# A Retrospective Cohort Study of Mortality Associated with Tuberculosis in North Carolina, 1993-2003

By

Lisa T. Nguyen

A Master's Paper submitted to the faculty of

The University of North Carolina at Chapel Hill

in partial fulfillment of the requirements for

the degree of Master of Public Health in

the Public Health Leadership Program

Chapel Hill

2005

**ABSTRACT**

*Introduction* Previously reported predictors of mortality have focused on mortality during TB treatment. We propose instead to examine TB deaths relative to TB treatment. We predict that different characteristics will predict death before TB treatment, early in TB treatment and later in TB treatment.

*Methods* A retrospective cohort study was performed using data collected on all patients reported to the North Carolina TB Control Program in conjunction with data obtained from the U.S. National Death Index. Bivariate, multivariate and survival analyses were performed to examine relationships between patient characteristics and time of death relative to treatment.

*Results* Age (adjusted OR=1.04 per year of age, 95%CI 1.03-1.05, HIV/TB co-infection (adjusted OR=3.44, 95%CI 2.04-5.79) and being an American Indian (adjusted OR=4.00, 95%CI 1.47-10.93) were predictors of death before initiation of TB treatment. Age (adjusted HR=1.06 each year of age, 95%CI 1.05-1.07), black race (adjusted HR=1.35, 95%CI 1.05-1.75), HIV/TB co-infection (adjusted HR=1.66, 95%CI 0.99-2.76), history of alcohol abuse (adjusted HR=1.68, 95%CI 1.17-2.41) and residence in a long-term care facility (adjusted HR=1.70, 95%CI 1.23-2.34) were predictors of death in the first 8 weeks of treatment. After the initial 8 weeks, only age (adjusted HR=1.05 for each year of age, 95%CI 1.04-1.06) and HIV/TB co-infection (adjusted HR=5.53, 95%CI 3.65-8.44) continued to be predictors of mortality.

*Discussion* Overall, increasing age and HIV/TB co-infection were predictors of death prior to starting TB therapy and during all stages of TB therapy. Additional TB patient characteristics also existed that predict death specifically before treatment or in the early weeks of treatment.

## INTRODUCTION

*Burden of Disease*

Tuberculosis (TB) is a contagious but curable disease that continues to affect millions of people worldwide. Caused by *Mycobacterium tuberculosis*, TB can be spread to others when those with active pulmonary TB cough, propelling respiratory droplets laden with TB bacilli into the air. It is estimated that there were 8.3 million new TB cases worldwide in 2000, with an annual case rate increase of 1.8% each year between 1997 and 2000[1]. Additionally, despite directly observed treatment, short-course (DOTS) strategy, TB related mortality figures remain unacceptably high around the world.

Although the Americas do not carry the burden of disease that other regions of the world carry, 2004 TB incidence rates range from 5.5 per 100,000 people in Canada to 188.0 per 100,000 people in Peru[2]. In the United States, 14,511 new cases (4.9 cases per 100,000 people) of confirmed TB in the United States were documented in 2004. Though this is the lowest case rate to be reported since 1953, the 3.3% decline from 2003 is only the second smallest yearly decline since 1993[3]. The U.S. also saw 802 deaths (0.3 deaths per 100,000 people) directly attributed to TB in 2002, representing a 5.0% increase from the previous year and the first increase in U.S. TB deaths since1989[4]. Data on the 2003 and 2004 TB deaths are not currently available

*Predictors of Mortality*

TB associated mortality may occur prior to initiation of TB therapy, during TB therapy or subsequent to TB treatment completion. However, most studies that have examined predictors of TB-associated death have focused only on death during TB treatment. Reported predictors of mortality during TB treatment include medical co-morbidities[5-10], previous TB treatment[7, 11], HIV/TB co-infection[10, 12-14], low weight[9, 15] and alcoholism[11, 16]. Less frequently reported risk factors include homelessness[8], significant weight loss[11] and multidrug resistance[13]. Older age has been shown to be a predictor of TB death in some community-based treatment settings [5, 7, 16, 17], but not in others[8, 15, 18]. In general, the studies discussed thus far focus on risk factors that predict death in patients undergoing TB treatment, with little distinction between characteristics associated with death early in treatment versus later in the treatment period. However, TB associated deaths occur at many points in the course of TB treatment and it may be possible to clarify some of the variation by examining mortality risk factors relative to time of TB treatment.

A handful of studies have reported the frequency of death prior to TB treatment[11, 17, 18] (Appendix A). Additionally, Farah et al. reported that the median age of those who died prior to TB treatment was 71 years of age [17]. Walpola et al. presented a limited case series of 25 patients who died prior to treatment; 28% of these patients died prior to or within one day of presentation

while the other 72% presented more than one day before death but were not diagnosed with TB until after death [18].

After these initial deaths prior to TB treatment, death can be viewed as occurring in two phases during TB therapy: the initial weeks of TB therapy and the later weeks of treatment. The early treatment time period may include hospital admission and represent a time of high acuity of illness. A study by Sacks et al. reported that 32% of hospitalized TB patients died within the first 7 days of admission; 50% of admitted TB patients died by day 19 of hospitalization[9]. On the other hand, the later treatment time period (representing those who died after 8 weeks of treatment) may involve toxicity to treatment medications, treatment failure or medical co-morbidities. The identification of risk factors associated with death early in treatment compared to factors associated with death later in treatment may prove useful in the development of specific strategies to prevent TB mortality. Likewise, the identification of predictors of death before initiation of TB treatment may allow for targeted public health efforts that will decrease TB related death. Lastly, continued study of death during TB treatment is important to confirm previously reported risk factors, as well as identify factors that have not been studied thus far.

This study sets out to explore TB patient characteristics associated with death in the state of North Carolina, which is located in the southeastern United States. The southeastern United States has the highest percentage of households with

incomes below the federal poverty level of any region in the country[19], and is different from the urban populations usually studied in the United States as it comprises a predominantly rural population whose source of health care is geographically scattered. Additionally, the 2000 United States National Census revealed that the Hispanic/Latino population in North Carolina grew by 379% between 1990 and 2000, the largest change in proportion of any state in the U.S.[20]. Given that foreign born individuals make up an increasing proportion of the TB cases in the United States[21], further analysis of TB risk factors in North Carolina may provide useful clues for public health and individual health care providers regarding the future of TB in America. Hence, the study of TB in North Carolina offers a perspective on TB that is unique from past U.S. studies in setting while also providing data on a population that is in fact similar to other non-urban U.S. populations.

*Study Aims and Hypotheses*

The primary goals of this study were to determine the demographic and behavioral risk factors associated with mortality among patients diagnosed with TB in North Carolina during the ten year period, 1993 to 2003. TB-associated mortality was evaluated relative to treatment, using the following subgroups: (1) death prior to initiating TB treatment, including those who were already dead at TB diagnosis (2) death early in TB treatment and (3) death later in TB treatment. We hypothesize that we will be able to identify patient-specific characteristics that are significantly associated with the different times of death.

Additional specific hypotheses that we postulated include: environmental factors would be identified that were significantly associated with overall mortality; patients under age 5 and over age 65 would be more likely to die early in TB treatment than patients age 5-64; patients with history of homelessness and/or alcohol abuse would have higher rates of death prior to initiation of TB treatment than those without history of homelessness or alcohol abuse; patients who were homeless will have higher mortality rates later in TB treatment than TB patients who were not homeless.

## METHODS

### *Study design*

We performed a retrospective cohort study comparing the impact of various patient characteristics on death in TB patients who were reported to the North Carolina State TB Control Program between January 01, 1993 and December 31, 2003.

### *Institution Approval*

The project was performed subsequent to approval by the Institutional Review Boards (IRBs) of Duke University Health System, the University of North Carolina-Chapel Hill's School of Public Health, and the North Carolina Department of Health and Human Services' Division of Public Health, respectively. Each IRB granted a waiver of consent and HIPAA authorization, and we sufficiently met all requirements for data storage and protection of confidentiality. Additionally, approval to query the U.S. National Death Index (NDI) was granted by the National Center for Health Statistics.

### *Sample*

Our cohort study includes data that are routinely collected on adult and pediatric patients diagnosed with active TB via the Centers of Disease Control and Prevention (CDC) data collection instrument, the Report of Verified Case of TB (RVCT). This instrument captures all TB cases within the state of North Carolina, including cases diagnosed after death via autopsy or culture specimens that grow

*M. tuberculosis* after the patient has died, and cases that are based on a clinical diagnosis. This data is entered into a CDC database, the Tuberculosis Information Management System (TIMS), and downloaded into the North Carolina TB Control Program's Microsoft Access™ database. The North Carolina TB Control Program's data set was used in conjunction with information obtained from the NDI. The NDI is a national mortality database that has been shown to be a reliable source of U.S. mortality data for medical and health research[22-24]. The national database contains identifying data from state-mandated death certificates from all fifty states, New York City, the District of Colombia, Puerto Rico and the Virgin Islands.

*NDI Query Methods*

Subjects who died prior to or during TB therapy were identified in the RVCT records. The NDI was used to confirm time of death for these subjects, as well as capture any deaths that were not identified by RVCT records, by sending the identifying data of all subjects obtained from the RVCT to the NDI to query for linked records. Data sent for linking included subjects' Social Security number (SSN), full name, date of birth (DOB), race, gender and last known state of residence, as entered in the North Carolina TB Control Program's Microsoft Access™ database.

Once the results of the NDI query were received, the records that correctly linked subjects found in the North Carolina TB Control Program's Access database with

those in the NDI database were separated from the inaccurate or false record matches. To do so, specific link criteria (listed in Appendix B) were applied. Records that did not fulfill any of the above requirements were discarded as inaccurate or false matches. The dates of death obtained from the correctly linked records were used in analyses of death relative to TB treatment.

*Inclusion/Exclusion Criteria*

All patients reported to the North Carolina TB Control Program were included in the analyses. At the time of this study, death records up to December 31, 2003 were available from the NDI for all patients. All deaths that occurred by December 31, 2003 were included in the analyses.

*Outcome Groups*

Analyses focused on three outcome subgroups derived from timing of death. The subgroup referred to as 'death prior to initiation of treatment' comprises all reported TB patients who were diagnosed with TB but died before any TB therapy was started; this subgroup includes patients who were diagnosed at autopsy. The subgroup called 'death early in TB treatment' refers to all TB patients who began TB therapy with the North Carolina TB Control Program but died within the initial eight weeks of treatment and hence prior to completion of treatment. The subgroup referred to as 'death later in TB treatment' comprises all TB patients who initiated TB therapy, survived past eight weeks but died prior to completion of TB treatment.

*Exposure Variables*

The elements reported in the RVCT were used to examine which patient characteristics predicted death in the different subgroups. The demographic, clinical and social (such as homelessness or excess alcohol use) characteristics were based on either documented patient medical history or by patient self-report, as recorded by public health nurses via the RVCT. The variables used in our analyses are listed in Appendix C.

With regard to the race variable, in January 2003 the RVCT changed how it categorized patients' race. Prior to 2003, patients were characterized as one of four races: White, Black, American Indian or Alaskan Native, and Asian or Pacific Islander. The 2003 RVCT separated 'Asian or Pacific Islander' into two distinct categories, resulting in a total of five possible race choices. Patients are now characterized as White, Black or African American, American Indian or Alaskan Native, Asian, or Native Hawaiian or Other Pacific Islander. For the data analysis of this study, the patients who were separated into Asian and Hawaiian or Other Pacific Islander categories by the 2003 RVCT were collapsed into one Asian-Pacific Islander category.

*Statistical Analysis*

The primary outcome of this study is time to death. Statistical analyses were performed with Stata 8.1 (Stata Corporation, College Station, TX) and SAS, version 9.1 (SAS Institute, Inc., Cary, NC) software packages. Bivariate analysis

was performed to examine the relationship between various patient characteristics and the time of death relative to treatment. Differences in proportions were assessed using the chi-square test or Fisher's exact test, as appropriate. Differences in survival among groups with different demographic and risk profiles were examined using the Kaplan-Meier method with survival functions compared with the log-rank test.

Logistic regression modeling and Cox proportional hazards regression modeling were used to examine the independent effects of multiple factors on time of death. With regard to variables in which values were labeled as "positive", "negative" or "unknown", such as HIV status, those with "unknown" values were assigned to the "negative" category. Recognizing that this may result in the misclassification of an unknown number of subjects, multiple imputation via the Markov chain Monte Carlo method [25-27] was used to determine the potential effect of missing data on the multivariate models. To do so, SAS 9.1's PROCMI command was used to generate 10 imputed datasets. The PROC MIANALYZE command was then used to combine odds ratio or hazards ratio estimates from regression models performed on each of these datasets and generate confidence intervals that incorporated the missing-data uncertainty; these imputed point estimates were compared to the estimates obtained from our logistic and Cox proportional hazards regression models.

Odds ratios, hazards ratios and 95% confidence intervals were calculated where appropriate. Age was treated as a categorical variable, using TIMS-specified age groups, in the univariate analysis and as a continuous variable in the multivariate analyses. For all statistical tests, a p-value $\leq 0.05$ (two-tailed) was considered significant.

*Power Calculation*

Statistical power of the overall sample was approximated using a survival outcomes calculator found at the following website: http://www.jhsph.edu/Research/Centers/CCT/javamarc/SSP1/SSP1v4cct.htm. We based our calculation on an estimated sample size of 5000 patients, representing our entire study cohort. We assumed 10% exposure prevalence, with exposure referring to the presence of one of the clinical or social variables under study, such as HIV status; this exposure prevalence is based on an initial query of our database. We will use Variable X to refer to one of those variables in our description. Assuming that 10% of the population has a positive history of Variable X, the control survival rate, or rate of survival in those without a history of Variable X, was set at 80% and the relative risk of dying in the exposed versus the control group was conservatively estimated to be 1.5. Using these figures, at $\alpha = 0.05$, the probability that our sample will be able to detect a true difference in overall survival, based on Variable X, is 89.8%. This power increases with decreased control survival or increased exposure prevalence.

## RESULTS

*Overall Patient Characteristics*

A total of 5,311 patients were captured by the North Carolina TB Control Program between 1993 and 2003, and their overall demographic and social characteristics are shown in Table 1.

30.4% (n = 1,614) of the study population fell between 25 and 44 years old while another 30.6% (n=1,624) were at least 65 years old. Over one-third (34.5%, n= 1,834) of the cohort was female. 18.1% (n = 4,348) of patients were born outside of the United States.

10.3% (n = 549) of the study population was HIV-positive, though 39.7% (n = 2,109) of patients were of unknown HIV status because the patients either refused the test, were not offered the test or the result of the test was not recorded. 2.0% (n = 106) of the study population was incarcerated at the time of the TB diagnosis, and 4.7% (n = 250) were living in a long-term care facility when diagnosed. 7.1% (n = 377) reported being homeless within the past year. 1.8% (n = 96) were injection drug users, and 9.1% (n = 483) used non-injection drugs. Excess alcohol use within the past year was reported in over one-fifth (21.6%, n = 1,147) of the study population.

Little drug resistance was seen in the study cohort, as only 1.7% (n = 90) of patients' isolates' susceptibility testing showed mono-resistance to INH; 1.4% (n

= 76) showed resistance to both INH and at least one other drug, excluding RIF resistance. 0.4% (n = 21) of subjects had evidence of both INH and RIF resistance. Three-quarters (n = 3,982) of the cohort had pulmonary TB, and an additional 4.6% (n = 243) had both pulmonary and extra pulmonary disease.

Additional clinical characteristics of those with pulmonary TB are listed in Table 2. 28.6% (n = 1,208) of pulmonary TB patients were reported as "cavitary" on chest radiograph and almost half (49.8%, n = 2,103) had a positive sputum smear. The majority of pulmonary TB patients in the study cohort (70.0%, n = 2,953) were sputum culture positive for *M. tuberculosis*.

*Patient Mortality*

Of the total study cohort, 3.4% (n=181) died before initiation of TB treatment (see Table 3). The remaining patients were started on antituberculous therapy but a total of 10.8% (n=540) died before completion of therapy. 5.9% (n= 305) of those who started treatment died within the first eight weeks of treatment, while 4.9% (n=235) of those who survived the initial eight weeks of TB treatment subsequently died prior to treatment completion. 86.4% (4,590/5,311) of the original patients initiated and completed TB therapy.

*Mortality Prior to Initiation of Treatment*

Bivariate analyses showed that age, race, ethnicity, country of origin, HIV status, long-term care facility residence, IDU, non-IDU and excess alcohol use were all

significantly associated with death prior to starting antituberculous treatment (Tables 4-6).

Once multivariate analyses were performed, increasing age, HIV/TB co-infection and American Indian race were significant predictors of death in the time period prior to initiation of TB therapy (Table 7). For each decade increase in age, the mortality odds before TB treatment increased by 0.48 (age as a continuous variable, adjusted OR=1.48, 95%CI 1.34-1.63). Those with HIV/TB co-infection had 3.44 times the odds of mortality prior to TB treatment (adjusted OR=3.44, 05%CI 2.04-5.79) and compared to their white counterparts, those of American Indian or Alaskan Native race had 4.00 times the odds of dying before they start TB treatment (adjusted OR=4.0, 95%CI 1.47-10.93).

Gender, black race, Asian race, Hispanic ethnicity, prior TB infection, history of homelessness, history of excess alcohol use, history of injection drug use, history of non-injection drug use, incarceration at diagnosis and residency in a long-term care facility at diagnosis did not significantly predict death in the time period prior to TB treatment initiation in our model . Of note, the subgroups representing mortality before TB treatment based on Asian race, Hispanic ethnicity, history of previous TB, history of homelessness, history of injection drug use, history of non-injection drug use, and incarceration at diagnosis each comprised less than 20 ($n < 20$) patients, respectively. Hence, results must be interpreted with caution.

The multiple imputation procedure produced odds ratio estimates (see Table 9) of variables predicting death before treatment initiation similar to the estimates reported above.

*Mortality in the Early Weeks of Treatment*

Bivariate analyses of patients who started TB therapy but died within the first eight weeks of treatment revealed that age, race, ethnicity, country of origin, HIV status, residency in a long term care facility, incarceration at time of diagnosis, homelessness, and non-IDU were significantly associated with death in these early weeks of treatment (Tables 4-6).

After Cox proportional hazards modeling, significant predictors of death in the initial eight weeks of TB therapy were increasing age, being a U.S.-born person of black race, history of excess alcohol use within the previous 12 months, and residency in a long-term care facility at the time of diagnosis (Table 8).

The mortality risk in the early weeks of treatment increased by 0.79 for each decade increase in age (age as a continuous variable, adjusted HR=1.79, 95%CI 1.63-1.97). Persons of black race had 1.35 times the risk of mortality in the early weeks when compared to persons of white race (adjusted HR=1.35, 95%CI 1.05-1.75), subjects with a history of excess alcohol use had 1.68 times the risk of mortality in the early weeks(adjusted HR=1.68, 95%CI 1.17-2.41), and residents of long term care facilities had 1.70 times the mortality risk in the early weeks of

treatment (adjusted HR=1.70, 95%CI 1.23-2.34). HIV/TB co-infection approaches statistical significance as a predictor of death within the first 8 weeks of TB therapy. Those who died in the early weeks of TB treatment had 1.66 times the risk of mortality when compared to those who did not have HIV/TB co-infection (adjusted HR=1.66, 95%CI 0.99-2.76).

Variables that were not significant predictors of death in the multivariate model were gender, Asian race, American Indian race, Hispanic ethnicity, prior TB infection, history of homelessness, history of injection drug use, history of non-injection drug use and incarceration at diagnosis. Of note, the following subgroups had less than 20 ($n < 20$) patients who died early in treatment and thus results must be interpreted with caution: Asian race, American Indian race, Hispanic ethnicity, history of homelessness, history of injection drug use, history of non-injection drug use and incarceration at diagnosis.

The multiple imputation procedure produced hazards ratio estimates of the variables that predicted death early in TB treatment (see Table 9) similar to the estimates reported above.

*Mortality in the Later Weeks of Treatment*

Age, race, ethnicity, country of origin, gender, HIV status, history of previous TB, TB disease site, residence in a long-term care facility, IDU and excess alcohol use were all associated with death later in treatment in bivariate analyses of patients

who were started on TB therapy but who subsequently died after eight weeks of treatment (see Tables 4-6).

Once Cox proportional hazards modeling was performed, only increasing age and HIV/TB co-infection predicted death in the later weeks of TB therapy (see Table 8). With each decade increase in age, there was 0.63 times the mortality risk in the later weeks of treatment (age as a continuous variable, adjusted HR=1.63, 95%CI 1.48-1.79). HIV/TB co-infected subjects had 5.53 times the risk of mortality in the later weeks of treatment (adjusted HR=5.53, 95%CI 3.65-8.44).

The variables that did not significantly predict death in the later weeks in the multivariate model were black race, Asian race, American Indian race, Hispanic ethnicity, prior TB infection, history of homelessness, history of excess alcohol use, history of injection drug use, history of non-injection drug use, residency in a long term care facility at time of diagnosis and incarceration at diagnosis. The subgroups representing death later in treatment by Asian race, American Indian race, Hispanic ethnicity, history of homelessness, history of injection drug use and incarceration at diagnosis each had less than 20 ($n < 20$) patients, respectively. Therefore these results must be interpreted with caution.

The multiple imputation procedure produced hazards ratio estimates of characteristics that predicted death in the later weeks of TB treatment (see Table 9) similar to the hazard ratio estimates reported above.

## DISCUSSION

This analysis goes beyond previous TB-mortality studies by examining mortality risk factors relative to TB treatment, and examining the various patient characteristics which may differentially affect dying prior to initiation of treatment, dying early in treatment, and dying later in treatment. We found that increasing age and HIV/TB co-infection are predictors of TB mortality at nearly all points of time relative to treatment. In addition, we found that being a person of American Indian race specifically predicts death prior to TB treatment while being a person of black race, being a resident of a long-term care facility or having a history of excess alcohol use specifically predict death in the first eight weeks of treatment. Other than increasing age and HIV/TB co-infection, no other variables specifically predicted death in the later weeks of treatment.

With regard to the specific hypotheses postulated by this project, it was hypothesized that environmental factors, or factors relating to the social surroundings of the TB patient, would be significantly associated with overall mortality; rates of TB and overall death are significantly higher in drug and alcohol abusers than the general population[28]. Though we found that residents of long-term care facilities and those with excess alcohol use experienced significantly higher mortality in the early weeks of treatment, these associations were not observed in the time period before treatment initiation or beyond the first few weeks of treatment. There was no association between any specific social characteristic, such as illicit drug use, alcohol use or homelessness, and overall

mortality in our study cohort. However, it is worth nothing that HIV/TB co-infection has been treated thus far as a clinical characteristic in this study. The argument could be made though, that as HIV continues to disproportionately affect young, impoverished and frequently minority adults, HIV/TB co-infection is indeed as much related to the social environment of a patient as it is related to the clinical picture of the patient. Harries et al. suggests that the social, cultural and economic issues of poverty, sexual activity, illiteracy and stigma affect the access to care, diagnosis and delivery of care to HIV/TB co-infected patients[28]. If thus treated as a social characteristic of a patient, then our results support HIV/TB co-infection as an environmental factor that is significantly associated with overall mortality in TB patients.

Another postulated hypothesis was that patients under age 5 and over age 65 would be more likely to die early in treatment than patients aged 5-64. Indeed, we found that increasing age is significantly associated with increased mortality in every phase studied. The overall decreased survival associated with increasing age that we observed in this cohort confirms previously cited studies that also associated increased age with increased mortality [5-7, 16, 17]. This age group's association with increased TB mortality, both in the early treatment weeks and overall, may be due to TB disease itself, due to confounding medical co-morbidities that we were unable to explore in our database, or simply due to the overall frailty of old age. Regarding patients under age 5, only one patient (0.9%) in this age group died prior to or during TB treatment. Though the single child

who died within this age group in fact died within the first 8 weeks of TB therapy, no association could be found between young age and decreased survival in the early part of treatment as there were too few cases to draw conclusions. Thus, we reject the hypothesis that patients under age 5 are more likely to die early in treatment but accept the hypothesis that older patients are more likely to die in the first few weeks of treatment.

It was also postulated that patients with a history of homelessness and/or alcohol abuse would have higher rates of death prior to starting TB therapy than those without history of homelessness or alcohol abuse. We were not able to show a significant association between these factors and increased mortality before initiation of treatment in our multivariate analyses and reject the postulated hypothesis. However, it is notable that these subgroups were small and hence these negative results may be due to underpowered subgroup analyses.

Similarly, we hypothesized that homeless TB patients would have decreased survival in the later weeks of TB treatment, under the assumption that such patients would be lost to follow-up or would not be able to comply with the lengthy and complicated treatment regimen. According to Lobato et al., only 26% of homeless patients completed INH treatment for latent TB infection[29]. Given this low treatment completion rate, we predicted that patients with history of homelessness would have increased mortality in the late weeks of treatment. However, we did not detect a significant difference in mortality based on

homelessness in those who died late in TB treatment in our cohort. This may be because the number of homeless patients who died late in treatment was small (n=11), making it difficult to draw conclusions. Future studies with adequate statistical power should reexamine the hypothesis that patients with history of homelessness will have increased mortality in the later weeks of treatment.

As we examine the results of our analyses, certain themes emerge. One recurring motif is increased mortality in social groups traditionally disenfranchised from U.S. society: the elderly, the physically and mentally frail who occupy our long-term care facilities, American Indians, blacks, alcoholics and the HIV-infected. The increased TB death in our senior citizens may be due to factors already discussed previously, or they may be partially attributed to the social isolation that faces many of the elderly in America. Studies on the health effects of social isolation on the elderly have reported that pre-stroke social isolation predicted poorer post-stroke outcomes like myocardial infarct[30] and that advanced age and living alone are associated with heat-wave related death[31]. Elderly who live alone may experience delayed TB detection and diagnoses and hence increased disease severity by the time of diagnosis and treatment. In addition, though we were unable to find an association between TB mortality and the youngest patients in our study cohort, the low mortality observed in this age group could be because pediatric TB cases often go undiagnosed. Patients under age 5 may not be captured by public health surveillance, as TB in children can often present with nonspecific symptoms [32]. Additionally, according to Feja et al., a

disproportionate proportion of pediatric TB cases are found in Hispanic, non-Hispanic Black and foreign-born children. These populations may be beyond the reach of the U.S. health system either from lack of access or fear of immigration services, and thus go undetected by standard TB surveillance. It is unclear if the lack of deaths in our young TB patients may be confounded by these complex social issues or in fact simply due to a very low mortality rate within this age group.

Race also plays an interesting role as a predictor of death in TB patients, as our analyses showed that being an American Indian or Alaskan native predicted decreased survival prior to initiation of treatment while being black predicted decreased survival in the early weeks of treatment. American Indians and Alaskan natives, as a racial minority, have been significantly disempowered by U.S. society. Those who live on Indian reservations live amidst poverty, low education, high rates of drug abuse and overall poor health outcomes; a report from the Indian Health Service showed that 31.6% of Indians residing in current reservations were below the federal poverty level and only 8.9% were college graduates, compared to 13.1% and 20.3%, respectively, of the overall U.S. population [33]. Given such social conditions, it is likely that Native American TB patients may not have the access to health care that would lead to prompt TB diagnoses, and hence may die before they are even diagnosed. Additionally, bureaucratic barriers between county-based public health and reservation-based health care delay TB diagnosis and contribute to the association of American

Indian race with mortality before TB treatment. To study this association further, we intend to geographically map the cases of Native American TB death in North Carolina to assess for clustering within specific counties and to try to correlate these clusters with proximity to county public health services.

Blacks in America are another traditionally disenfranchised population and reports of disparities between blacks and whites in specific health outcomes are becoming increasingly commonplace. In 2004, blacks had a disproportionately increased TB case rate (11.1 per 100,000 people) when compared to whites (1.3 per 100,000 people) and the overall U.S. case rate (4.9 per 100,000) [3]. However, the same report also states that the similar percentages of blacks and whites receive DOT and complete treatment on time. Our results support this finding, as being black was not associated with decreased survival in the later weeks of treatment, when death is presumed to result from treatment failure or co-morbid conditions. The increased mortality in our black TB patients in the early weeks of TB treatment is troubling however. These patients may be at increased risk of death due to many reasons, such as delayed diagnoses, misdiagnoses, or the inability to access health care. In addition, a study of the southeastern region of the U.S. showed that black TB patients in this region were more likely than their white counterparts to have risk factors associated with lower socioeconomic status, such as increased rates of excess alcohol use, drug use, incarceration and HIV/TB co-infection[19], which may complicate TB diagnosis and treatment in these patients. A CDC study is currently underway to examine barriers to health-

seeking and treatment compliance in blacks with TB, barriers to TB guideline adherence by providers who treat blacks with TB, interventions to overcome these barriers and improve collaborations among TB programs, providers and organizations serving black communities in the U.S.[3].

Though the trend of increased mortality in these disempowered social groups is troubling, it also reveals one strong point of this study. In using the North Carolina TB Control Program's RVCT-collected data, comprised of all TB patients mandatorily reported to a state TB control program over an extended period of time, this study population is likely comparable to the TB populations in other states within the U.S. There is less concern for the effects of selection bias introduced by a study cohort who, for instance, were enrolled in a specific clinical trial, were actively recruited to join a study or even patients listed in a tumor registry, who had enough access to health care to be evaluated for a malignancy. Hence, our results may be more generalizable to other TB populations than studies that derive their study populations in another manner or which specifically focus on population subgroups, such as hospitalized, pediatric, homeless or incarcerated TB patients.

Although the RVCT-collected data provides a broadly representative group for study, there are flaws inherent with the database. One weakness of the database is the proportion of missing data, particularly regarding social risk factors. For instance, approximately 14-15% of the patients within our study cohort had

unknown substance abuse behaviors. Though plausible that social factors such as homeless status could not be collected on individuals who died prior to starting treatment, especially if diagnoses occurred at autopsy or in other situations after death, the high proportion of social information not collected via the RVCT could also be due to lack of documentation in the medical record, patient failure to self-report, differences in the data collected because of a lack of standard definitions, and differences in interpretation of medical records and patient report by health professionals across the state, over a ten year time period. Failure of the health care provider to query about these specific social history factors may also contribute to the missing data. For example, a study by Stout et al. reports that despite recommended universal HIV testing for patients with TB, only 67% of TB patients from 1993 to 1999 were offered HIV testing in North Carolina [34]. We addressed our concern about the proportion of missing data with the use of multiple imputations of our multivariate models to determine the potential effect of the missing data on our results. We found that imputations of the missing data did not affect significant associations between certain patient characteristics and mortality relative to TB treatment.

Additional concerns include the small sample sizes of our risk factor subgroups and the inability to detect other potentially important risk factors via current CDC TB surveillance techniques. The small sample sizes of certain exposure groups, for instance the subgroup homelessness in those who died early in treatment (n = 11/235; 3.1%), diminishes the statistical power to detect a true difference in these

exposure groups, and may preclude definitive conclusions. Unfortunately, these small sample sizes dominate several other exposure groups of interest as well, such as injection and non-injection drug use, and incarceration. And though the RVCT-collected data contains extensive information on patients' TB disease, like drug susceptibility and sputum culture conversion, the TB surveillance does not include data related to patients' socioeconomic status (SES), such as income or SES proxies such as education level. The RVCT also does not collect data on TB patients' co-morbid conditions, such as malignancy or malnourishment, which may contribute to mortality in these patients.

With regard to future endeavors, we have analyzed risk factors for mortality before TB treatment, during the first weeks and then the later weeks of TB treatment thus far. We also intend to explore mortality after TB treatment completion. We observed that 17.3% of our study cohort who survived TB treatment subsequently died by December 31, 2003. This number was larger than expected, and may be an important group to study, as becoming ill with active TB may be a harbinger of declining health status. While TB may be diagnosed and cured, people with a history of TB may have a higher mortality rate following completion of TB treatment compared to a demographically matched population. Furthermore, known sequelae of TB disease, such as bronchiectasis with recurrent bacterial infection, may contribute to a decreased life span in patients who complete TB treatment. Little research has been done to identify those who die shortly after completion of TB treatment; no studies could be found by the author.

Future studies directed at mortality in patients who completed TB treatment may provide insight into predictors of death in this population.

In summary, our study used a new paradigm in which to examine TB mortality by examining death relative to TB treatment. We found that age and HIV/TB co-infection are associated with increased mortality both before and during TB treatment, and also found specific risk factors associated with dying prior to starting treatment and dying in the early weeks of TB treatment. We hope that these specific factors can be used to generate targeted public health efforts that will decrease TB related mortality.

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**Appendix A:** Studies that examined deaths prior to initiation of TB treatment, and their respective findings.

| Study | Country | Overall Study Size | Total TB Deaths | Death Prior to TB Treatment |
|---|---|---|---|---|
| Farah et al. (2005) | Norway | N = 655 | n = 58 | • 32.8% of total TB deaths<br>• 2.9% of total TB cases<br>• 0.6% of TB cases were diagnosed at autopsy;<br>• median age of those who died before TB treatment was 71 years |
| Garcia-Garcia et al. (2002) | Mexico | N = 454 | n = 34 | • 5.9% of total TB deaths<br>• 0.4% of total TB cases |
| Walpola et al. (2003) | Australia | N = 1083 | n = 87 | • 37.9% of total TB deaths<br>• 3.0% of total TB cases<br>• 2.3% of TB cases were diagnosed at autopsy |

**Appendix B.** Link criteria applied to the results of the NDI query to distinguish correctly linked NDI/RVCT records from false or inaccurate links.

| **If the patient's SSN is available:** |
|---|
| 1) SSN, first name, last name, middle initial, DOB, gender, race and state of residency |
| 2) first name, last name, middle initial, DOB, gender, race and SSN with either one incorrect digit or 2 consecutive incorrect digits |
| 3) SSN, DOB, gender and race |
| 4) SSN, first name, last name, day and/or month of birth and year of birth +/- 3 years |
| 5) SSN, last name, day of birth, month of birth and year of birth +/-10 years. |
| **If the SSN was not available and the subject's last name was not among the two hundred fifty most frequent U.S. last names,[1] then the following criteria were used:** |
| 1) first name, last name, middle initial, DOB, state of residence and gender |
| 2) first name, last name, middle initial, DOB, gender and race |
| 3) first name, last name, DOB, gender, and race |
| 4) first initial, middle initial, last name, DOB and state of residence |
| 5) first name, New York State Identification and Intelligence System (NYSIIS)-coded last name, DOB, state of residence, gender and race |
| 6) first name, last name, DOB +/- 1 year, state of residence, gender and race. |

[1] The NDI provides files listing the top two hundred fifty most frequent last names in the United States in both alphabetical order and in order of decreasing frequency.

**Appendix C.** The demographic, clinical and social variables reported by the RVCT that were subsequently used in our analyses.

**Demographic**
- Age
- Gender
- Race
- Ethnic origin
- Country of origin

**Clinical**
- Major site of TB infection
- Sputum smear results
- Sputum culture results
- Chest radiograph results
- HIV status
- Initial drug susceptibility results

**Social**
- Excess alcohol use in preceding 12 months
- Homeless in preceding 12 months
- Resident of long-term care facility at diagnosis
- Incarceration at time of diagnosis
- Injection drug use in preceding 12 months
- Non-injection drug use in preceding 12 months

**Table 1.** Baseline characteristics of all TB patients captured by the NC TB Control Program from 1993-2003. N=5,311

| | |
|---|---|
| **Age** | |
| <5 years old | 2.1% (n = 111) |
| 5-14 years old | 2.3% (n = 121) |
| 15-24 years old | 6.0% (n = 319) |
| 25-44 years old | 30.4%(n = 1,614) |
| 45-64 years old | 28.7% (n = 1,522) |
| ≥65 years old | 30.6% (n = 1,624) |
| **Gender** | |
| Female | 34.5% (n = 1,834) |
| **Race** | |
| White | 35.2% (n = 1,871) |
| Black | 58.9% (n = 3,128) |
| Asian/Pacific Islander | 5.8% (n = 308) |
| American Indian/Alaskan Native | 0.8% (n = 44) |
| **Ethnicity** | |
| Hispanic | 10.5% (n = 559) |
| **Country of Origin** | |
| United States | 81.9% (n = 4,348) |
| **Previous Diagnosis of TB** | |
| Yes | 5.6% (n = 296) |
| **Disease Site** | |
| Pulmonary: | 75.0% (n = 3,982) |
| Pulmonary and Extrapulmonary: | 4.6% (n = 243) |
| Extrapulmonary Alone: | |
| Lymphatic | 5.2% (n = 278) |
| Miliary | 2.2% (n = 119) |
| Pleural | 5.4% (n = 286) |
| Bone/Joint | 2.4% (n=126) |
| Other[1] | 5.2% (n = 277) |
| **HIV Status** | |
| Positive | 10.3% (n = 549) |
| Negative | 49.9% (n=2,650) |
| Status Unknown | 39.7% (n = 2,109) |
| **Resident of Correctional Facility at Time of TB Diagnosis** | |
| Yes | 2.0% (n = 106) |
| **Resident of Long Term Care Facility at Time of TB Diagnosis** | |
| Yes | 4.7% (n = 250) |
| **Homeless Within Past Year** | |
| Yes | 7.1% ( n = 377) |
| **Injection Drug Use (IDU) Within Past Year** | |
| Yes | 1.8% (n = 96) |
| No | 83.2% (n = 4,420) |
| Unknown | 15.0% (n = 795) |
| **Non-injection Drug Use Within Past Year** | |
| Yes | 9.1% (n = 483) |
| No | 76.2% (n = 4,047) |
| Unknown | 14.7% (n = 781) |
| **Excess Alcohol Use Within Past Year** | |
| Yes | 21.6% (n = 1,147) |
| No | 64.2% (n = 3,411) |
| Unknown | 14.2% (n = 753) |

[1] "Other" includes meningeal TB, genitourinary TB, peritoneal TB and any other TB sites

**Table 2.** Disease-related characteristics

| Of pulmonary TB patients.* N = 4225 | |
|---|---|
| **Chest Radiograph Result** | |
| Abnormal | 97.0% (n = 4,099) |
| **Chest Radiograph Impression** | |
| Cavitary | 28.6% (n = 1,208) |
| Radiograph suggestive of TB, without cavitation | 65.9% (n = 2,687) |
| Radiograph not suggestive of TB, without cavitation | 4.5% (n = 185) |
| **Sputum Smear Result** | |
| Positive | 49.8% (n = 2,103) |
| Negative | 35.1% (n = 1,482) |
| Sputum Smear Not Done | 15.1% (n = 636) |
| **Sputum Culture Result** | |
| Positive | 70.0% (n = 2,953) |
| Negative | 14.8% (n = 624) |
| Sputum Culture Not Done | 15.2% (n = 639) |
| Of all patients. N = 5311 | |
| **Initial Organism Drug Susceptibility** | |
| Resistant to INH alone | 1.7% (n = 90) |
| Resistant to INH and to ≥1 drug other than Rifampin | 1.4% (n = 76) |
| Resistant to Rifampin and INH | 0.4% (n = 21) |
| Resistant to Rifampin alone | 0.2% (n = 10) |
| Other Result | 96.3% (n = 5114) |

*Includes those with both pulmonary and extrapulmonary TB disease.

**Table 3**. Frequency of TB death, at different times relative to treatment.

| Time of Death | No. Died/ No. Surviving Up to the Specified Time of Death | Mortality Frequency (%) |
|---|---|---|
| Prior to initiation of treatment | 181 / 5,311 | 3.41 |
| Early during treatment (Initial 8 weeks of treatment) | 305 / 5,130 | 5.95 |
| Later during treatment (After the first 8 weeks of treatment) | 235 / 4,825 | 4.87 |
| After treatment completion* | 793 / 4,590 | 17.28 |

* Deaths captured up until December 31, 2003

**Table 4.** Demographic Characteristics of Study Patients, by Outcome Group. N = 5311

| Characteristic | Died Before Treatment | | | Died Early in Treatment | | | Died Later in Treatment | | |
|---|---|---|---|---|---|---|---|---|---|
| | Died N=181 % (n) | Survived N=5130 % (n) | p-value | Died N=305 % (n) | Survived N=4825 % (n) | p-value | Died N=235 % (n) | Survived N=4590 % (n) | p-value |
| **Age (years)** | | | <0.001 | | | <0.001 | | | <0.001 |
| <5 | 0.0(0) | 111(100) | | 0.9(1) | 99.1(110) | | 0.0(0) | 100(110) | |
| 5-14 | 0.0(0) | 121(100) | | 0.8(1) | 99.2(120 | | 0.00(0) | 100(120) | |
| 15-24 | 0.6(2) | 99.4(317) | | 0.0(0) | 100(317) | | 1.6(5) | 98.4(312) | |
| 25-44 | 1.8(29) | 98.2(1585) | | 1.4(22) | 98.6(1563) | | 2.4(37) | 97.6(1526) | |
| 45-64 | 3.2(48) | 96.9(1474) | | 3.7(54) | 96.3(1420) | | 3.6(51) | 96.4(1369) | |
| ≥65 | 6.1(98) | 93.9(1514) | | 14.8(224) | 85.2(1290) | | 10.9(141) | 89.1(1149) | |
| **Race** | | | 0.002 | | | 0.001 | | | 0.001 |
| White | 3.3(61) | 96.7(1811) | | 5.3(96) | 94.7(1715) | | 4.4(75) | 95.6(1640) | |
| Black | 3.6(112) | 96.4(2972) | | 6.7(200) | 93.3(2772) | | 5.7(157) | 94.3(2615) | |
| Asian/PI | 1.0(3) | 99.0(305) | | 1.6(5) | 98.4(300) | | 0.7(2) | 99.3(298) | |
| Amer. Indian | 11.4(5) | 88.6(39) | | 10.3(4) | 89.7(35) | | 2.9(1) | 97.1(34) | |
| **Ethnicity** | | | 0.047 | | | <0.001 | | | <0.001 |
| Hispanic | 2.0(11) | 98.0(548) | | 1.3(7) | 98.7(541) | | 0.9(5) | 99.1(536) | |
| Non-Hispanic | 3.6(170) | 96.4(4582) | | 6.5(298) | 93.5(4284) | | 5.4(230) | 94.6(4054) | |
| **Gender** | | | 0.233 | | | 0.889 | | | 0.045 |
| Male | 3.2(111) | 96.8(3366) | | 5.9(199) | 94.1(3167) | | 4.4(140) | 95.6(3027) | |
| Female | 3.8(70) | 96.2(1764) | | 6.0(106) | 94.0(1658) | | 5.7(95) | 94.3(1563) | |
| **Country of Origin** | | | <0.001 | | | <0.001 | | | <0.001 |
| U.S. | 3.9(168) | 96.1(4180) | | 7.1(295) | 92.9(3885) | | 5.9(229) | 94.1(3656) | |
| Foreign-Born | 1.2(11) | 98.8(948) | | 1.1(10) | 98.9(938) | | 0.6(6) | 99.4(932) | |

**Table 5.** Clinical Characteristics of Study Patients, by Outcome Group. N = 5311

| Characteristic | Died Before Treatment | | | Died Early in Treatment | | | Died Later in Treatment | | |
|---|---|---|---|---|---|---|---|---|---|
| | Died N= 181 % (n) | Survived N=5,130 % (n) | p-value | Died N=305 % (n) | Survived N=4825 % (n) | p-value | Died N=235 % (n) | Survived N=4590 % (n) | p-value |
| **H/o Previous TB** | | | 0.744 | | | 0.434 | | | 0.019 |
| Yes | 3.0(9) | 97.0(287) | | 7.0(20) | 93.0(267) | | 7.9(21) | 92.1(246) | |
| No | 3.4(170) | 96.6(4839) | | 5.9(283) | 94.2(4556) | | 4.7(214) | 95.3(4342) | |
| **TB Site** | | | 0.572 | | | 0.070 | | | 0.016 |
| Extrapulmonary | 3.8(41) | 96.2(1045) | | 4.8(50) | 95.2(995) | | 5.9(59) | 94.1(936) | |
| Pulmonary | 3.4(134) | 96.6(3848) | | 6.1(235) | 93.9(3613) | | 4.4(159) | 95.6(3454) | |
| Both | 2.5(6) | 97.5(237) | | 8.4(20) | 91.6(217) | | 7.8(17) | 92.2(200) | |
| **Initial Drug Susceptibility** | | | 0.599 | | | 0.676 | | | 0.623 |
| Resist. to RIF alone | 0.0(0) | 100(10) | | 10.0(1) | 90.0(9) | | 0.0(0) | 100(9) | |
| Resist. to INH alone | 1.1(1) | 98.9(89) | | 7.9(7) | 92.1(82) | | 7.3(6) | 92.7(76) | |
| Resist. to RIF and INH | 0.0(0) | 100(21) | | 4.8(1) | 95.2(20) | | 0.0(0) | 100(20) | |
| Resist. to INH and ≥1 other drug | 2.6(2) | 97.4(74) | | 2.7(2) | 97.3(72) | | 4.2(3) | 95.8(69) | |
| Other Result | 3.5(178) | 96.5(4,936) | | 6.0(294) | 94.0(4642) | | 4.9(226) | 95.1(4416) | |
| **HIV Status** | | | <0.001 | | | <0.001 | | | <0.001 |
| Negative | 0.9(24) | 99.1(2626) | | 3.7(98) | 96.3(2528) | | 2.3(59) | 97.7(2469) | |
| Positive | 4.6(25) | 95.4(524) | | 4.0(21) | 96.0(503) | | 9.7(49) | 90.3(454) | |
| Unknown | 6.2(131) | 93.8(1978) | | 9.4(186) | 90.6(1792) | | 7.1(127) | 92.9(1665) | |

*Based on diagnostic tests performed on pulmonary TB patients

**Table 6.** Social Characteristics of Study Patients, by Outcome Group. N = 5311

| Characteristic | Died Before Treatment | | | Died Early in Treatment | | | Died Later in Treatment | | |
|---|---|---|---|---|---|---|---|---|---|
| | Died N= 181 % (n) | Survived N=5,130 % (n) | p-value | Died N=305 % (n) | Survived N=4825 % (n) | p-value | Died N=235 % (n) | Survived N=4590 % (n) | p-value |
| **Homeless**[1] | | | 0.001 | | | 0.039 | | | 0.286 |
| Yes | 2.4(9) | 97.6(368) | | 4.9(18) | 95.1(350) | | 3.1(11) | 96.9(339) | |
| No | 3.4(167) | 96.6(4731) | | 6.0(282) | 94.0(4449) | | 5.0(223) | 95.0(4226) | |
| Unknown | 13.9(5) | 86.1(31) | | 16.1(5) | 83.9(26) | | 3.8(1) | 96.2(25) | |
| **Incarcerated**[2] | | | 0.383 | | | 0.030 | | | 0.063 |
| Yes | 1.9 (2) | 98.1(104) | | 1.0(1) | 99.0(103) | | 1.0(1) | 99.0(102) | |
| No | 3.4(179) | 96.6(5026) | | 6.1(304) | 93.9(4722) | | 5.0(234) | 95.0(4488) | |
| **Resident of Long Term Care Facility**[2] | | | <0.001 | | | <0.001 | | | <0.001 |
| Yes | 8.8(22) | 91.2(228) | | 21.5(49) | 78.5(179) | | 15.1(27) | 84.9(152) | |
| No | 3.1(158) | 96.9(4902) | | 5.2(256) | 94.8(4646) | | 4.5(208) | 95.5(4438) | |
| **IDU**[1] | | | <0.001 | | | 0.442 | | | 0.024 |
| Yes | 4.2(4) | 95.8(92) | | 6.5(6) | 93.5(86) | | 8.1(7) | 91.9(79) | |
| No | 2.6(116) | 97.4(4304) | | 5.8(248) | 94.2(4056) | | 4.5(183) | 95.5(3873) | |
| Unknown | 7.7(61) | 92.3(734) | | 7.0(51) | 93.0(683) | | 6.6(45) | 93.4(638) | |
| **Non-IDU**[1] | | | <0.001 | | | 0.021 | | | 0.059 |
| Yes | 1.5(7) | 98.5(476) | | 3.4(16) | 96.6(460) | | 4.8(22) | 95.2(438) | |
| No | 2.9(117) | 97.1(3930) | | 6.0(237) | 94.0(3693) | | 4.5(168) | 95.5(3525) | |
| Unknown | 7.3(57) | 92.7(724) | | 7.2(52) | 92.8(672) | | 6.7(45) | 93.3(627) | |
| **Excess Alcohol Use**[1] | | | <0.001 | | | 0.303 | | | 0.001 |
| Yes | 2.2(25) | 97.8(1122) | | 5.3(1122) | 94.7(1063) | | 3.2(34) | 96.8(1029) | |
| No | 3.0(101) | 97.0(3310) | | 6.0(197) | 94.0(3113) | | 5.0(155) | 95.0(2958) | |
| Unknown | 7.3(55) | 92.7(698) | | 7.0(49) | 93.0(649) | | 7.1(46) | 92.9(603) | |

[1] Within the previous 12 months [2] At time of diagnosis

**Table 7**. Mortality before initiation of TB treatment; statistically significant results from multivariate logistic regression modeling.

| Characteristic | Adjusted Odds Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| Age[1]<br>Per year of life<br>Per decade of life | <br>1.04<br>1.48 | <br>1.03-1.05<br>1.34-1.63 | <0.001 |
| HIV/TB co-infection | 3.44 | 2.04-5.79 | <0.001 |
| American Indian/Alaskan Native | 4.00 | 1.47-10.93 | 0.001 |

[1] Analyzed as a continuous variable

**Table 8**. Mortality early in TB treatment and mortality later in TB treatment; significant results from extended Cox Proportional Hazards modeling.

| Characteristic | Died Early in Treatment | | | Died Later in Treatment | | |
|---|---|---|---|---|---|---|
| | Adjusted Hazard Ratio | 95% Confidence Interval | p-value | Adjusted Hazard Ratio | 95% Confidence Interval | p-value |
| Age[1]<br>Per year of life<br>Per decade of life | <br>1.06<br>1.79 | <br>1.05-1.07<br>1.63-1.97 | <0.001 | <br>1.05<br>1.63 | <br>1.04-1.06<br>1.48-1.79 | <0.001 |
| Black race | 1.35 | 1.05-1.75 | 0.021 | ** | ** | ** |
| HIV/TB co-infection | 1.66 | 0.99-2.76 | 0.053 | 5.53 | 3.65-8.44 | <0.001 |
| Excess Alcohol Use[2] | 1.68 | 1.17-2.41 | 0.005 | ** | ** | ** |
| Resident of Long Term Care Facility[3] | 1.70 | 1.23-2.34 | 0.001 | ** | ** | ** |

[1] Analyzed as a continuous variable
[2] Within the previous 12 months
[3] At time of diagnosis
** Not significant in the model

**Table 9.** Mortality before and during TB treatment. Results of the multiple imputations[a] of the multivariate logistic regression model[b] and the extended Cox Proportional Hazards models[c] to account for missing data.

| Characteristic | Died Before Treatment | | | Died Early in Treatment | | | Died Later in Treatment | | |
|---|---|---|---|---|---|---|---|---|---|
| | Imputed Odds Ratio | 95% Confidence Interval | p-value | Imputed Hazard Ratio | 95% Confidence Interval | p-value | Imputed Hazard Ratio | 95% Confidence Interval | p-value |
| Age[1] | 1.04 | 1.03-1.05 | <0.001 | 1.05 | 1.05-1.06 | <0.001 | 1.05 | 1.04-1.06 | <0.001 |
| HIV/TB co-infection | 3.53 | 2.16-5.77 | <0.001 | 1.28 | 0.84-1.94 | 0.244 | 2.98 | 1.71-5.20 | <0.001 |
| Black race | ** | ** | ** | 1.34 | 1.04-1.72 | 0.025 | ** | ** | ** |
| American Indian/Alaskan Native | 3.81 | 1.38-10.56 | 0.010 | ** | ** | ** | ** | ** | ** |
| Excess Alcohol Use[2] | ** | ** | ** | 1.48 | 1.02-2.15 | 0.039 | ** | ** | ** |
| Resident of Long Term Care Facility[3] | ** | ** | ** | 1.68 | 1.21-2.32 | 0.002 | ** | ** | ** |

[a] Described in *Methods: Statistical Analyses* [b] Used in analysis of "Died Before Treatment" [c] Used in analysis of "Died Early in Treatment" and "Died Late in Treatment"
[1] Analyzed as a continuous variable [2] Within the previous 12 months [3] At time of diagnosis ** Not significant in the model