospitalizations without DM incurred approximately $70k in mean inpatient charges per year, while TB hospitalizations with DM incurred approximately $72k in mean inpatient charges per year. TB hospitalizations with type 1 DM incurred on average $90k inpatient charges per year and those with type 2 DM incurred an average of $71K per year. However, there was a positive trend in average inpatient charges among TB hospitalizations with DM from $53,460 in 2000 to $84,338 in 2011, representing a 57% increase over the study period. These data suggested the average increase in inpatient charges among TB hospitalizations with coexisting DM was 5.2% per year. Data previously reported using the Statewide Inpatient Databases to examine average hospital costs found that, after adjusting for inflation, average hospital costs increased by 2% per year on average [34].

In unadjusted analyses, several crude predictors of in-hospital death among TB hospitalizations DM were identified, including expected first payer, hospital admission source, comorbid chronic obstructive pulmonary disease, comorbid cancer, and comorbid chronic kidney disease. Expected first payer may be a proxy measure for low SES, a known risk factor TB, DM, and death [35-42]. A prior study examining TB mortality using the NIS found that emergency department admission was an independent predictor of death [24]. Chronic obstructive pulmonary disorder has previously been shown to be associated with TB, but there have been mixed results concerning its importance as a risk factor for mortality in TB patients [8, 43]. Moreover, DM is known to cause kidney disease and kidney failure, both of which are associated with higher mortality [44]. Surprisingly, tobacco dependency was shown to be protective against death in those with TB and comorbid DM. This may reflect the limitations of the ICD-9-CM code chosen to examine tobacco use. The code used in this study was entered when clinicians provided treatment to patients for tobacco dependency [45].

This study has a number of limitations. First, this analysis was based on administrative data and is therefore subject to coding errors. However, several other studies have successfully assessed patient outcomes using NIS datasets [24, 25, 46-48]. Second, this study focused on TB as a primary diagnosis in order to capture outcomes that are most likely attributable to TB illness, so it may underestimate the true outcomes of all TB hospitalizations. Third, several important risk factors that may have impacted mortality and the other study outcomes, such as homelessness, history of incarceration, injection drug use, body mass index, drug-resistant TB, TB treatment adherence, and time to diagnosis and treatment initiation could not be ascertained from this administrative dataset. Fourth, this study was among a hospitalized cohort and may not be reflective of all TB patients, as the majority of TB patients are outpatients. Fifth, the size of the TB population with type 1 DM was significantly smaller than the population with type 2 DM and without DM. This may have resulted in imprecise estimates among TB hospitalizations with type 1 DM. Sixth, the measure of patient income was at the zip code level instead of the individual level, which may have led to misclassification of income status [3, 49-51]. Seventh, because the study measured all-cause mortality, it was not possible to determine the deaths that were due to TB disease. Lastly, all results are based on unadjusted estimates and therefore do not control for other important predictors of mortality, LOS, total inpatient charges or the observed temporal trends.

Despite these limitations, this study has several strengths. The NIS is the largest all-payer inpatient care database that is publicly available in the US. The NIS is also a nationally representative sample, therefore TB hospitalizations in this study are representative of all US TB hospitalizations. This study also examined the potential differential impact of DM type (Type 1 versus 2) on outcomes among TB hospitalizations.

This study represents to the first to use a national dataset to describe and compare outcomes among TB patients with and without DM. The observed increasing trend in TB-DM hospitalization are consistent with the burgeoning DM epidemic here in the US and elsewhere [52]. The study findings suggest the coexisting DM among hospitalized

TB patients may result in increased healthcare utilization as measured by LOS and inpatient charges. Moreover, inpatient charges among TB patients hospitalized with coexisting DM have increased by 5.2% annually over the period 2000 through 2011, illustrating the potential economic burden placed on the US healthcare system when the two conditions coexist. These findings are also responsive to the Collaborative Framework for Care and Control of Tuberculosis and Diabetes in the US which suggests conducting cross-sectional studies to determine the rates of hospitalization and additional medical costs associated with DM among TB cases [14].

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Tables

Table 1. Comparison of socio-demographic characteristics of hospitalized TB patients with and without coexisting DM, NIS, US, 2000 – 2011.

	TB with DM N=16,796		TB without DM N=85,276	
Characteristics	N	(%)	N	(%)
Female	6,043	(36.0)	30,248	(35.5)
Age group (years)				
< 44*	3,135	(18.7)	40,341	(47.3)
45 – 64*	7,511	(44.7)	25,322	(29.7)
65+*	6,151	(36.6)	19,507	(22.9)
Race				
White*	2,534	(15.1)	18,316	(21.5)
Black*	2,998	(17.8)	18,198	(21.3)
Hispanic*	4,915	(29.3)	17,233	(20.2)
Asian or Pacific Islander*	2,733	(16.3)	9,210	(10.8)
Native American	168	(1.0)	685	(0.8)
Other	1,106	(6.6)	5,485	(6.4)
Missing*	2,342	(13.9)	16,143	(18.9)
Median Household Income				
First quartile	4,606	(27.4)	22,346	(26.2)
Second quartile	2,660	(15.8)	12,985	(15.2)
Third quartile	2,255	(13.4)	10,949	(12.8)
Fourth quartile	2,207	(13.1)	9,922	(11.6)
Missing*	5,069	(30.2)	29,057	(34.1)
Expected first payer				
Medicare*	5,725	(34.1)	18,795	(22.0)
Medicaid	3,699	(22.0)	19,858	(23.3)
Private including HMO*	2,871	(17.1)	18,775	(22.0)
Self-pay*	2,740	(16.3)	17,702	(20.8)
No charge*	320	(1.9)	2,403	(2.8)
Other	1,379	(8.2)	7,199	(8.4)
Missing	57	(0.3)	443	(0.5)
Hospital Admission Source				
Emergency room	8,586	(51.1)	42,730	(50.1)
Another hospital	538	(3.2)	2,554	(3.0)
Another facility, incl. long term care^	325	(1.9)	1,208	(1.4)
Court/law enforcement^	44	(0.3)	389	(0.5)
Routine/birth/other^	3,807	(22.7)	21,643	(25.4)
Missing	3,491	(20.8)	16,752	(19.6)
Comorbidities				

HIV*	313	(1.9)	3,850	(4.5)
Tobacco dependency*	2,116	(12.6)	14,198	(16.6)
History of tobacco use*	1,477	(8.8)	4,898	(5.7)
Chronic obstructive pulmonary disorder	2,526	(15.0)	13,368	(15.7)
Cancer^	1,228	(7.3)	4,938	(5.8)
Drug dependency	161	(1.0)	1,056	(1.2)
Chronic kidney disease*	400	(2.4)	678	(0.8)
Hospital Bed Size				
Small	1,717	(10.2)	8,641	(10.1)
Medium	4,187	(24.9)	20,283	(23.8)
Large	10,813	(64.4)	56,115	(65.8)
Missing^	79	(0.5)	237	(0.3)
Hospital Control				
Government or private, collapsed category*	10,788	(64.2)	60,454	(70.9)
Government, nonfederal, public	976	(5.8)	4,415	(5.2)
Private, non-profit, voluntary*	2,855	(17.0)	11,570	(13.6)
Private, invest-own^	1,922	(11.4)	7,838	(9.2)
Private, collapsed category	176	(1.1)	761	(0.9)
Missing	79	(0.5)	237	(0.3)
Hospital Region				
Northeast*	3,044	(18.1)	18,707	(21.9)
Midwest^	2,065	(12.3)	11,919	(14.0)
South^	6,467	(38.5)	35,976	(42.2)
West*	5,220	(31.1)	18,674	(21.9)
Hospital Location & Teaching Status				
Rural	858	(5.1)	4,898	(5.7)
Urban Non-Teaching*	6,282	(37.4)	26,546	(31.1)
Urban Teaching*	9,577	(57.0)	53,595	(62.8)
Missing	79	(0.5)	237	(0.3)

^ p-value < 0.05 determined by χ^2 test.

* p-value < 0.001 determined by χ^2 test.

Table 2. Socio-demographic characteristics of patients hospitalized with TB, NIS, US, 2000, 2005, & 2011.

Year	2000		2005		2011	
Participating States, n	28		37		46	
	N	(%)	N	(%)	N	(%)
TB Hospitalizations	11,231	-	8,987	-	5,972	-
DM						
Type 1	285	(2.54)	79	(0.88)	38	(0.64)
Type 2	1,492	(13.28)	1,202	(13.37)	1,163	(19.47)
Sex						
Male	7,197	(64.08)	5,683	(63.24)	3,888	(65.10)
Female	4,035	(35.93)	3,262	(36.30)	2,069	(34.65)
Age, yrs.						
< 44	4,685	(41.71)	3,947	(43.92)	2,337	(39.13)
45 - 64	3,456	(30.77)	2,959	(32.93)	2,156	(36.10)
65+	3,090	(27.51)	2,066	(22.99)	1,463	(24.50)
Race						
White	2,452	(21.83)	1,699	(18.91)	1,552	(25.99)
Black	2,399	(21.36)	1,563	(17.39)	1,305	(21.85)
Hispanic	2,197	(19.56)	1,842	(20.50)	1,443	(24.16)
Asian or Pacific Islander	1,203	(10.71)	785	(8.73)	832	(13.94)
Native American	79	(0.71)	75	(0.83)	89	(1.48)
Other	493	(4.39)	599	(6.66)	457	(7.65)
Missing	2,408	(21.44)	2,424	(26.97)	294	(4.92)
Median Household Income						
First quartile	2,269	(20.20)	3,275	(36.44)	2,301	(38.53)
Second quartile	3,148	(28.03)	2,196	(24.44)	1,220	(20.43)
Third quartile	2,457	(21.88)	1,784	(19.85)	1,172	(19.62)
Fourth quartile	2,457	(21.88)	1,449	(16.12)	1,116	(18.69)
Missing	345	(3.07)	283	(3.15)	163	(2.73)
Expected first payer						
Medicare	2,873	(25.58)	1,999	(22.24)	1,546	(25.89)
Medicaid	2,602	(23.17)	2,109	(23.47)	1,329	(22.25)
Private including HMO	2,503	(22.29)	1,791	(19.93)	1,198	(20.06)
Self-pay	1,898	(16.90)	2,183	(24.29)	1,083	(18.13)
No charge	219	(1.95)	249	(2.77)	151	(2.53)
Other	1,072	(9.55)	565	(6.28)	616	(10.31)
Missing	63	(0.56)	91	(1.01)	50	(0.84)
Hospital Admission Source						
Emergency room	6,193	(55.14)	5,264	(58.57)	987	(16.52)
Another hospital	373	(3.33)	375	(4.18)	78	(1.31)

Another facility, incl. long term care	192	(1.71)	146	(1.63)	36	(0.60)
Court/law enforcement	65	(0.58)	54	(0.60)	66	(1.10)
Routine/birth/ other	4,097	(36.48)	3,142	(34.96)	537	(8.99)
Missing	311	(2.77)	5	(0.06)	4,268	(71.47)
Comorbidities						
HIV/AIDS	559	(4.98)	333	(3.71)	161	(2.69)
Tobacco dependency	1,036	(9.22)	1,486	(16.53)	1,333	(22.32)
History of tobacco use	250	(2.23)	602	(6.70)	715	(11.97)
Chronic obstructive pulmonary disease	1,586	(14.12)	1,181	(13.14)	937	(15.68)
Cancer	616	(5.48)	392	(4.37)	447	(7.48)
Drug dependency	186	(1.66)	91	(1.01)	108	(1.81)
Chronic renal failure	0	-	33	(0.37)	126	(2.10)
Hospital Bed Size						
Small	1,300	(11.58)	978	(10.88)	522	(8.74)
Medium	2,894	(25.77)	2,221	(24.71)	1,453	(24.33)
Large	7,023	(62.53)	5,787	(64.39)	3,903	(65.35)
Missing	14	(0.12)	0	(0.00)	94	(1.57)
Hospital Control						
Government or private, collapsed category	7,710	(68.65)	5,787	(64.39)	4,034	(67.55)
Government, nonfederal, public	762	(6.78)	450	(5.01)	292	(4.89)
Private, non-profit, voluntary	1,642	(14.62)	1,226	(13.64)	915	(15.32)
Private, invest-own	939	(8.36)	942	(10.49)	592	(9.91)
Private, collapsed category	165	(1.47)	74	(0.83)	46	(0.76)
Missing	14	(0.12)	0	-	94	(1.57)
Hospital Region						
Northeast	2,213	(19.70)	1,691	(18.82)	1,202	(20.13)

Midwest	1,980	(17.63)	1,411	(15.70)	640	(10.72)
South	4,178	(37.20)	4,051	(45.08)	2,625	(43.96)
West	2,860	(25.47)	1,834	(20.41)	1,505	(25.20)
Hospital Location & Teaching Status						
Rural	860	(7.65)	1,834	(20.41)	269	(4.50)
Urban Non-Teaching	3,479	(30.98)	2,960	(32.94)	2,030	(33.99)
Urban Teaching	6,879	(61.25)	5,571	(61.99)	3,579	(59.93)
Missing	14	(0.12)	0	-	94	(1.57)

Table 3. Outcomes[a] of TB hospitalizations with and without DM, NIS, US, 2000 – 2011, N=102,072.

Outcome	TB without DM	TB with DM	TB with type 1 DM	TB with type 2 DM
Length of stay, days	14.4 ± 1.15	15.9 ± 1.05^	17.76 ± 6.31	15.74 ± 0.90^
Inpatient charges	\$60,981.60 ± 10,506.40	\$71,996.40 ± 14,122	\$89,244.80 ± 50,328.60	\$70,779.80 ± 14,286.80

[a] Values are given as mean ± SD

^ Compared to TB hospitalizations without DM, p-value < 0.05 determined by *t* test.

Table 4. Crude predictors of death among patients hospitalized with TB, NIS, US, 2000 – 2011, N=102,072.

	Total (N)	No. died	(%)	RR	95% CI
Sex					
Male	65,257	2,488	(3.81)	Ref.	
Female	36,262	1,516	(4.18)	1.10	0.95, 1.26
Age group, yrs.					
< 44	43,393	403	(0.9)	0.10	0.07, 0.12
45 – 64	32,761	1,145	(3.5)	0.36	0.31, 0.42
65+	25,618	2,456	(9.6)	Ref.	
Race					
White	20,791	1,180	(5.68)	Ref.	
Black^	21,166	851	(4.02)	0.71	0.58, 0.86
Hispanic^	22,101	648	(2.93)	0.52	0.42, 0.63
Asian or Pacific Islander^	11,918	503	(4.22)	0.74	0.57, 0.95
Native American	849	20	(2.40)	0.42	0.13, 1.34
Other^	6,577	222	(3.38)	0.60	0.42, 0.84
Missing^	18,466	579	(3.14)	0.55	0.44, 0.68
Median Household Income					
First Quartile	26,889	1,021	(3.80)	1.10	0.83, 1.43
Second Quartile	15,620	603	(3.86)	1.11	0.83, 1.48
Third Quartile	13,185	475	(3.60)	1.04	0.77, 1.39
Fourth Quartile	12,126	421	(3.47)	Ref.	
Missing	34,038	1,484	(4.36)	1.26	0.96, 1.63
Expected first payer					
Medicare^	24,457	2,152	(8.80)	4.50	3.58, 5.64
Medicaid^	23,519	798	(3.39)	1.74	1.34, 2.23
Private including HMO	21,599	480	(2.22)	1.14	0.84, 1.53
Self-pay	20,418	399	(1.96)	Ref.	
No charge	2,718	51	(1.88)	0.96	0.5, 1.76
Other	8,558	110	(1.28)	0.65	0.40, 1.06
Missing	499	9	(1.77)	0.90	0.18, 4.33
Hospital Admission Source					
Emergency room^	51,226	2,258	(4.41)	1.59	1.31, 1.93
Another hospital^	3,078	289	(9.39)	3.39	2.48, 4.64
Another facility, incl. long term care^	1,528	101	(6.63)	2.40	1.56, 3.68
Court/law enforcement	429	0	-	-	-

Routine/birth/ other	25,414	703	(2.76)	Ref.	
Missing	20,193	653	(3.23)	1.17	0.91, 1.49
Comorbidities					
DM					
Yes	16,771	689	(4.11)	1.05	0.87, 1.26
No	85,102	3,315	(3.90)	Ref.	
HIV/AIDS					
Yes	4,158	114	(2.74)	0.69	0.46, 1.02
No	97,716	3,890	(3.98)	Ref.	
Tobacco dependency^					
Yes	16,284	276	(1.70)	0.39	0.29, 0.51
No	85,589	3,728	(4.36)	Ref.	
History of tobacco use					
Yes	6,360	208	(3.26)	0.82	0.60, 1.12
No	95,513	3,797	(3.98)	Ref.	
Chronic obstructive pulmonary disease^					
Yes	15,870	1,075	(6.77)	1.99	1.70, 2.31
No	86,004	2,929	(3.41)	Ref.	
Cancer^					
Yes	6,155	544	(8.83)	2.44	2.01, 2.96
No	95,718	3,461	(3.62)	Ref.	
Drug dependency					
Yes	1,217	20	(1.62)	0.41	0.15, 1.04
No	100,656	3,985	(3.96)	Ref.	
Chronic kidney disease^					
Yes	1,078	95	(8.84)	2.28	1.47, 3.53
No	100,796	3,909	(3.88)	Ref.	
Hospital Bed Size					
Small	10,326	421	(4.1)	Ref.	
Medium	24,402	963	(3.9)	0.97	0.72, 1.28
Large	66834	2611	(3.9)	0.96	0.73, 1.25
Missing	311	9	(3.0)	0.74	0.18, 2.93
Hospital Control					
Government, nonfederal, public	5,382	258	(4.8)	1.12	0.78, 1.59
Private, non-profit, voluntary	14,396	706	(4.9)	1.14	0.86, 1.50
Private, invest-own	9,719	417	(4.3)	Ref.	
Missing	311	9	(3.0)	0.70	0.17, 2.77
Hospital Region					
Northeast	21,675	912	(4.2)	1.17	0.86, 1.56
Midwest	13,983	505	(3.6)	Ref.	

South	42,334	1,634	(3.9)	1.07	0.81, 1.39
West	23,881	953	(4.0)	1.10	0.82, 1.48
Hospital Location & Teaching Status					
Rural	5,746	288	(5.0)	Ref.	
Urban Non-Teaching	32,750	1,567	(4.8)	0.96	0.71, 1.28
Urban Teaching	63,067	2,140	(3.4)	0.68	0.50, 0.91
Missing	311	9	(3.0)	0.60	0.15, 2.40

^ p-value < 0.05 determined by χ^2 test.

Figures

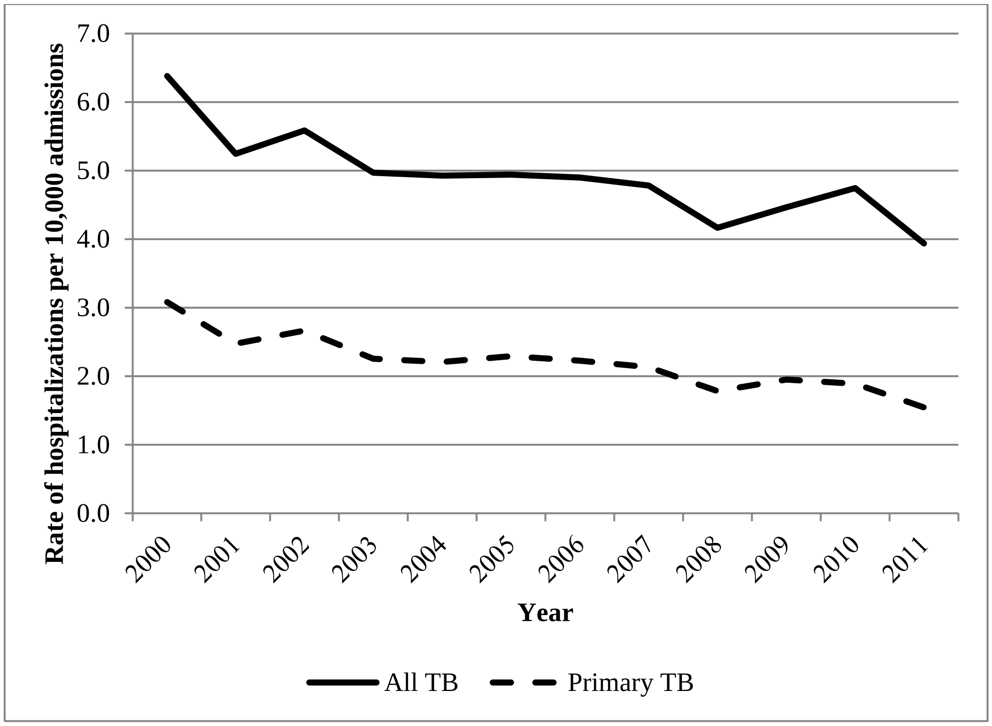

Figure 1. Rates of TB hospitalizations per 10,000 all-cause hospital admissions per year in the NIS, US. TB defined as ICD-9-CM codes 010.xx – 018.96.

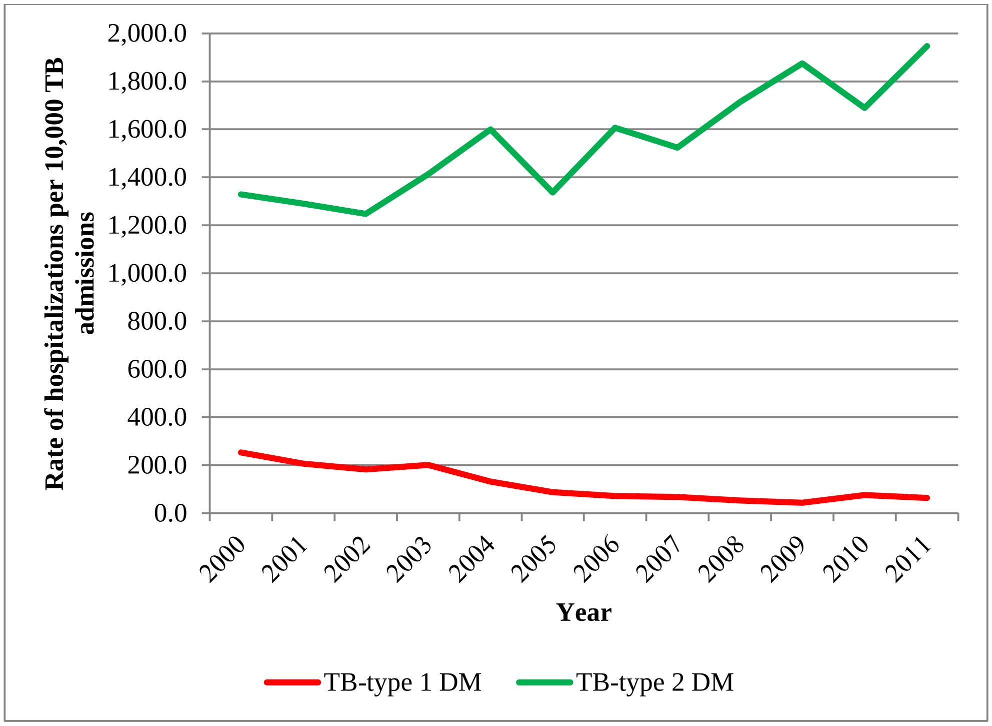

Figure 2. Rates of TB with comorbid DM hospitalizations per 10,000 TB admissions per year. TB defined as ICD-9-CM codes 010.xx – 018.96. DM defined as ICD-9-CM code 250.x1 (Type I), 250.x3 (Type I), 250.x0 (Type II), and 250.x2 (Type II).

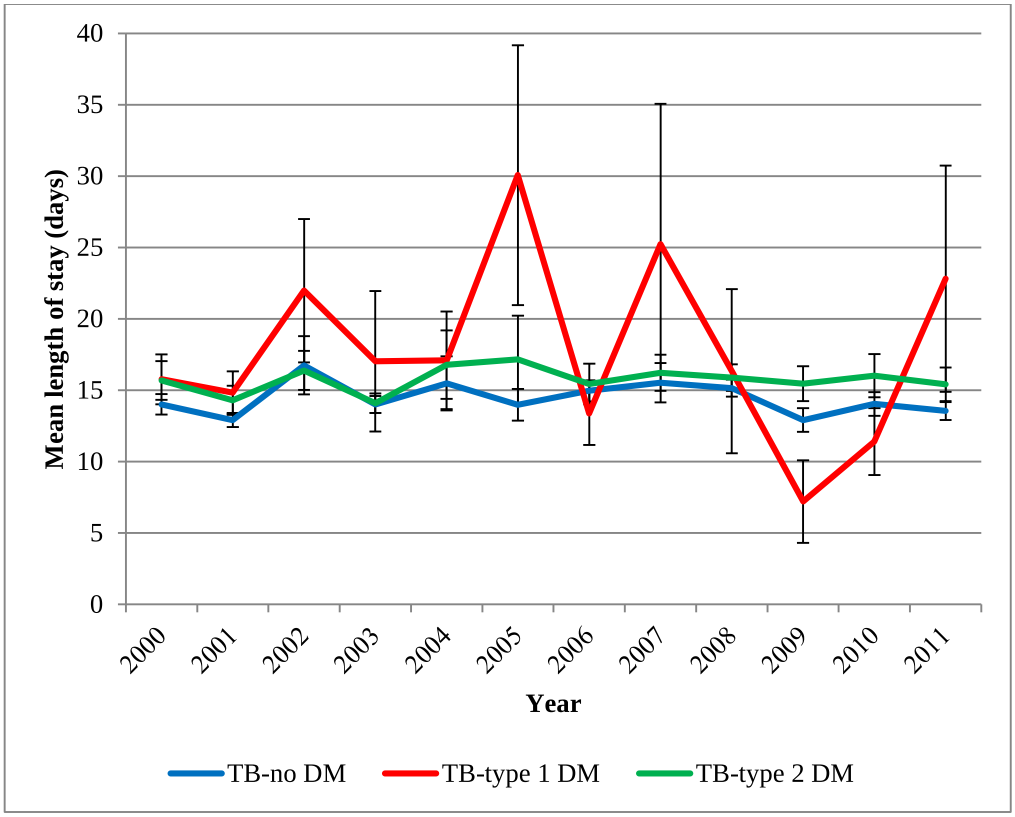

Figure 3. Mean length of stay (LOS) (days) associated with TB hospitalizations with and without DM. TB defined as ICD-9-CM codes 010.xx – 018.96. Type 1 DM defined as ICD-9-CM code 250.x1 and 250.x3. Type 2 DM defined as ICD-9-CM code 250.x0 and 250.x2.

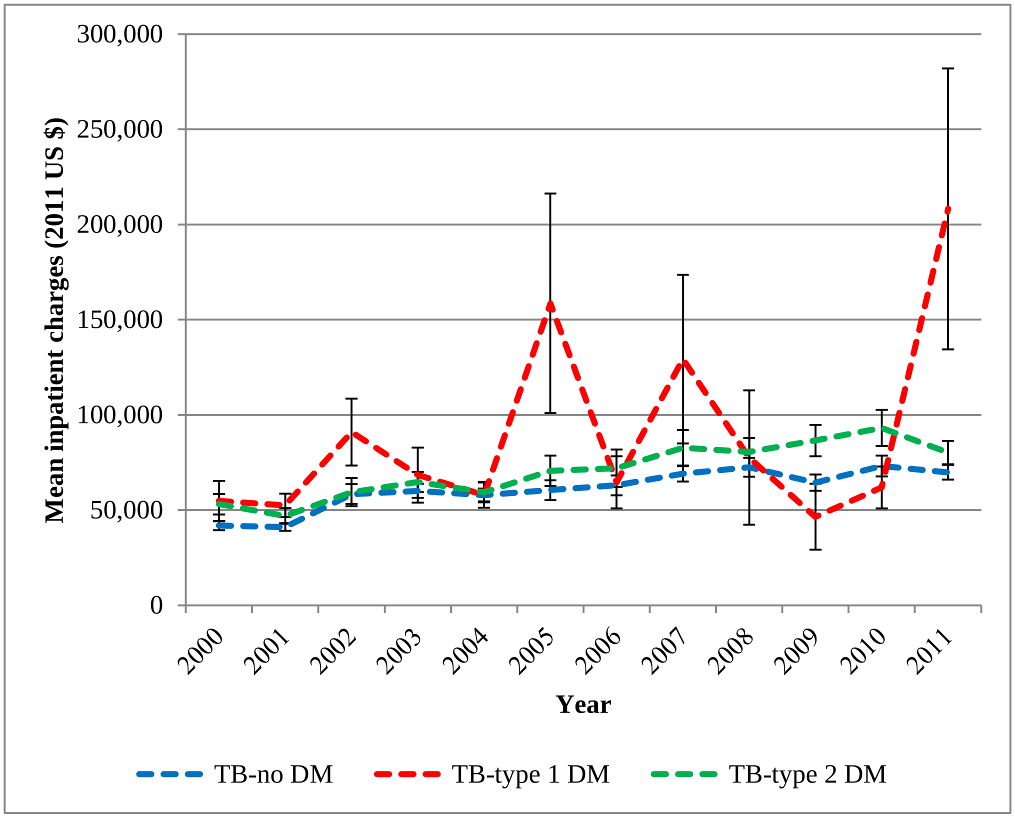

Figure 4. Mean inpatient charges (2011 US dollars) associated with TB hospitalizations with and without DM. TB defined as ICD-9-CM codes 010.xx – 018.96. Type 1 DM defined as ICD-9-CM code 250.x1 and 250.x3. Type 2 DM defined as ICD-9-CM code 250.x0 and 250.x2.

Chapter III: Summary

Summary

This study investigated the trends TB-DM hospitalizations and mortality, hospital LOS, and total inpatient charges among TB hospitalizations with and without using data reported to the NIS from 2000 through 2011. During the 12-year study period, the rate of primary TB hospitalizations (per 10,000 all-cause hospitalizations) decreased by 50%. Whereas, the rate of primary TB hospitalizations with coexisting DM (per 10,000 primary TB hospitalizations) increased by 27.6%. Previous studies have suggested that DM may have a negative effect on outcomes among TB patients, therefore all-cause mortality, LOS, and total charges were compared between TB hospitalizations with and without DM [3, 4, 8].

The overall percentage of in-hospital deaths for primary TB hospitalizations (3.9%) was nearly double that for in-hospital deaths for all-cause hospital admissions excluding primary TB (2.1%), and there was no difference in the mean percentage of in-hospital deaths among TB hospitalizations with and without DM. This suggests that the average percentage of deaths among TB hospitalizations with DM was similar to those without DM over the study period. Also, over the 12-year period, there was no significant trend in the mean proportion of deaths among TB hospitalizations with or without DM over the study period. Similarly, the average LOS for TB hospitalizations with and without DM, as well as by type of DM, did not significantly change over the study period. TB hospitalizations with DM had a statistically significant greater mean LOS of 1.5 days compared to those without DM. After adjustment to 2011 US dollars, there was a significant positive trend in mean inpatient charges due to TB with DM throughout the study period, which increased from $53,460 in 2000 to $84,338 in 2011. Comparisons between the mean inpatient charges among TB hospitalizations with and without DM revealed no significant difference in charges when both types of DM are combined. However, when examined by type of DM, those TB hospitalizations with type 1 DM incurred on average significantly higher inpatients charges than those without DM. This estimate had a higher standard deviation than the other mean charges estimates, reflecting its uncertainty. Significant crude predictors of all-cause mortality included expected first payer, hospital admission source, comorbid chronic obstructive pulmonary disease, comorbid cancer, and comorbid chronic kidney disease. DM was not identified as a crude significant predictor of all-cause mortality.

All trends reported here are based on unadjusted estimates, therefore they do not control for other predictors of all-cause mortality, LOS, or total inpatient charges. Significant differences in baseline socio-demographic characteristics between TB hospitalizations with and without DM suggest the need to control for socio-demographic characteristics in future studies. Additionally, comorbidities such as HIV/AIDS and chronic kidney disease have known high risks of mortality, and also need to be included in mortality models of TB hospitalizations with and without DM. Future directions include a logistic regression model of mortality, and linear regression models of LOS and inpatient charges, which control for other predictors of mortality, LOS and charges, to compare outcomes of TB hospitalizations with type 1 DM and type 2 DM to those without DM.

Public Health Implications

TB cases have been on the decline in the US for the last 15 years, but the increasing burden of comorbid chronic conditions such as DM may hamper further declines and planned elimination efforts. In the US, an increasing proportion of TB cases have occurred among foreign-born persons compared to US-born persons since 1993 [31]. The estimated prevalence of DM in US persons born in Mexico, the Philippines, and China were 15.6%, 9.6% and 8.8%, while US-born persons had an estimated DM prevalence of 9.3% [40]. Mexico, the Philippines, and China represent three of the top five countries of origin of foreign-born persons with TB in the US, suggesting that comorbid DM among TB hospitalizations will continue to rise [31, 40].

Mean inpatient charges were higher among TB patients with coexisting DM and were largely borne by public payers (47% paid by Medicare and Medicaid). This is similar to the conclusion by Marks *et al.* that demonstrated that government insurance paid for 57% of TB hospitalization costs [11]. The federal government need to be aware of the significant increase in charges produced by TB hospitalizations with DM, as they are bearing the burden of these additional charges.

These findings suggest the coexisting DM among hospitalized TB patients may result in increased healthcare utilization as measured by LOS and inpatient charges. Moreover, inpatient charges among TB patients hospitalized with coexisting DM has increased by 5.2% annually over the period 2000 through 2011, illustrating the potential economic burden placed on the US healthcare system when the two conditions coexist. Data such as these may provide evidence for Medicare and Medicaid to subsidize programs that prevent and treat DM, which may reduce inpatient charges during hospitalization for TB or other diseases.

Future Directions

The current study demonstrated that the proportion of TB hospitalizations with comorbid DM increased significantly over the 12 years study period. Future research should control for potential confounders (e.g., age, race, socioeconomic status and other comorbidities) to adequately assess the independent relationship between DM and all-cause mortality among patients hospitalized with primary TB. Likewise, linear regression models are needed to better determine predictors of LOS and inpatient charges and the independent relationship of DM to these outcomes among patients hospitalized with primary TB. Glycemic control may have an effect on TB treatment outcomes, so future studies should also examine whether the level of diabetes control impacts outcomes such as death, LOS, and hospital charges among patients hospitalized with TB.

Appendix 1

Table 1. Classification of comorbidities, NIS, 2000 – 2011.

Comorbidity	CCS code	ICD-9-CM code(s)
Type 1 DM	-	250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93
Type 1 DM	-	250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92
HIV	5	042, 0420 – 0422, 0429 – 0433, 0439 – 0440, 0449, 07953, 27910, 27919, 79571, 7958,V08
Chronic obstructive pulmonary disease and bronchiectasis	127	490, 4910 – 4912, 49120 – 49122, 4918 – 4920, 4928, 494, 4940, 4941, 496
Chronic kidney failure	-	585.9
Tobacco dependency	-	305.1
History of tobacco use	-	V15.82
Drug dependency	-	30400 – 30403, 30410 – 30413, 30420 – 30423, 30430 – 30433, 30440 – 30443, 30450 – 30453, 30460 – 30463, 30470 – 30473, 30480 – 30483, 30490 – 30493
Cancer		
Head and neck	11	1400, 1401, 1403 – 1406, 1408 – 1416, 1418 – 1422, 1428 – 1431, 1438 – 1441, 1448 – 1456, 1458 – 1473, 1478 – 1483, 1488 – 1498, 1499, 1600 – 1605, 1608 – 1613, 1618, 1619, 1950, 2300, 2310, V1001, V1002, V1021
Esophagus	12	1500 – 1505, 1508, 1509, 2301, V1003
Stomach	13	1510 – 1516, 1518, 1519, 20923, 2302, V1004
Colon	14	1530 – 1539, 1590, 20910 – 20916, 2303, V1005

Rectum and anus	15	1540 – 1543, 1548, 20917, 2304 – 2306, 79670 – 79674, 79676, V1006
Liver and intrahepatic bile duct	16	1550 – 1552, 2308, V1007
Pancreas	17	1570 – 1574, 1578, 1579
Other GI organs; peritoneum	18	1520 – 1523, 1528, 1529, 1560 – 1562, 1568 1569, 1580, 1589, 1591, 1598, 1599, 20900 – 20903, 2307, 2309, V1000, V1009
Bronchus; lung	19	1622 – 1625, 1628, 1629, 20921, 2312, V1011
Other respiratory and intrathoracic	20	1620, 1630, 1631, 1638, 1639, 1650, 1658, 1659, 2311, 2318, 2319, V1012, V1020, V1022
Bone and connective tissue	21	1700 – 1719
Melanomas of skin	22	1720 – 1729, V1082
Other non-epithelial cancer of skin	23	1730, 17300 – 17302, 17309, 1731, 17310 – 17312, 17319, 1732, 17320 – 17322, 17329, 1733, 17330 – 17332, 17339, 1734, 17340 – 17342, 17349, 1735, 17350 – 17352, 17359, 1736, 17360 – 17362, 17369, 1737, 17370 – 17372, 17379, 1738, 17380 – 17382, 17389, 1739, 17390 – 17392, 17399, 20931 – 20936, 2320 – 2329, V1083
Breast	24	1740 – 1746, 1748 – 1750, 1759, 2330, V103
Uterus	25	179, 1820, 1821, 1828, 2332, V1042
Cervix	26	1800, 1801, 1808, 1809, 2331, 7950, 79506, V1041, 79501 – 79504
Ovary	27	1830, V1043
Other female genital organs	28	181, 1832 – 1835, 1838 – 1849, 2333, 23330 – 23332, 23339, 79516, V1040, V1044
Prostate	29	185, 2334, V1046
Testis	30	1860, 1869, V1047
Other male genital organs	21	1871 – 1879, 2335, 2336, V1045, V1048, V1049

Bladder	32	1880 – 1889, 2337, V1051
Kidney and renal pelvis	33	1890, 1891, 20924, V1052, V1053
Other urinary organs	34	1892 – 1894, 1898, 1899, 2339, V1050, V1059
Brain and nervous system	35	1910 – 1923, 1928, 1929, V1085, V1086
Thyroid	36	19,3 25802, 25803, V1087
Hodgkin`s disease	37	20100 – 20108, 20110 – 20128, 20140 – 20148, 20150 – 20158, 20160 – 20168, 20170 – 20178, 20190 – 20198, V1072
Non-Hodgkin`s lymphoma	38	20000 – 20008, 20010 – 20018, 20020 – 20028, 20030 – 20038, 20040 – 20048, 20050 – 20058, 20060 – 20068, 20070 – 20078, 20080 – 20088, 20200 – 20208, 20210 – 20218, 20220 – 20228, 20270 – 20278, 20280 – 20288, 20290 – 20298, V1071, V1079
Leukemias	39	20240 – 20248, 2031, 20310 – 20312, 2040, 20400 – 20402, 2041, 20410 – 20412, 2042, 20420 – 20422, 2048, 20480 – 20482, 2049, 20490 – 20492, 2050, 20500 – 20502, 2051, 20510 – 20512, 2052, 20520 – 20522, 2053, 20530 – 20532, 2058, 20580 – 20582, 2059, 20590 – 20592, 2060, 20600 – 20602, 2061, 20610 – 20612, 2062, 20620 – 20622, 2068, 20680 – 20682, 2069, 20690 – 20692, 2070, 20700 – 20702, 2071, 20710 – 20712, 2072, 20720 – 20722, 2078, 20780 – 20782, 2080, 20800 – 20802, 2081, 20810 – 20812, 2082, 20820 – 20822, 2088, 20880 – 20882, 2089, 20890 – 20892, V1060 - V1063, V1069
Multiple myeloma	40	2030, 20300 – 20302, 2038, 20380 – 20382
Other and unspecified primary	41	1640, 1641 – 1643, 1648, 1649, 1760 – 1765, 1768, 1769, 1900 – 1909, 1940, 1941, 1943 –

			1946, 1948, 1949, 1951 – 1955, 1958, 20230 – 20238, 20250 – 20258, 20260 – 20268, 20922, 20925 – 20927, 2340, 2348, 2349, 7951, 79510 – 79514, V1029, V1081, V1084, V1088, V1089, V109, V1090, V1091, V711
	Secondary malignancies	42	1960 – 1963, 1965, 1966, 1968 – 1978, 1980 – 1987, 19881, 19882, 19889, 20971 – 20974, 51181, 78951
	Malignant neoplasm without specification of site	43	1990 – 1992, 20920, 20929, 20930, 20970, 20975, 20979