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The Impact of Isoniazid and Pyrazinamide Mono-resistance on Mortality among Tuberculosis Patients in Los Angeles County, 2010-2014

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by

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ABSTRACT OF THE THESIS

The Impact of Isoniazid and Pyrazinamide Mono-resistance on Mortality among Tuberculosis Patients in Los Angeles County, 2010-2014

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Background: Isoniazid and pyrazinamide mono-resistant tuberculosis (TB) may be associated with poor treatment outcomes, but previous studies have found conflicting results. We assessed the impact of isoniazid (INH) or pyrazinamide (PZA) mono-resistance on mortality during TB treatment in Los Angeles County.

Methods: We retrospectively reviewed drug susceptibility test patterns and treatment outcomes among TB cases reported to the Los Angeles County Tuberculosis Control Program from 2010 to 2014. Multiple logistic regression was used to determine the association between isoniazid or pyrazinamide mono-resistance and death while controlling for patient characteristics.

Results: Of 1,927 TB patients included in the analysis, in the multiple-logistic-regression model adjusting for age, gender, race, foreign-born, extra pulmonary status, and history of TB, patients with INH or PZA mono-resistance had higher odds of death than patients with drug-susceptible TB [OR 1.57 (0.93, 2.64); and OR 2.43 (0.92, 6.44), respectively].

Conclusion: Patients with INH or PZA mono-resistance were more likely to die than patients with drug-susceptible TB. Efforts are needed to improve treatment outcomes for INH or PZA mono-resistant TB patients.

The thesis of Kaewalee Soontornmon is approved.

Sung-Jae Lee

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LIST OF ACRONYMS

95% CI	95% Confidence Interval
AFB	Acid-fast bacilli
aOR	Adjusted Odds Ratio
CDC	Center for Disease Control and Prevention
cOR	Crude Odds Ratio
CXR	Chest X-Ray
DM	Diabetes mellitus
DOT	Directly observed therapy
DPH	Department of Public Health
DST	Drug susceptibility testing
EMB/E	Ethambutol
HIV	Human Immunodeficiency Virus
IGRA	Interferon Gamma Release Assay
INH/H	Isoniazid
LAC	Los Angeles County
LTBI	Latent Tuberculosis Infection
M.tb	Mycobacterium tuberculosis
MTBC	Mycobacterium Tuberculosis complex
MDR	Multidrug resistance
NAAT	Nucleic Acid Amplification Test
NTSS	National TB Surveillance System
PZA/Z	Pyrazinamide
RIF/R	Rifampin
S	Streptomycin
TB	Tuberculosis
TBC	Tuberculosis Clinic (public health department)
TBCP	Los Angeles County Department of Public Health Tuberculosis Control Program
TRIMS	Tuberculosis Registry Information Management System
TST	Tuberculin Skin Test

CHAPTER I: INTRODUCTION

Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide with 10.4 million new TB cases in 2015. There were 1.4 million TB deaths and 0.4 million deaths from TB/HIV coinfection. Despite the decrease in the number of TB deaths by 22% from 2000 to 2015, TB still remains one of top ten causes of death in 2015 (1). In the United States, 9,287 cases were provisionally reported as new TB cases in 2016 which is the lowest number of TB cases recorded and slightly reduced from 2015 by 2.7%. Although the incidence rates have steadily declined since the strengthening of nationwide TB control programs in 1993, the goal of U.S. TB elimination will not be achieved in the near future.

On the other hand, national TB mortality rates seemed to be leveled off at 0.2 per 100,000 population since 2003 to 2014, and the percentage of deaths of any cause among TB patients had remained stable around 6.1 to 6.7% from 2007 to 2013 (2). Despite effective anti-TB therapeutics and chemoprophylaxis, targeted TB screening programs and strong TB Control Programs embedded in communities around the United States, deaths with TB remain unacceptably high. In order to meet the post-2015 global TB target of reducing deaths by 95% by the year 2035, it is essential to identify all risk factors that promote TB death. (3). For this study, we will focus on the aspect of drug resistant pattern on TB mortality.

California (CA) is ranked 3rd in TB incidence rate in U.S., with a rate of 5.4 cases per 100,000 population and a total of 2,133 cases in 2015, compared to the national incidence rate of 3.0 cases per 100,000 population (2). Based on a report on TB in California in 2015, the trend of TB mortality was stable at 10% since 1993. (4); however, Los Angeles County (LAC) reported TB

mortality at 12 % from 2010-2014, reflecting a higher magnitude of TB mortality in LAC than CA (5, 6). Among TB cases reported to CA in 2013, there were 215 deaths out of 2,164 cases (9.9%), whereas LAC reported 82 deaths out of 660 cases (12.4%). This underscores the urgent need to reduce TB deaths in the huge and diverse metropolitan area of LAC.

Drug-resistant *M. tb* could be a strong predictor of TB mortality. We can categorize drug resistance tuberculosis (DR-TB) in 2 parts: multidrug resistance (MDR) and non-MDR resistance. For MDR TB, *M. tb* organism resist both (but not limited to) isoniazid (INH) and rifampicin (RIF). Non-MDR, other mono or poly- drug resistance without INH and RIF concurrent infection. Most of the literature studying the association between drug-resistance and TB mortality focuses on multidrug resistance (MDR) TB; however, the non-MDR resistance might be considered as a concern especially in the area with high burden of non-MDR resistance.

There were some controversial issues about drug resistance patterns and TB mortality. For example, most of previous studies reported that INH mono-resistance was associated with unfavorable outcome (7-16). In contrast, two studies from U.S. and Denmark reveal that there was no significant association between INH mono-resistant TB and poor treatment outcome (17, 18). Therefore, Stagg and colleagues raised the issue whether non-MDR INH resistance is a cause for concern. There was no definite answer across the globe, the magnitude of non-MDR resistant problem relied on the burden of INH resistance in each country, the pattern and extent of resistance-conferring mutations (19). In addition, pyrazinamide (PZA) mono-resistance was believed to be a risk factor for poor clinical outcome. A study from Quebec revealed the worse treatment result of PZA mono-resistance when compared with a drug susceptible (20), but the

study from San Francisco reported no significant difference between these two groups. (21). The results from both studies could be explained by the fact that DR-TB might not increase mortality in TB programs that can tailor the treatment based on drug susceptibility testing (DST) results. For example, receiving longer TB treatment in PZA mono-resistance could influence treatment outcomes.

Along with the previous studies, our study highlighted both drug resistant patterns (INH and PZA) on TB mortality in the setting such as LAC where the treatment regimen was tailored based on drug resistant pattern. For non-MDR INH resistance, we hypothesized that tailoring the treatment regimen and intensive TB management could reduce the TB mortality in non-MDR INH resistant cases. For non-MDR PZA resistance, we confirmed the concept of poor treatment outcome. The primary objective of this study was to evaluate the association of drug resistance patterns (INH, PZA and MDR) on TB mortality. We did not investigate other types of first-line anti-TB drug resistant pattern because there were too few cases for meaningful analysis (RIF and ethambutol (ETM) mono-resistance). To meet this objective, we conducted a retrospective cohort study to evaluate TB mortality during anti-TB treatment in LAC over a 5-year period. TB patients alive at diagnosis and who had a full record of DST and genotype data were selected for inclusion in the study cohort.

Moreover, we examined the issues of difference in resistant conferring mutation, the requirement of tailored regimens for drug resistance, and the relationship between non-MDR and MDR resistance support the importance of non-MDR-TB. Finally, improved understanding of the risk

of mortality among patients with non-MDR resistance might help to guide efforts to improve treatment regimen and achieve the best treatment outcome.

Primary Research Question

Do TB cases with INH mono-resistance or PZA mono-resistance have an increased mortality risk during the course of TB treatment when compared to TB cases with drug-susceptible group among TB cases reported to the Tuberculosis Control Program in Los Angeles County between 2010-2014?

I hypothesize that TB patients who have INH or PZA mono-resistance will have an increased risk of death during TB treatment, compared to patients who has drug-susceptible.

CHAPTER II: BACKGROUND

INH is an effective drug for treating active TB disease. It was first synthesized in 1912 in Prague, Czech Republic (22). Considered a prodrug, INH is stimulated by the catalase-peroxidase katG of *M.tb*. Later, by binding inhA, an enoyl-acyl, carrier protein reductase, it obstructs fatty (mycolic) acid synthesis, a necessary component of bacterial cell wall. INH has two roles based on the reproduction speed of bacteria, INH is bactericidal in rapidly dividing bacteria, but bacteriostatic in slow dividing bacteria. INH was thought to be a highly effective drug at the beginning; however, RIF took over the property in bactericidal activity while PZA acting as sterilizing drug. PZA plays a role to kill semi-dormant TB bacilli which are hard to kill by other drugs (23, 24). Adding PZA to INH and RIF regimen could shorten the duration of TB treatment from 9 to 6 months (25, 26).

Between 1994 and 2009, INH resistance was detected in 44.9% of all strains causing active tuberculosis in the Eastern European region, but 13.9% in all other regions (27). In 2014, the global frequency of non-MDR INH resistance was 9.5 %, 8.1% of new cases and 14.0% of retreatment case (28). According to the report from the global project on anti-TB drug resistance surveillance 2002-07, MDR-TB contributed 4.8% to all estimated incident TB cases. This proportion of INH resistance and MDR in global report suggest that a major of INH resistance were INH mono and poly-resistance, not MDR (INH with concurrent RIF resistance) (29).

The US National TB Surveillance System (NTSS) reported that PZA mono-resistant incidence among *M. tb complex* cases is 2.0-3.3% and is assumed to increase over time (30). Furthermore, the PZA resistance is harbored in 38% of MDR (31). PZA resistance testing is difficult to perform by growth-based testing because the PZA is active only in an acidic microenvironment (pH 5.5).

If inoculum is too heavy, the pH may be increased and drug activity will decrease (false resistance). In contrast, if inoculum is too light, pH may go down and *M. tb* will not grow well (false susceptibility) (32, 33). Because of this technical difficulty, most of mycobacteriology laboratories in the U.S. and other countries do not test for PZA. We lack prevalence of PZA resistance in global level from this problem. However, PZA phenotypic assay was done in LAC.

The culture result only reported Mycobacterium Tuberculosis Complex (MTBC), which includes *Mycobacterium tuberculosis, Mycobacterium africanum* (subtypes I and II), *Mycobacterium bovis* (along with the attenuated *M. bovis bacillus Calmette-Guérin* [BCG]), and *Mycobacterium microti* (34). *Mycobacterium bovis* is intrinsically resistant to PZA and PZA mono-resistance is the unique characteristic of *M. bovis* (35, 36). *M. bovis* infects humans by unpasteurized dairy product ingestion and mostly manifest by extra pulmonary involvement (37, 38). Normally, *M. bovis* contributes a small proportion of TB cases in humans; on the other hand, *M. bovis* itself plays an important role in global wild and domestic animals (38). The way to differentiate *M. tb* from *M. bovis* from MTBC is using spacer oligonucleotide typing (spoligotyping) and mycobacterial interspersed repetitive unit variable number tandem repeats (MIRU-VNTR) techniques (37, 39). In this study, we focused on PZA mono-resistance in *M. tb* not *M. bovis*.

In the light of variables selected in a multivariable analysis, previous studies have controlled for different potential confounders. However, many of the potential confounders identified may not significantly related to specific drug resistance patterns. Most researchers decide to include them in the final model (e.g. age, gender, race/ethnicity, U.S. born, and pulmonary/extra pulmonary status). With increasing age, male gender, race/ethnicity, nativity (U.S.-born vs. foreign born), and

site of disease were independently associated with mortality (40-42). INH mono-resistance was associated with only prior treatment for latent or active tuberculosis (18). PZA mono-resistance MTBC was associated with age, Hispanic race, and extra pulmonary disease (30), but a study in Quebec revealed that there was no significant association in mean age, gender, site of TB involvement between PZA mono-resistance and pan-susceptible (20). Although the association between these factors (age, gender, race, nativity, site of disease) and drug resistance pattern are inconclusive, we included these factors in our final model to adjust for baseline demographic as shown in figure 1.

CHAPTER III: METHODS

Overall study design

To evaluate the association of drug resistant patterns on the outcome of mortality, a retrospective cohort study testing the odds ratios of mortality among TB patients was conducted.

Primary data source

Data were extracted from the Tuberculosis Registry Information Management System (TRIMS) database. TRIMS database is maintained by the LAC DPH TB Control Program (TBCP). California Code of Regulation Title 17 Section 2500 which states that all cases of suspected TB have to be reported by health care provider in LAC within one working day. California Health and Safety Code Section 121362 also requires TBCP update and maintain a record of clinical follow up of all TB patients. TRIMS is the repository of all baseline and follow up information. TRIMS comprises many tables of patient demographics, disease characteristics, outcomes, inpatient admission and discharge dates, plan of treatment and case management and investigate close contacts. Since 2007, TRIMS has added genotyping information for culture-confirmed cases genotyped by CDC.

Study population

TB cases included in the final analysis had to meet these inclusion criteria: (1) 15 years or older; (2) newly diagnosed TB disease in TRIMS database; (3) culture confirmation; (4) completed DST

results; (5) completed genotypic results. All TB cases were reported to Los Angeles Tuberculosis Control Program and managed under the LAC jurisdiction between the January 1, 2010 and December 31, 2014. The date used to specify the period of study was the date when the patient was confirmed as TB case. TB cases in this study included patients with isolation of *Mycobacterium tuberculosis* complex from a clinical specimen. New cases are defined as patients with tuberculosis who have never been treated with anti TB drugs or have received them for less than 1 month.

In order to assess the *M. TB* with PZA mono-resistance on all-cause mortality in TB patients validly, we have to eliminate *M. bovis* infection from our analysis. We differentiate *M. TB* and *M. bovis* for a sub-set of MTBC by using spacer oligonucleotide typing (spoligotyping) and mycobacterial interspersed repetitive unit variable number tandem repeats (MIRU-VNTR) techniques. (37, 39, 43, 44).

All TB cases from 2010-2014 who were alive at the time of diagnosis and have a start date for anti-TB therapy recorded were eligible (Figure 2). Patients were excluded if they had a TB case closure status of moved, lost to follow up, refused treatment, had adverse treatment event, pending, others, or missing (Figure 2).

Primary exposure definition

For the purpose of this analysis, the exposure of interest was the type of TB drug resistance pattern: all drug susceptible, INH mono-resistance, PZA mono-resistance, MDR-TB was also included in

the analysis, but we excluded the other resistance patterns. During 2010-2014, LAC public health laboratory used the MGIT 960 AST, Bactec 460 and agar proportion method on selected drugs. The critical concentration used in the standard test were >1% growth of M. tuberculosis complex in the concentration of INH at 0.2 µg/ml or 1 µg/ml on agar proportion method. PZA susceptibility testing was operated by using liquid culture in the Bactec460 or MGIT 960 system at a PZA concentration of 100 µg /ml. The Clinical and Laboratory Standard Institute suggested the BACTEC 460TB (BD, Sparks, MD, USA) as a reference method for PZA susceptibility (45). When production for reagent for BACTEC 460TB was stopped in 2011, BACTEC Mycobacterial Growth Indicator Tube (MGIT) 960 system (BD, Sparks, MD, USA) was used for PZA drug susceptibility testing in LAC public health laboratory. For the turnaround time, Bactec 460 and MGIT 960 (Commercial Broth System) take 12-14 days from the date drug susceptibility test was started, and 7H10 agar (Agar Proportion Method) takes 3 weeks from the date drug susceptibility test was started.

Primary outcome definition

The primary outcome of interest was all-cause mortality death among all TB cases. The definition of death rely on CDC, which counts any death that happens from the time of diagnosis to the time of treatment completion (46). Because the TBCP surveillance database provided only TB-related and non TB-related, the specific cause of death was not available for analysis.

Description of variables

Specific fields were extracted from the TRIMS database to assess patient demographics (e.g. age, gender, race/ethnicity, US. vs. foreign born), clinical characteristics (pulmonary vs. extra pulmonary), underlying disease status (HIV infection, Diabetes Mellitus, kidney disease), and behavioral factors (excess alcohol use). (See Appendix, Table 4). Age is continuous variable, and others are categorical variables: (1) dichotomous variables (yes vs. no)-gender, diabetes mellitus, kidney disease; (2) nominal variables- race/ethnicity, US. born, excessive alcohol use, HIV status, disease characteristics, anti-TB drug resistance at baseline.

Ethics Statement

All data analyzed in this study came from the Los Angeles County Department of Public Health Tuberculosis Control Program as a part of surveillance data for public health scheme.

Statistical Analysis

All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina). Descriptive statistics were used to explain patient demographics, disease characteristics, excess alcohol use, diabetes mellitus, and status of HIV infection for the overall cohort. Continuous variables were reported by mean/median. Categorical variables were reported by the frequency and percentage. Age as a continuous variable was categorized at purposeful cut-points depended on the surveillance reports and previous studies.

We investigated factors associated with all-cause mortality during anti-TB treatment by estimating odds ratios (ORs) and 95% confidence intervals (95%CIs) in bivariate analyses. We chose predictors that were known as potential confounders of drug resistance and death from any cause during anti-TB treatment (e.g., age, gender, race, U.S. vs. foreign born, disease characteristic) by first constructing a directed acyclic graph (DAG) in figure 1. Predictors were included in the multiple logistic model if the predictor was associate with the exposure and outcome variables, but this inclusion did not rely on a pre-specified significant value. We also used the Hosmer-Lemeshow test to assess model fit (47).

CHAPTER IV: RESULTS

Overall, there were 2,201 (68.2%) cultured confirmed cases of *M. tb* reported to Los Angeles County Tuberculosis Control Program between January1, 2010 and December 31, 2014 (Figure 2). Of these, 119 cases (3.7%) stopped TB treatment for reasons other than completion and death that were identified as: (1) adverse treatment 2 cases; (2) Lost to follow up 26 cases; (3) Move 39 cases; (4) Other 40 cases; (5) Pending 1 case; (6) refused 4 cases; (7) missing 7 cases were excluded from the analysis because the treatment outcomes were unknown. Forty-four cases (1.4%) died before and at time of notification of TB diagnosis, leaving 2,038 cases alive and active TB cases at diagnosis. Among those alive at time of TB diagnosis, we also excluded 21 cases (1.0%) who died before receiving treatment, 25 cases (1.2%) who are younger than 15 years old and no death in this age category, and 63 cases (3.1%) who were relapse/reinfection of TB leaving only newly confirmed *M. tb* cases for analysis.

Of 2,201 cases, 1,932 cases (88%) from the years 2010-2014 met final inclusion criteria for the retrospective cohort study (Figure 2). The majority of cases were male (63.6%) and the median age was 54 years old. (Table 1). One third of participants were in age group of 45-64 years old. Asian ethnicity accounted for 44.3% of cases and Hispanic ethnicity accounted for 41.5% of cases. At the time of diagnosis, 82.7 % of 1,932 cases were born outside U.S., 11.4 % reported using excess alcohol, 28.8% had Diabetes Mellitus, and 4.7% were HIV positive. For the disease characteristic of all TB cases, 63.7% were determined to be pulmonary without cavitation.

Of 1,929 cases, there were 1,701 cases (88%) in the drug-susceptible group and 228 cases (12%) in the drug-resistant group. In the drug resistant group, a majority of drug resistant cases were INH

mono-resistance (n=149/228, 65%). Also, there were 29 cases (13%) in MDR-TB group and 28 cases (12%) in PZA mono-resistance. The mortality rate in the drug susceptible group was 10.3% and the mortality rate in the drug resistant group was 14.5% (14%, 3.4%, and 25% in INH mono-resistance, MDR, PZA mono-resistance, respectively) (table1).

We found a higher death rate of INH mono-resistance and PZA mono-resistance when compared to drug susceptible cases (14.1% vs. 25% vs. 10.3%) (Table2). INH mono-resistance and PZA mono-resistance were more likely to occur in older age group than drug-susceptible (median age 58 vs. 60.5 vs. 54 years), more likely to be foreign-born (90.6% vs. 89.3% vs. 81.8%) especially from Asia, and had a higher proportion of diabetes cases when compared with all drug susceptible patients (32.2% vs. 39.3% vs. 28.4%).

For INH mono-resistance, other risk factors were quite similar to the drug-susceptible group, including male gender (63.8% vs 63.9%), known positive HIV infection (4.7% vs. 4.6%) and excess alcohol use (10.1% vs. 11.7%) (table2). For PZA mono-resistance, known positive HIV infection also mostly found in PZA mono-resistant group (10.7% vs. 4.6%). Moreover, one fourth of PZA mono-resistant cases were extra pulmonary (25% vs. 13.4%). In contrast, there was no excess alcohol use in this group.

Trend of INH mono-resistant proportion from total TB cases increased from 2012 to 2014 (6.1% to 9.8%), corresponding to the increasing in Asian race/ethnicity proportion in TB patients in LAC (39.9% to 47.6%). At the same time, the trend of PZA mono-resistant proportion from total TB

cases was rising from 2010 to 2011 (0.3% to 2.1%) then distributed evenly from 2011 to 2013 (2.1% and 1.9%) and slightly decreased to 1% in 2014 (figure3).

Among the 207 who died during TB treatment, 79 (38.2%) died within 30 days of treatment, 41 (19.8%) died between 30 and 60 days of treatment. More than half of deaths occurred within first two months or intensive of TB treatment (Figure 4). The median age was 73 years for all deaths. In 21 cases who died in INH mono-resistant group, almost half of cases (47.6%) died within two months of treatment; however, a majority of PZA mono-resistant (71.4%) died within two months of treatment.

Patients with INH mono-resistance had an unadjusted odds of all-cause mortality during TB treatment that was 1.4 times the odds of mortality when compared to patients having drug-susceptible (crude odds ratio [cOR] 1.43, 95% CI 0.88-2.33). After adjusting for potential confounding covariates (i.e. age, race, gender, U.S. vs. foreign born, extra pulmonary) using background knowledge and directed acyclic graph theory (see: Figure 1), the adjusted odds of all-cause mortality for INH mono-resistant was found to be 1.57 times the odds of all-cause mortality for all drug-susceptible with a confidence interval span from 0.93 to 2.64 and including one (adjusted odds ratio [aOR] 1.57, 95% CI 0.93-2.64).

In addition, patients with PZA mono-resistant had an unadjusted odds of all-cause mortality during TB treatment that was 2.91 times the odds of mortality when compared to patients having drug-susceptible (crude odds ratio [cOR] 2.91, 95% CI 1.22-6.94). After adjusting for potentially confounding covariates, the magnitude of association and the significance of odds ratio was

reduced. The adjusted odds of all-cause mortality for PZA mono-resistant decreased to 2.43 times the odds of all-cause mortality for all drug-susceptible with a confidence interval span from 0.92 to 6.44 and including one (adjusted odds ratio [aOR] 2.43, 95% CI 0.92-6.44).

After adjusting for confounding factors, the results of multiple logistic regression showed that INH and PZA mono-resistance may increase the mortality, while PZA mono-resistance had wider confidence interval than INH mono-resistance. Older age, male gender, and pulmonary involvement might increase TB mortality, although some of the confidence intervals included one (table3).

CHAPTER V: DISCUSSION

We identified the two major types of drug resistant TB and their associations with all-cause mortality during treatment. These results provide some understanding of drug resistance pattern in a low TB prevalence setting. The first pattern was INH mono-resistance that showed a moderate association with all-cause mortality. Secondly, PZA mono-resistant had a stronger association with all-cause mortality in this study samples.

INH mono-resistance

We found a high case fatality rate of 14% for 149 INH mono-resistant new TB patients. The percentage of total deaths had been documented as 10% of drug susceptible TB patients, including deaths due to TB and deaths unrelated to TB disease in LAC from 2010 to 2014. Our multiple logistic regression showed moderate association between INH resistance and all-cause TB mortality with a wide confidence interval consistent with many studies reporting that isoniazid resistance has been found to be a risk factor of unfavorable treatment outcome (i.e. loss to follow up, failure, transfer out, switch to MDR treatment) (7-9, 11-16, 48, 49). The relative small OR (1.5) comparing to OR 1.81 from van der Heijden's study in South Africa (7) and Hazard ratio 3.3 from Baez-Saldana study in Mexico (10) might be related to the differences in inclusion criteria, the treatment regimens used after knowing Drug susceptibility result, and a better TB program in LAC.

The difference in inclusion criteria for our study came from the strict criteria that included only primary INH resistance and newly confirm TB cases in our study and Cattamanchi's study (18).

Including these cases would select a healthier group of participant based on the result from Aibana's and Choi's study that showed patients with a previous TB history tended to have poor treatment outcome (50, 51). On the other hand, the rest of the studies which included both new and retreatment cases may have a biased study results (outcome worse than it should be). Although previous researchers adjusted for history of TB treatment, there is some residual bias from too broad category of previous TB treatment such as the episode of diagnosed TB disease: the second episode would not same as the fifth episode in the aspect of organ damage. In short, the previous studies which include retreatment cases may not have provided an accurate estimate of the association between INH mono-resistance and TB mortality.

The regimen adapted after knowing DST (Drug Susceptibility Test) result could have impacted the treatment outcome. In our study, the treatment would change to Rifampicin, Pyrazinamide, and Ethambutol upon confirmation of DST result for six to nine months or Rifampicin and Ethambutol and Fluoroquinolone for 9 to 12 months (if PZA toxicity becomes an issue) after INH mono-resistant result reported according to standard practice of physician in LAC at that time. This Rifampicin, Pyrazinamide, and Ethambutol regimen showing 95 to 98 percent success rate among 107 patients with INH mono-resistant TB (52), It is also supported by retrospective studies of Cattamanchi and Bang that adjusted regimen based on the result of drug susceptibility test. Both studies reported that there was no effect of INH mono-resistance on TB treatment outcome of standard modified treatment.

Nonetheless, the studies reporting poor treatment outcome reported using the WHO standard schedule of initiating therapy with 4 drugs (2HRZE/4HR) for newly diagnosed patients and 5 drugs

(2HREZES/1HRZE/5HRE) for previously treated patients and most of the program did not adjust for INH mono-resistance. Fluoroquinolones were not included in treatment schedules for these patients. The wide range of odds ratio based on wide CI in this study might came from the timing when health care providers tailoring regimen based on DST result. If they know DST early and change treatment regimen immediately, you might not see the difference between INH mono-resistance and the drug susceptible group. In contrast, if they don't know DST result or patients may have died prior to DST results being known, the treatment outcome in INH mono-resistance might be worse from continuing unadjusted regimen.

In this study, TB treatment was given by directly observed therapy (DOT) from health providers after knowing INH mono-resistant status according to standard practice in LAC. DOT by health providers is also supported by study of public health supervision effect on mortality with tuberculosis in Los Angeles County, 2010-2014. This study revealed that patients without any supervision from health department experienced approximately double the risk of death as those patients with supervision form health department (53). The results from this DOT study supported our result which was lower than expected between INH mono-resistance and mortality after receiving DOT by healthcare provider, it could be due to the use of DOT improved outcomes in some patients. However, most studies did not mention about treatment adherence or DOT status. In our study, we also did not adjust for type of supervision because it is not a confounding factor in our model.

PZA mono-resistance

We found a higher death rate of PZA mono-resistance when compared to drug susceptible cases or INH mono-resistance (25% vs. 10.3% vs.14.1%). In spite of the width of confidence interval, PZA mono-resistance might indicate the strong association by the high value of OR (2.43). It's could be explained by the fact that almost three fourth of PZA mono-resistant cases died within two months, so these early deaths occurred before the DST results were available. This result supported by the Yee's study from Quebec after excluding *M. bovis*. They also reported the worse clinical outcome of PZA mono-resistance compare to all drug susceptible (20). On the other hand, the result from Budzik from San Francisco did not find any significant association between PZA resistance and treatment failure (p=0.51) (21). However, Budzik's study included *M. bovis*, while our study focused on *M. tb*. Also, patients with *M. bovis* tended to have better treatment outcome compare to *M. tb,* which may explain the different result from Budzik's study to our study.

The strong association of PZA mono-resistant cases with less precision of statistical estimation and including null value may be due to the few number of cases after excluding *M. bovis* from PZA mono-resistance. Secondly, the misclassification from inaccurate PZA resistance that could happen from either false resistance (pH rising in heavy inoculum and the decrease in PZA activity) or false susceptibility (*M. tb* could not grow well in low pH from too light inoculum) that can create bias towards the null.

In PZA resistant cases from our study, about 56% were due to *M. bovis* (79/141). After excluding *M. bovis*, PZA resistance was identified only 2.6% (50 of 1929) of mycobacterial isolate tested

from new TB cases in LAC which was consistent with the report from national surveillance data (30). After excluding MDR-PZA (13 of 50) and any PZA resistance more than one drug, we had only 28 cases of PZA mono-resistance left (1.5%). This problem of small sample size might affect the power of the study, and be reflected wide confidence interval.

The difficulty in testing for PZA resistance originated by using MGIT 960 system for PZA drug susceptibility testing (DST). This system might create some potential for false-resistance test results for PZA (33, 54). According to of non- differential misclassification of PZA resistant status on our dichotomous outcome as complete and died, we could predict that our odds ratios presented can be biased toward the null base on the assumption that PZA resistant would not affect misclassification of the closure status, and the closure status would not affect the misclassification of PZA resistance, too.

Multidrug-resistant

MDR showed less precision of odds ratios for all-cause mortality ranging from 0.09 to 5.23. This conflicted with most of the previous studies that reported success rate for MDR-TB range from 30 to 80 percent (55-59). We can explain these unexpected outcomes by three factors. The first there were few cases of MDR-TB in LAC and only one death, thus we did not have enough effect size to estimate the magnitude of the association. The second factor might due to the strong TB program in LAC.

Given such a positive finding from MDR-TB treatment in LAC, the few number of deaths might come from the strong TB control program in LAC which dedicate all resource to treat MDR-TB patients. We can speculate that if INH mono-resistance and PZA mono-resistance receive the same level of treatment and care as MDR-TB, the TB mortality rate in INH and PZA mono-resistance would reduce dramatically and prevent the development from mono-resistance to poly-resistance or MDR-TB in the future.

Limitation

A potential limitation is the patient cohort for analysis was restricted to patients with a known case closure status, only completion of treatment and death. Those patients who had adverse treatment event, moved, lost to follow-up, pending case closure or refused treatment were excluded; patients who lost to follow up or refuse treatment can cause some bias to our study if they had unique characteristic which relate to our study. In order to ascertain our treatment outcome, 119 cases had to be excluded from the study. (n=119/3226, 3.7%). However, four percent is a very low proportion and not likely to have an effect on the findings.

In addition, we did not collect INH and PZA -resistance conferring mutation due to unavailability of pyrosequencing and Sanger sequencing in LAC public health laboratory. Given such an unclear result on *katG* and *inhA* on TB treatment outcomes, we could not draw inferences about which type of mutation are associated with worse treatment outcomes. Moreover, the techniques using for testing PZA in MGIT are subject to different interpretation of results, yielding either false resistance or false susceptibility. However, this misclassification would bias our result towards the null, so the effect of PZA mono-resistance might be even stronger.

Next, we cannot evaluate the efficacy of adapting regimen after INH and PZA DST result were reported because there is no data available from our surveillance system (TRIMS). Last, death with TB are not similar to death due to TB. Based on the CDC definition, all deaths that occur after a patient is diagnosed with TB and before they complete TB treatment is considered a TB death. As a result, this includes patients that may have died from TB-unrelated causes. Nonetheless, this study only included cases who died during TB treatment.

Recommendation

In this study, patients with INH or PZA mono-resistance were more likely to die than patients with drug-susceptible TB. Efforts are needed to improve treatment outcomes for INH or PZA mono-resistant TB patients. Recommendations for further studies include: (1) review of medical records to verify the actual cause of death and select only TB-related death and focus especially in INH and PZA mono-resistant cases due to high mortality in both groups; (2) investigation of the effectiveness of the regimens, time when starting adjusted treatment and dosage of anti-TB drug for the drug resistance groups; (3) identify the association of INH conferring mutation and treatment outcome; (4) explore the cause of an increasing trend in INH mono-resistance from 2012 to 2014.

APPENDICES

Figure 1. Drug Resistant Pattern and TB Mortality, Directed acyclic graph (DAG).

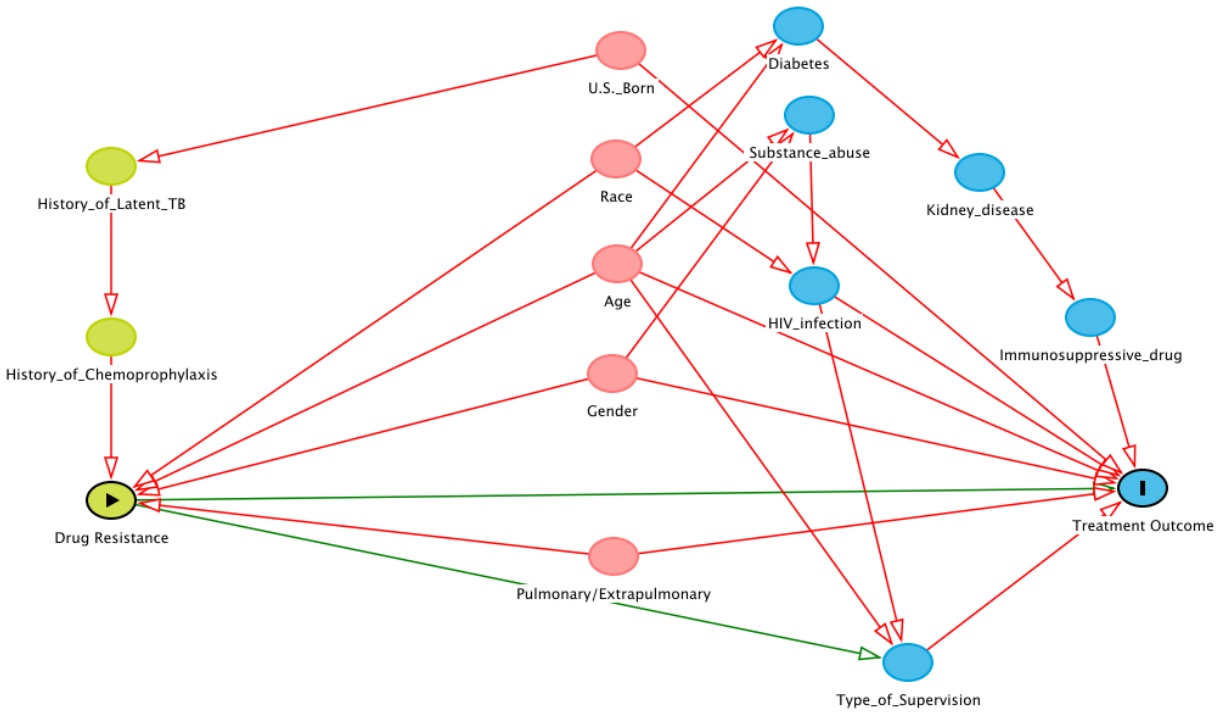

Figure 2. TB Cases Reported to Los Angeles County, 2010-2014.

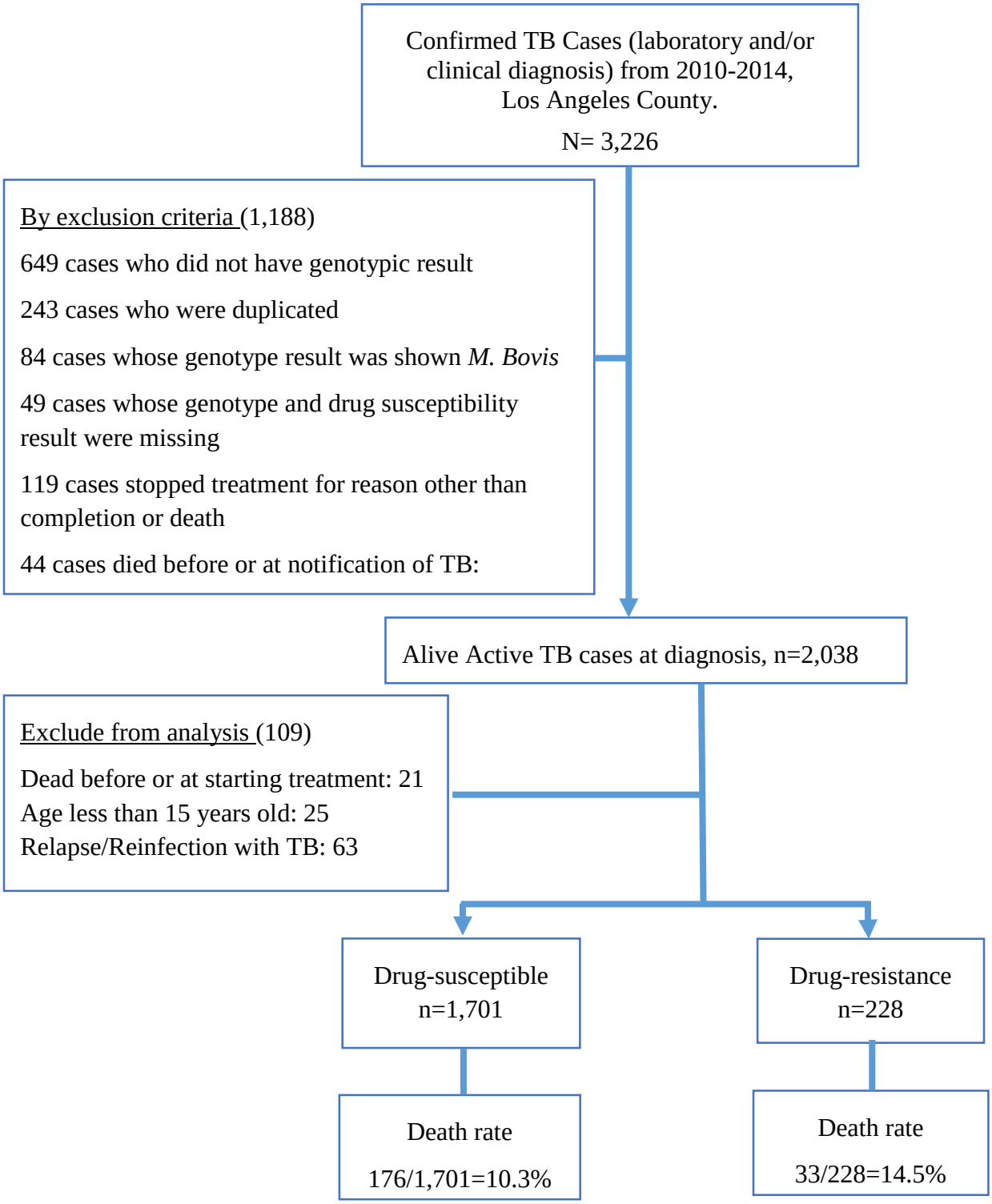

Figure 3. Number of TB cases with MDR, INH mono-resistant, PZA mono-resistant, and other resistant among TB Cases Reported to Los Angeles County, 2010-2014. (n=228)

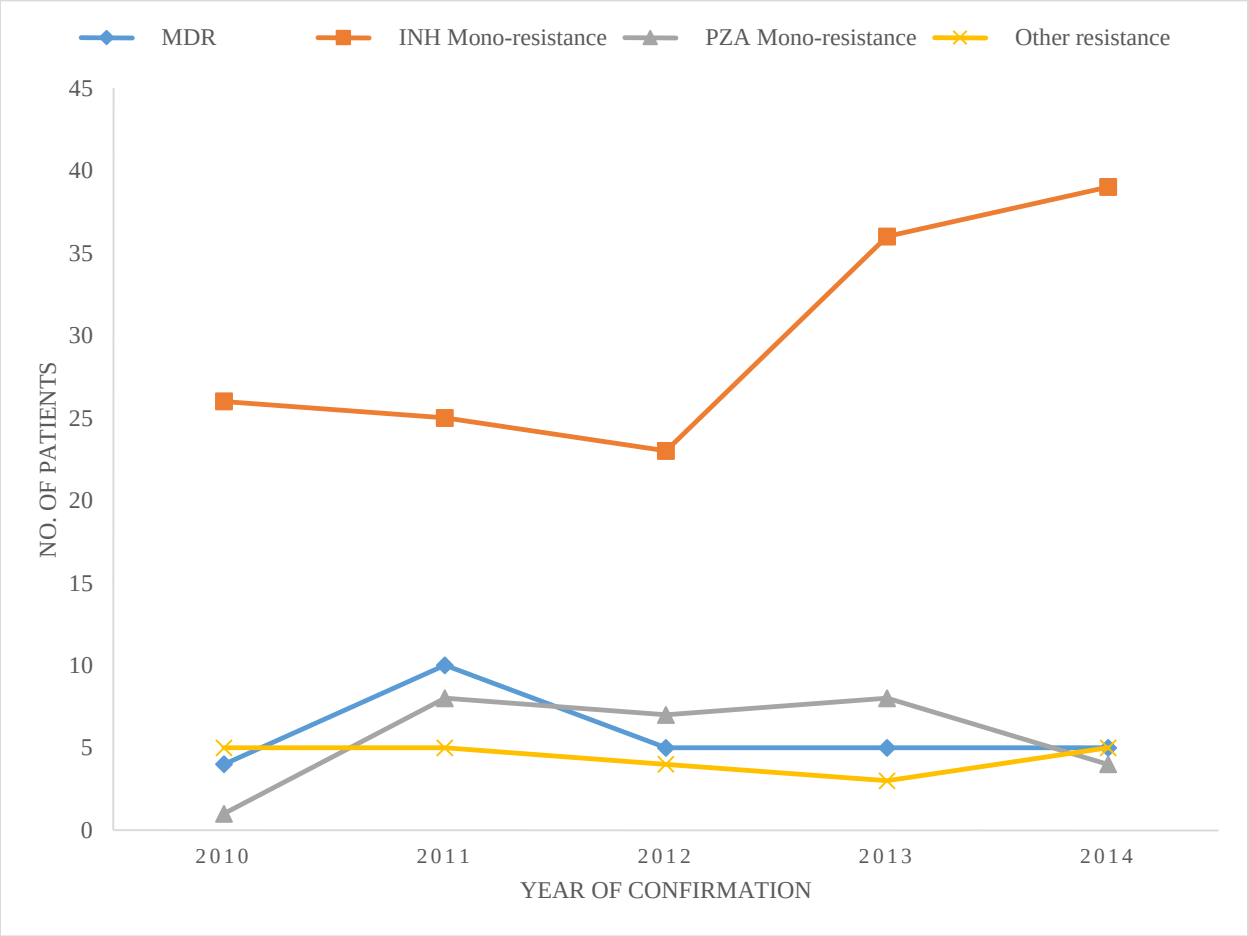

Figure 4. Time from tuberculosis treatment start to death, among patients who died, California, 2010-2014 (n=207).

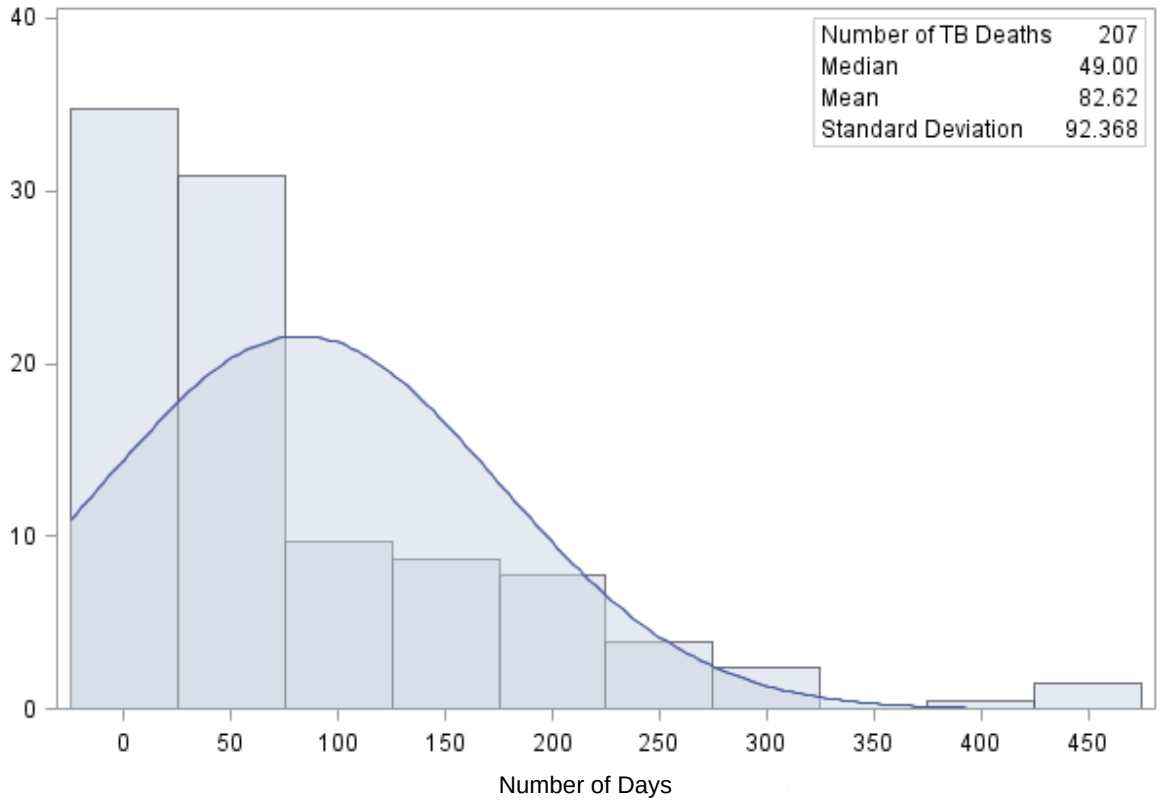

Table 1. Characteristics of TB cases by treatment outcome status, Los Angeles County 2010-2014. (n=1,929)

			Treatment Outcome			
	Overall[1]		Complete		Died	
	N	(%)	N	(%)	N	(%)
Total	1929	(100.0%)	1722	(100.0%)	207	(100.0%)
Male	1226	(63.6%)	1080	(62.7%)	146	(70.5%)
Age (years)						
15-34 years	369	(19.1%)	362	(21.0%)	7	(3.4%)
35-44 years	253	(13.1%)	245	(14.2%)	8	(3.9%)
45-54 years	343	(17.8%)	318	(18.5%)	25	(12.1%)
55-64 years	346	(17.9%)	315	(18.3%)	31	(15.0%)
65-74 years	263	(13.6%)	224	(13.0%)	39	(18.8%)
75-84 years	203	(10.5%)	173	(10.0%)	30	(14.5%)
85+ years	152	(7.9%)	85	(4.9%)	67	(32.4%)
Race/Ethnicity						
Non-Hispanic White	103	(5.3%)	87	(5.1%)	16	(7.7%)
Hispanic	800	(41.5%)	730	(42.4%)	70	(33.8%)
African American	172	(8.9%)	158	(9.2%)	14	(6.8%)
Asian	854	(44.3%)	747	(43.4%)	107	(51.7%)
U.S. Born	331	(17.2%)	299	(17.4%)	32	(15.5%)
Excessive Alcohol Use	220	(11.4%)	202	(11.7%)	18	(8.7%)
Diabetes Mellitus	556	(28.8%)	467	(27.1%)	89	(43.0%)
HIV Status						
Known Positive	91	(4.7%)	83	(4.8%)	8	(3.9%)
Known Negative	1732	(89.8%)	1577	(91.6%)	155	(74.9%)
Not done/Unknown result	70	(3.6%)	32	(1.9%)	38	(18.4%)
Refused	36	(1.9%)	30	(1.7%)	6	(2.9%)
Disease characteristics: site, cavitation						
Pulmonary and cavitary	445	(23.1%)	419	(24.3%)	26	(12.6%)
Pulmonary, not cavitary	1229	(63.7%)	1067	(62.0%)	162	(78.3%)
Extra pulmonary	255	(13.2%)	236	(13.7%)	19	(9.2%)
ANTI-TB DRUG RESISTANCE AT BASELINE						
All susceptible	1701	(88.2%)	1526	(88.6%)	175	(84.5%)
INH Mono-resistant	149	(7.7%)	128	(7.4%)	21	(10.1%)
RIF Mono-resistant	4	(0.2%)	4	(0.2%)	0	(0.0%)
PZA Mono-resistant	28	(1.5%)	21	(1.2%)	7	(3.4%)
Multi-drug resistant	29	(1.5%)	28	(1.6%)	1	(0.5%)
Other	18	(0.9%)	15	(0.9%)	3	(1.5%)

[1] Percentages may not sum to 100% due to missing data.

Table 2. Characteristics of TB cases by drug resistant pattern, Los Angeles County 2010-2014. (n=1,929)

	Drug resistant pattern					
	All susceptible		**INH mono-resistant**		**PZA mono-resistant**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
Total	1701	(100.0%)	149	(100.0%)	28	(100.0%)
Male	1087	(63.9%)	95	(63.8%)	15	(53.6%)
Age, median	54 years		58 years		60.5 years	
Age (years)						
15-34	330	(19.4%)	21	(14.1%)	1	(3.6%)
35-44	218	(12.8%)	21	(14.1%)	4	(14.3%)
45-54	303	(17.8%)	25	(16.8%)	4	(14.3%)
55-64	306	(18%)	28	(18.8%)	7	(25%)
65-74	231	(13.6%)	25	(16.8%)	3	(10.7%)
75-84	175	(10.3%)	22	(14.8%)	4	(14.3%)
85+	138	(8.1%)	7	(4.7%)	5	(17.9%)
Race/Ethnicity						
Non-Hispanic White	92	(5.4%)	5	(3.4%)	4	(14.3%)
Hispanic	731	(43%)	49	(32.9%)	6	(21.4%)
African American	164	(9.6%)	8	(5.4%)	0	(0%)
Asian	714	(42%)	87	(58.4%)	18	(64.3%)
US-born	310	(18.2%)	14	(9.4%)	3	(10.7%)
Excess alcohol	199	(11.7%)	15	(10.1%)	0	(0%)
Diabetes mellitus	483	(28.4%)	48	(32.2%)	11	(39.3%)
HIV status						
Known Positive	78	(4.6%)	7	(4.7%)	3	(10.7%)
Known Negative	1528	(89.8%)	133	(89.3%)	24	(85.7%)
Not done/Unknown result	61	(3.6%)	7	(4.7%)	1	(3.6%)
Refused	34	(2%)	2	(1.3%)	0	(0%)
Extra pulmonary	228	(13.4%)	16	(10.7%)	7	(25%)
Outcome						
Complete	1526	(89.7%)	128	(85.9%)	21	(75%)
Died	175	(10.3%)	21	(14.1%)	7	(25%)

Table 3. Crude and Adjusted odds ratio of risk of all-cause mortality among Bacteriological confirmed TB patients, LAC, 2010-2014 (n=1,927*)

	Crude odds ratio (cOR)		Adjusted odds ratio (aOR)	
	cOR	95% CI	aOR	95% CI
Gender				
Female	1.00	---	1.00	---
Male	1.42	1.04, 1.95	1.32	0.94, 1.86
Age Group				
15-34	1.00	---	1.00	---
35-44	1.69	0.60, 4.71	1.69	0.60, 4.74
45-54	4.06	1.73, 9.52	3.93	1.66, 9.29
55-64	5.09	2.21, 11.71	5.09	2.18, 11.86
65-74	9.00	3.96, 20.46	9.09	3.94, 20.94
75-84	8.96	3.86, 20.81	8.94	3.80, 21.02
85+	40.74	18.06, 91.90	40.57	17.64, 93.31
Race/Ethnicity				
Hispanic	1.00	---	1.00	---
Non-Hispanic White	1.92	1.07, 3.45	0.98	0.49, 1.95
Asian	1.49	1.09, 2.05	0.97	0.68, 1.39
African American	0.92	0.51, 1.68	0.83	0.39, 1.76
U.S. Born				
No	1.00	---	1.00	---
Yes	0.87	0.58, 1.29	1.25	0.71, 2.21
Pulmonary				
No	1.00	---	1.00	---
Yes	1.57	0.96, 2.57	1.52	0.90, 2.56
Drug susceptibility test pattern				
All susceptible	1.00	---	1.00	---
Multi-drug resistant	0.31	0.04, 2.30	0.68	0.09, 5.23
INH Mono-resistant	1.43	0.88, 2.33	1.57	0.93, 2.64
PZA Mono-resistant	2.91	1.22, 6.94	2.43	0.92, 6.44
Other	1.37	0.40, 4.70	1.68	0.43, 6.51

Hosmer and Lemeshow Goodness-of-fit Test: P Value = 0.80
*2 observations were deleted due to missing values for the response or explanatory variables.

Table 4. Description of covariates abstracted from TRIMS database.

Variable	Type	Description	Additional notes
Age	Continuous	At time of diagnosis	
Sex	Categorical: Male, Female, no data	At time of diagnosis	
Race/ethnicity	Categorical: Non-Hispanic White, Hispanic, Asian, African American.		Due to small sample size, Native Hawaiian/Alaska Native was collapsed within the Asian category.
US Born	Categorical: Yes, No, Unknown.	Was the patient born in the United States	
Excessive Alcohol	Categorical: Yes, No, Unknown	Within the last year, at time of diagnosis. Patient self-report.	
Diabetes Mellitus	Dichotomous: Yes, No	Patient has a diagnosis of diabetes mellitus (I or II) either before or at the time of TB diagnosis.	Diabetes may either be controlled by diet or medication.
HIV Status	Categorical: Negative, No Data, Not Done, Positive, Refused,	The HIV status of the patient	
Site of TB Disease	Categorical: Pulmonary, extra-pulmonary.		Pulmonary is defined strictly as pulmonary only, excluding pleural and laryngeal.
Cavitary disease	Dichotomous: Yes, No	Any initial chest radiograph showing abnormalities consistent with TB and marked as cavitary.	Based on results of initial CXR only. Does not include CT results.

Variable	Type	Description	Additional notes
Anti-TB drug resistance	Categorical: All susceptible, INH mono-resistance, PZA mono-resistance, RIF mono-resistance, Multi-drug resistant TB, Other resistance.	Resistance variables based on DST results	MDR: Defined by CDC; resistance to at least INH and RIF (CDC). Includes those who are MDR.

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