FACULTAD DE CIENCIAS DE LA SALUD

ESCUELA DE MEDICINA

TUBERCULOSIS SENSIBLE Y DROGORRESISTENTE: MORTALIDAD Y SUS FACTORES ASOCIADOS

Para optar por el título profesional de:

MÉDICO CIRUJANO

AUTORES

CHUNG DELGADO, KOCFA

GUILLÉN BRAVO, SONIA PATRICIA

REVILLA MONTAG, ALEJANDRO

ASESOR

BERNABÉ ORTIZ, ANTONIO

CALIFICACIÓN

NOTABLE

23 de enero de 2015

Lima, Perú

DEDICATORIA

Para aquellos que—desde el inicio—creyeron en mí con inextinguible fe.

A mis padres, por sus consejos, apoyo y confianza durante todos los años de estudio, y por ser un ejemplo de trabajo, esfuerzo y dedicación.

A todos los jóvenes investigadores allá afuera para que sigan contribuyendo con la investigación científica. A mis papás porque este trabajo representa el final de mi carrera, larga y ardua, pero que traerá grandes frutos en un futuro.

AGRADECIMIENTOS

A nuestros maestros y guías
de este largo arte que se hace llamar 'Medicina',
por la inagotable paciencia, enseñanza y confianza.

TABLA DE CONTENIDO

3.2 Primera Revisión

3.2.1 Carta de Respuesta

Sept 22nd, 2014

Dear Academic Editor
Dr. Joan A Caylà, MD, PhD
PLoS One

Reference: Manuscript ID PONE-D-14-34677:
Title: "Mortality among MDR-TB cases: Comparison with sensitive tuberculosis and associated factors"

I'm writing on behalf of my co-authors Sonia Guillen-Bravo, Alejandro Revilla-Montag and Antonio Bernabe-Ortiz in response to the reviewer's comments regarding the manuscript of the reference.

Our responses are detailed below. We hope that we have addressed all the doubts and requirements requested by the reviewers.

Responses to Reviewers' comments:

1. **Although this analysis is presented as a comparison of mortality caused by two types of TB infection (drug susceptible and MDR TB), it does not accurately compare their mortality rates, because it fails to account for two important factors: different starting points of analysis for the two groups, and the likelihood of biased misassignment of patients with MDR to the drug susceptible group.**

   We agree with the reviewer. However, given the retrospective nature of the study, it was very difficult to find an appropriate starting point. In regards to our final decision of starting at the beginning of anti-tuberculosis treatment, we argue the following points:
   a. There is no "standard" as several reports use different starting points: from the beginning of symptoms to the start of treatment. These papers varied precisely because of this issue. The choice is associated with the nature of the analysis: prospective against retrospective.
   b. A systematic review published in Int J Tuberc Lung Dis [*15(7): 871-885*] does not exclude manuscripts due to different starting points.
   c. In despite of this limitation, our results are comparable with other studies showing more risk of death due to MDR forms of tuberculosis (*Int J Tuber Lung Die 2010; 14: 454-463* and *Clin Infect Dis 2001; 32: 373-380*).

   Based on this information—and the limitation of data—we agree with the reviewer in identifying the starting point as a limitation in our study. This has been updated and added in the Discussion section of our final manuscript.

There is a low risk of misclassifying MDR as sensitive. Our study shows a high proportion of MDR-TB cases (18%) compared to other studies from our country. For example, Kawai et al (using sputum culture and MODS) found the same proportion of cases of MDR-TB (18%, 51/287) as published in Am J Trop Med Hyg in 2006. Similarly, Asencios, using information of the National Control Program, found 5.3% of MDR-TB cases among new cases of TB and 23.6% among those with previous history of TB (Rev Peru Med Exp Salud Publica 2009). Thus, we believe, the impact of this potential bias is low. However, we have added a small comment in the Discussion section to address this point.

2. **The authors do not explicitly state the duration of their proportional hazards analysis, but their figure 1 suggests that they extended the analysis for 300 days, whereas the methods state that each patient was censored from analysis at time of treatment completion. Given that typical first-line treatment only lasts ~6 months, the drug-susceptible sample size beyond about 180 days is likely to be very small, and it is unclear why the analysis continues beyond that point.**

We agree with the reviewer. We have executed a new analysis censoring time of follow-up from all participants to 6 months (180 days time). The pertinent changes and modifications have been made in the Methods section (Analysis plan). As well, Figure 1 has been modified to show censoring at 180 days.

3. **The authors exclude defaults, failures, and transfers, which are likely to differ between drug susceptible and MDR groups (defaults and transfers because of the different treatment durations, failures because of the reduced effectiveness of second line drugs). For robustness, analyses should consider in what ways patients with these excluded outcomes are similar or different from patients who died or completed treatment, and authors should consider the impact of censoring when these outcomes occur as opposed to excluding these individuals from analysis from the outset.**

Although their data was collected, transferred patients, treatment failures and abandonment were excluded from our analysis because the sociodemographic profile of these patients is different from those who died or alive. Below is a table showing some of the differences found during the analysis:

	Cured	Transferred	Abandon	Failure	Death
Sex					
Male	611 (58.1%)	2 (40.0%)	83 (74.8%)	5 (50.05)	43 (67.2%)
Age					
Low tertile	407 (38.7%)	2 (40.0%)	42 (37.9%)	3 (30.0%)	21 (32.8%)
Middle tertile	314 (29.9%)	2 (40.0%)	33 (29.7%)	3 (30.0%)	21 (32.8%)
Top tertile	331 (31.5%)	1 (20.0%)	36 (32.4%)	4 (40.0%)	36 (56.3%)
Education					
11+ years	556 (52.9%)	3 (60.0%)	46 (41.4%)	5 (50.0%)	17 (26.6%)
7 – 10 years	326 (31.0%)	2 (40.0%)	36 (32.4%)	2 (20.0%)	21 (32.8%)
6 or less years	170(16.1%)	0 (0.0%)	29 (26.1%)	3 (30.0%)	26 (40.6%)
Smoking					
Yes	146 (13.9%)	0 (0.0%)	16 (14.4%)	4 (40.0%)	15 (23.4%)
Alcohol					
Yes	191 (18.2%)	3 (60.0%)	28 (25.2%)	2 (20.0%)	18 (28.1%)

Thus, we decided to exclude transferred patients because the small number of cases, and abandon and failure because the different profile compared to the other groups.

4. **Anemia was listed in the results as associated with mortality but was not listed in methods as a variable to be considered).**

The corresponding correction has been made in the manuscript.

5. **The y axis of the survival curve is misleading in not starting from zero, and it is unclear how long the subjects were actually followed given that the lines extend without any deaths after day 180.**

This has been now clarified in this version of the manuscript. A new Kaplan-Meier survival curve figure has been added as requested by the reviewer.

6. **The claim that "MDR-TB is strongly associated to other co-morbidities such as HIV infection, diabetes and chronic kidney disease, as well as particular lifestyles including alcohol abuse, smoking, drugs use, etc" is unsupported in the manuscript and is not to my knowledge accurate.**

This has been rephrased and restructured to be accurate based upon the conclusions found in this investigation. The corresponding correction has been made in the manuscript.

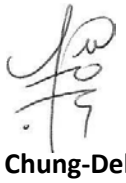
7. **Data policy: They may have complied if they submitted a data file with their manuscript to which I do not have access, but I have no evidence that they have done this. The authors state that they have made the data available within the paper and supporting files, but the data contained in the paper itself and supporting figure and tables is only a summary and is not the complete original data.**

The complete original data set is available upon personal request.

8. **There are numerous minor deviations from standard English grammar and usage. The manuscript would benefit from editing by a fluent English speaker.**

The manuscript has been revised by the authors for English grammar and style. A fluent English speaker has edited and proofread the final manuscript, as recommended by the reviewer.

We do foremost appreciate all the time and dedication put into our investigation.
Looking forward to continue working with you,
Sincerely,



UPC
Kocfa Chung-Delgado
Sociedad Científica de Estudiantes de Medicina
SOCIEMUPC

Universidad Peruana de Ciencias Aplicadas – UPC
Email: kocfachung@gmail.com u813250@upc.edu.pe
Telf: (+51) 99-272-4343
Lima, Peru

3.2.2 Artículo Modificado

FULL TITLE:

Mortality among MDR-TB cases: Comparison with sensitive tuberculosis and associated factors

AUTHORS:

Kocfa Chung-Delgado[1]; Sonia Guillen-Bravo[1]; Alejandro Revilla-Montag[1]; Antonio Bernabe-Ortiz, MD, MPH[1]

AFFILIATIONS:

[1] Escuela de Medicina, Universidad Peruana de Ciencias Aplicadas, Lima, Peru.

Corresponding Author:

Kocfa Chung-Delgado

Universidad Peruana de Ciencias Aplicadas

Av. Alonso de Molina 1326 Dpto. 402, Surco. Lima 33. Lima, Peru.

Telephone: (+51) 99272-4343 / (+511) 635-8277

E-mail: kocfachung@gmail.com / u813250@upc.edu.pe

ABSTRACT

Background: An increase in multidrug-resistant tuberculosis (MDR-TB) cases is evident worldwide. Its management implies a complex treatment, high costs, more toxic anti-tuberculosis drugs use, longer treatment time and increased treatment failure and mortality. The aims of this study were to compare mortality between MDR- and sensitive-tuberculosis cases, and to determine risk factors associated with mortality in MDR-TB. **Methods and Results:** A retrospective cohort study was performed using data from clinical records of the National Strategy for Prevention and Control of Tuberculosis in Lima, Peru. In the first objective, MDR-TB was the main exposure variable and time to death (in days) the outcome of interest. For the second objective, different variables obtained from clinical records were assessed as potential risk factors for death among MDR-TB cases. Cox regression was used to determine hazard ratios (HR) and 95% confidence intervals. A total of 1,116 patients were analyzed: mean age 31.1±14.3 years, 58.6% were males. 64 patients (5.7%) died during treatment and the MDR-TB prevalence was 18.0%. MDR-TB increased the risk of death (HR=8.1; IC95%: 4.5–14.6) after controlling for potential confounders. Education level (p=0.02), previous TB episodes (p=0.001), diabetes history (p<0.001) and HIV infection (p=0.03) were factors associated with mortality in MDR-TB cases. **Conclusions:** MDR-TB is associated with an increased risk of death during treatment. Lower education, greater number of previous TB episodes, diabetes history and HIV infection were independently associated with this mortality. New strategies for appropriate MDR-TB management should be implemented, including drug sensitivity tests, diabetes and HIV screening, as well as guarantee for a complete adherence to therapy.

INTRODUCTION

Tuberculosis (TB) was declared a "global emergency" by the World Health Organization (WHO). Recent surveillance data shows a more frequent report of multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) cases. The WHO estimated 450,000 new cases of MDR-TB in 2012 [1]. About 6% of these drug-resistant cases were XDR-TB [2,3]. This growth trend has notably been observed in Peru: currently, 5.3% of all diagnosed tuberculosis cases are MDR-TB [4], yet studies suggest that this value might be underestimated [5-7].

The management and treatment of MDR-TB is complex; it includes an elevated treatment cost [8], the use of highly toxic anti-tuberculosis drugs with potential adverse effects [9], longer treatment time [6], and it burdens an increased treatment failure and mortality rate [10,11]. In Peru, MDR-TB mortality varies from 20% to 55% [12,13], much greater compared to the 4.5% to 17% mortality of sensitive-TB [14,15].

Some factors have been previously described as associated with high mortality in tuberculosis cases such as drug-resistant forms [11], HIV infection [16-18], diagnosis of diabetes mellitus [19], malignancy [20], daily alcohol intake and malnutrition [21]. The risk of death during treatment is directly correlated with the number of risk factors present [22]. However, further investigation is needed assessing independent factor association with MDR-TB mortality, as its prevalence and burden worldwide becomes more evident—especially in high-incidence epidemiologic scenarios. This information is vital in order to propose and implement new, appropriate strategies for the control of this "global emergency" [1]. Thus, this investigation has two objectives: (a) to compare mortality rates between sensitive and MDR tuberculosis cases, and (b) to determine risk factors associated with mortality among MDR-TB cases.

METHODS

Study design

A retrospective cohort study was conducted at hospitals and TB control health centers chosen by convenience of the National Strategy for Prevention and Control of Tuberculosis (ESNPCT) in Lima, Peru. The data collected were all the records of patients enrolled in the ESNPCT and their follow-up information during their anti-tuberculosis treatment until therapy completion or death (censorship).

Study settings and patients

We retrieved information from all patients aged 18 years and over that began and completed their anti-tuberculosis treatment for a non-XDR pulmonary TB disease in the San Juan de Miraflores - Villa María del Triunfo Health Network (SJM-VMT) in Lima, Peru between January 2000 and December 2012. If the dates of start and end of the anti-tuberculosis treatment were not available in the clinical records, patients were excluded from analysis; thus, transferred patients were excluded. In addition, treatment failures and those who abandoned therapy were also excluded due to their different sociodemographic profile.

Variable definition

The main outcome of interest for both objectives was death, defined as the deceased condition of a patient during treatment confirmed by the presence of a death notification form or by explicit indication in the clinical record. For the survival analysis, the follow-up time was 180 days. Any treatment time beyond this time frame was censored. The time until event was defined as the time elapsed, in days, from the beginning of the anti-tuberculosis treatment to the date of completion or death.

For the first objective, type of tuberculosis was dichotomized as sensitive or MDR-TB, defined as stated in the clinical record during the beginning of treatment. The

definition and diagnosis of MDR-TB is made following international standards and national guideline protocols. This information was confirmed by checking treatment schemes as well as laboratory results.

For both objectives, several other variables were included: sex (male vs. female), age (in tertiles), education level (≤6 years vs. 7-10 years vs. ≥11 years), previous TB episodes (0 vs. 1 vs. 2 or more), diabetes history (yes vs. no), anemia (positive vs. negative), HIV infection (positive vs. negative), self-reported smoking (yes vs. no), self-reported alcohol use (yes vs. no), self-reported illicit drug use (yes vs. no) and body mass index (BMI) (underweight vs. normal vs. overweight/obesity). All variables were assessed at baseline (at the beginning of the anti-tuberculosis treatment).

Procedures and data collection

Sputum smear is indicated to those in whom tuberculosis is suspected, according to Peruvian national guidelines [23]. The ESNPCT enrolls any patient with a positive result and the patient starts first-line anti-tuberculosis treatment. If any of the following risk factors are present in a patient, then a culture with drug-sensitivity test is performed in order to investigate a possible MDR case: confirmed MDR-TB contact, immunodeficiency (HIV or diabetes history), treatment relapse within six months after an active TB disease, TB cases treated multiple times, health workers, convicts, illegal drug users, contact with a person who died with TB or failed to complete treatment, hospitalization, irregular treatment schemes and adverse drug reaction to the treatment [23]. The patient's treatment scheme is then adapted accordingly, if necessary. Patients are followed during the duration of their whole treatment.

Data was collected directly from the patient's clinical onto a single database. Only the investigators performed data collection during this study.

Sample size and statistical analysis

Power and sample size software was used for sample size calculation. Assuming a confidence level of 95% and a power of 80%, a minimum total of 1090 patients were required to find a Hazard Ratio (HR) of 2.0 or over for any variable of interest. Calculations assumed a MDR-TB prevalence of 5.4% and an expected mortality of 6%.

After a double data entry process, statistical analysis was performed using STATA for Windows (STATA Corp, College Station, TX, USA). Patients with treatment abandonment, failure or transfer were excluded from analysis because of the different individual risk factors associated and the possible resulting bias. Mortality curves were obtained through the Kaplan-Meier method. Each variable was evaluated with a Log-Rank test to verify potential association with mortality. A Cox Regression was used to compare sensitive to MDR-TB mortality, a crude and two adjusted models. Hence, a Hazard Ratio (HR) with a 95% confidence interval (95%CI) was reported. Factors associated with mortality in MDR-TB cases were then re-assessed with a Cox regression. All the models were initially evaluated for the proportional hazard assumption.

Ethics

This investigation was approved by the Ethics Committee of the Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru and by the Institutional Ethics and Investigation Committee of Hospital María Auxiliadora, head of the SJM-VMT Health Network. The identity of participants was not recorded in order to guarantee anonymity.

RESULTS

Data from a total of 1,242 patients was recorded. Of them, 126 (10.1%) were excluded: 111 patients for treatment abandonment (8.9%), 10 patients for treatment failure (0.8%) and 5 patients for transfer before treatment completion (0.4%). Therefore, a total of 1,116 records were included in the analysis. The mean age was 31.1 ± 14.3 years and the proportion of males was 58.6%. Of the enrolled patients, 201 (18.0%) had MDR-TB and 64 (5.7%) died during treatment. Of the total deceased, 44 corresponded to an MDR-TB disease (72.1%).

A detailed description of the population characteristics according to the outcome of interest is shown in Table 1. Factors associated with overall TB mortality were: age, education level, previous TB episodes, diabetes history, anemia, HIV infection, self-reported smoking, self-reported alcohol use, self-reported drug use, BMI and type of tuberculosis.

MDR-TB was associated with an increased mortality in the crude model ($p < 0.001$), as detailed in Table 2. Results were consistent after adjusting for age, sex, and education level, as well as all other potential confounders (diabetes history, anemia, HIV infection, self-reported smoking, self-reported alcohol use, self-reported drug use, and BMI). The final result after adjusting for these variables was HR = 8.1 (95% CI: 4.5 – 14.6). The survival function based on type of tuberculosis can be seen in Figure 1.

Factors independently associated with mortality among MDR-TB cases only were: education level ($p = 0.049$), previous TB episodes ($p = 0.001$), diabetes history ($p < 0.001$) and HIV infection ($p = 0.03$). Detailed information is shown in Table 3.

DISCUSSION

The main conclusions that arise from this investigation are: (a) MDR-TB is associated with an increased risk of mortality even after adjusting for several potential confounders and (b) lower education level, having previous TB episodes, previous history of diabetes, and HIV infection were factors independently associated with a higher mortality among MDR-TB cases.

MDR-TB and mortality

Our results demonstrate that multidrug-resistant strains of tuberculosis increase in more than eight times the risk of death during specific anti-tuberculosis treatment. Recent studies have found similar findings where MDR-TB is associated with a higher mortality rate [24,25], with HR estimates ranging from 7.8 to 8.5. Our results have been controlled for several confounders, which makes a stronger adjusted association.

The cause behind this increased risk of death attributable to multidrug-resistant forms is multifactorial. MDR-TB is commonly seen as a co-morbidity to other conditions such as HIV infection, diabetes and chronic kidney disease, as well as particular lifestyles including alcohol abuse, smoking, drugs use, etc [21]. Furthermore, MDR-TB has been associated with elevated rates of treatment failure and relapse, which directly increases the proportions of death amongst these patients [10]. The longer exposure to anti-tuberculosis drugs might also increase the risk of death as antibiotics used for MDR-TB have proven higher toxicity profiles and greater incidence of adverse effects [10]. There is no doubt, then, that a multidisciplinary management of drug-resistant TB is needed and of great importance.

Scientific literature indicates that drug-resistant tuberculosis has increased over time. In 1990, Peru was believed to have a MDR-TB prevalence of 1%; however, recent

publications have reported a prevalence of up to 5.3% [5], and our study suggests than up to 18% might have MDR-TB. This rise in resistant tuberculosis proportion over time might be related to many factors, namely treatment abandonment and other epidemiologic circumstances such as the existence of clusters or overcrowded households—especially in resource-limited settings [26]; nonetheless, the use of new diagnostic tools for detecting drug-resistant strains may be exposing the actual context of MDR-TB, reassuring the existence of this public health problem.

Factors independently associated with MDR-TB mortality

Education level: According to our final regression model, MDR-TB patients with lower education level have a greater risk of death during their specific treatment. Of importance, education has been associated with a better adherence to treatment as it increases awareness regarding the disease [26]. Education has also been recognized as an economic status marker; in this case, lower education may be associated with lack of resources, overcrowding and unsanitary conditions.

Previous TB episodes: A greater number of previous tuberculosis episodes has been similarly associated with a high risk of death. Patients under multiple regimens of anti-tuberculosis treatment might create greater antibiotic resistance with the subsequent development of MDR- and XDR-TB cases [2]. This causal link between number of past episodes and the appearance of drug-resistant strains has been thoroughly mentioned in scientific literature [6, 12]. However, the reasons for the association reported in this study require further investigation.

Diabetes history: Diabetes history increases the risk of mortality because it reduces cellular immunity, which favors the progression of the disease [28]. This association has been demonstrated in previous studies [19, 20]. Given the high frequency of diabetes as

a co-morbidity among MDR-TB patients [27], screening for this disease should be encouraged in order to guarantee an appropriate treatment and control of both pathologies, as its awareness can reach up to 60% [28].

HIV Infection: HIV infection was also associated with a greater death proportion in MDR-TB patients. Investigations regarding this topic state that around 12% to 20% of all tuberculosis-related deaths may be attributed to an HIV co-infection [22,29], even if highly active antiretroviral therapy (HAART) has shown to reduce the overall mortality [18,30]. The results in our analysis might be the reflection of the HIV screening protocol done to all MDR-TB cases that was recently implemented by the ESNPCT.

Strengths and Limitations

This study includes over 200 cases of MDR-TB under a directly-observed treatment scheme (DOTS), which is a notable strength. This sample size allowed us to control for several variables in our proposed models. Nevertheless, this study is limited, first and foremost, by the possibility of having included non-TB related deaths such as accidents or other chronic diseases as the death certificate stating specific cause of death was not available. Although this might propose a bias in our findings, the results are greatly compatible and comparable with literature. Second, the analysis used secondary data from clinical records in hospitals chosen by convenience. However, data from the ESNPCT maintains a certain level of objectivity and uniformity as it bases its clinical records on clinical forms and notifications. Third, the starting point of evaluation, especially in the situation of MDR-TB cases, can be an issue as potentially resistant forms of tuberculosis may need longer periods of diagnosis and have previously administered treatment. Nonetheless, our results are comparable to the investigations previously mentioned—many of which consider the beginning of treatment as their

starting point of analysis. Lastly, there is a possibility of misclassification of MDR-TB into the drug-susceptible group. Nevertheless, we believe this possibility is low due to the fact that our study shows a high proportion of MDR-TB cases: greater than previous studies using cultures to detect resistant cases [11] and even greater than the official ESNPCT surveillance report [5]. Therefore, the potential impact of this bias, if any, is almost negligible. Finally, the data concerning smoking, alcohol and drug use was collected as a self-report notification. No clinical parameters, questionnaires or scales were applied to properly define the use of these substances. Due to its small amount, we believe that the risk of misclassification is non-differential, thus allowing the report of a true association.

CONCLUSIONS

MDR-TB is associated with increased risk of death during treatment when compared to sensitive TB cases. Lower education, number of previous TB episodes, diabetes history and HIV infection were independently associated with mortality in MDR tuberculosis.

New strategies and methods of management must be applied to this changing disease. MDR-TB patients should have a more consistent follow-up: patients should be thoroughly educated on their condition, making special mention in guidelines regarding the treatment adherence, possible adverse effects and infectivity of the disease; a thorough clinical history should be made to investigate possible cases of past TB episodes; diabetes and HIV screening and control should be incorporated into the follow-up evaluation. As such, the already-existing DOTS program should be modified and renewed to fit the requirements of MDR-TB patients and not vice-versa, with particular interest in countries where the MDR- and XDR-TB incidence rates are in ascent.

ACKNOWLEDGEMENTS

All authors contributed to the drafting, revision and approval of the final manuscript.

The following greatly contributed to the elaboration of the investigation: Dr. Graciela Risco de Domínguez, Dr. Denisse Champin, Dr. Percy Mayta and Dr. Alejandro Piscoya.

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Table 1: Population characteristics according to the outcome of interest

	Alive (n = 1055)	Deceased (n = 61)	p-value*
Sex, n (%)			
Female	441 (95.5%)	21 (4.5%)	0.23
Male	614 (93.9%)	40 (6.1%)	
Age [tertiles], n (%)			
Low tertile	407 (98.3%)	7 (1.7%)	<0.001
Middle tertile	316 (94.3%)	19 (5.7%)	
High tertile	332 (90.5%)	35 (9.5%)	
Education level, n (%)			
≥11 years	558 (97.4%)	15 (2.6%)	<0.001
7 – 10 years	326 (94.0%)	21 (6.0%)	
≤6 years	171 (87.2%)	25 (12.8%)	
Previous TB episodes, n (%)			
No previous episodes	853 (98.5%)	13 (1.5%)	<0.001
1 episode	170 (89.0%)	21 (11.0%)	
2+ episodes	32 (54.2%)	27 (45.8%)	
Diabetes history, n (%)			
No	1033 (95.6%)	48 (4.4%)	<0.001
Yes	22 (62.9%)	13 (37.1%)	
Anemia, n (%)			
No	924 (95.1%)	48 (4.9%)	0.04
Yes	131 (91.0%)	13 (9.0%)	
HIV infection, n (%)			
No	1044 (95.0%)	55 (5.0%)	<0.001
Yes	11 (64.7%)	6 (35.3%)	
Smoking, n (%)			
No	908 (95.1%)	47 (4.9%)	0.05
Yes	147 (91.3%)	14 (8.7%)	
Alcohol use, n (%)			
No	861 (95.0%)	45 (5.0%)	0.10
Yes	193 (92.3%)	16 (7.7%)	
Drug use, n (%)			
No	984 (95.3%)	49 (4.7%)	<0.001
Yes	70 (85.4%)	12 (14.6%)	
Body mass index, n (%)			
Normal	729 (95.9%)	31 (4.1%)	0.001
Overweight/obese	126 (94.7%)	7 (5.3%)	
Underweight	199 (89.6%)	23 (10.4%)	
Type of tuberculosis, n (%)			
Sensitive	898 (98.1%)	17 (1.9%)	<0.001
MDR	157 (78.1%)	44 (21.9%)	

* P-values were calculated using Log-rank test

Table 2: Cox regression model for mortality in tuberculosis patients

Type of Tuberculosis	Crude model HR (95%CI)	Adjusted model 1* HR (95%CI)	Adjusted model 2** HR (95%CI)
Sensitive	1 (Reference)	1 (Reference)	1 (Reference)
MDR-TB	12.8 (7.3 – 22.5)	10.6 (6.0 – 18.7)	8.1 (4.5 – 14.6)

** Adjusted for age, sex and education level*

*** Adjusted for age, sex, education level, anemia, diabetes history, HIV infection, smoking, alcohol use, drug use, and BMI.*

Table 3: Factors independently associated with mortality among MDR-TB patients

	Bivariable model HR (95%CI)	**Multivariable model* HR (95%CI)**
Sex		
Female	1 (Reference)	
Male	1.10 (0.60 – 2.04)	
Age [tertiles]		
Low tertile	1 (Reference)	
Middle tertile	2.26 (0.81 – 6.27)	
High tertile	**4.07 (1.56 – 10.64)**	
Education level		
11+ years	1 (Reference)	1 (Reference)
7 – 10 years	1.41 (0.62 – 3.19)	1.85 (0.77 – 4.49)
6 or less years	**3.53 (1.73 – 7.17)**	**2.87 (1.34 – 6.12)**
Previous TB episodes		
No previous episodes	1 (Reference)	1 (Reference)
1 episode	2.81 (0.92 – 8.61)	2.97 (0.95 – 9.25)
2+ episodes	**10.35 (3.62 – 29.62)**	**6.75 (2.26 – 20.15)**
Diabetes history		
No	1 (Reference)	1 (Reference)
Yes	**4.59 (2.40 – 8.79)**	**5.24 (2.54 – 10.81)**
Anemia		
No	1 (Reference)	
Yes	0.46 (0.14 – 1.28)	
HIV infection		
No	1 (Reference)	1 (Reference)
Yes	2.37 (0.85 – 6.62)	**3.38 (1.12 – 10.24)**
Smoking		
No	1 (Reference)	
Yes	0.39 (0.12 – 1.27)	
Alcohol use		
No	1 (Reference)	
Yes	0.52 (0.22 – 1.24)	
Body mass index		
Normal	1 (Reference)	
Overweight/obese	1.29 (0.52 – 3.19)	
Underweight	**2.17 (1.15 – 4.12)**	

Significant estimates ($p<0.05$) are in bold

* This model only includes variables independently associated with mortality.

FIGURE LEGENDS

Figure 1: MDR-TB survival curves using Kaplan-Meier estimates.