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

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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

3.3 SEGUNDA REVISIÓN

3.3.1 Carta de Respuesta

Nov 9th, 2014

Dear Academic Editor
Dr. Joan A Caylà, MD, PhD
PLOS ONE

Reference: Manuscript ID PONE-D-14-34677R1:
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 new 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. **They authors make a claim about absolute mortality between DS and DR TB which they do not have the data to support. If they wish to only speak to mortality during first-line vs. second-line treatment, then they should make this clear (even if they can find other publications that have been imprecise about the distinction), and they should refer to their results as representing risk for death during treatment, and for patients clinically diagnosed with DS vs. MDR TB (without complete culture confirmation). They should not claim in their abstract or test that they can compare actual DS vs. MDR TB mortality rates.**

   Changes in the manuscript have been performed to address this point:
   - The first one involved the comparison of mortality rates between MDR-TB cases and drug-susceptible TB cases (TB cases receiving first-line drugs as the program did not perform cultures and drug susceptibility test to all participants). In this case, MDR-TB was corroborated with culture and drug susceptibility in all cases; therefore, they were correctly classified as MDR-TB cases.
   - As MDR-TB cases were appropriately evaluated and diagnosed by the Program (cultures and drug susceptibility tests), we presented the results of the second

analysis as part of this manuscript (potential factors associated with death). Changes have been performed accordingly to this.

2. **Exclusion of patients who survived to default, transfer, or failure continues to be a concern, and is even less valid if these patients' demographics were different as the authors now state. At a minimum, if there is a reason that these patients' demographics excluded them from the population of interest, then all patients with such a demographic profile should be excluded prior to the analysis, regardless of their outcomes. But different durations of DS and MDR treatment also means that patients who were excluded because they failed, transferred, or defaulted in the latter stages of MDR treatment would have been counted as survivors had they been on a 6–month regimen for DS TB. At a minimum, patients who transferred or abandoned treatment should be included and counted as alive up until the time of censoring, but even that approach would have limitations that should be clearly accounted for. And some analysis should be done of whether these failures and losses to follow up, with their different baseline characteristics from the rest of the population, were unequally distributed between the DS and MDR groups, or between the different risk groups (e.g. diabetics) in the within-MDR analysis, because if so, that would be a major limitation of this analysis.**

We have decided to include in the analysis participants who were transferred and abandoned treatment during follow-up. We decided to exclude failures (n = 10) from the analysis as they pose a higher risk of misclassification and might affect estimates (because a great proportion of failures are drug resistant forms of tuberculosis). Therefore, as suggested by the reviewer, patients who were transferred or abandoned therapy were censored accordingly. We have detailed this inclusion in several parts of the manuscript. As only 10 patients (<1% of the total sample) were excluded from analysis, we do not believe it is important to compare them according to subgroups.

3. **MDR TB is widely underdiagnosed, including in Peru, and many patients get one or more courses of first-line therapy for MDR TB before they get DST. Using relapse or multiple prior treatments as a basis for performing DST shows that the "MDR" population was enriched for such patients. Comparing to national prevalence data is insufficient to exclude this, especially given higher MDR prevalence in Lima and given heterogeneity in prevalence within Lima. The authors need to give this possibility more serious consideration, consider how it would influence their results, and make the limitations of their Ds vs MDR classification more clear if they cannot account for it.**

We have included a detailed insight of this observation and changed the manuscript accordingly.

4. **Data available from authors by request does not meet PLOS's data policy.**

All data is available upon request according to PLOS Data Policy:

"*Data made available to all interested researchers upon request.* *The Data Availability Statement must specify "Data available on request" and identify the group to which requests should be submitted (e.g., a named data access committee or named ethics committee). The reasons for restrictions on public data deposition must also be specified.*"

The database is part of the information of the Peruvian National Tuberculosis Control Program (ESNPCT) and is available through approval by the Ethics Committee of the Universidad Peruana de Ciencias Aplicadas, Lima Peru.

6. **'Drug-sensitive' or 'drug-susceptible' rather than merely 'susceptible' TB is more standard and clearer terminology. "Factors independently associated with mortality among MDR-TB cases only" – I think you mean "Factors associated with mortality within the group of MDR-TB cases", which would be less ambiguous.**

The corresponding corrections have been made in the manuscript.

We appreciate all the time and dedication put into our investigation for future publication.

Sincerely,

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3.3.2 Artículo Modificado

FULL TITLE:

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

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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 multidrug-resistant and drug-susceptible cases of tuberculosis, and to determine risk factors associated with mortality among MDR-TB cases. **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, compared to drug-susceptible cases, was the main exposure variable and time to death, in days and censored at 180 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 analysis was used to determine hazard ratios (HR) and 95% confidence intervals (95%CI). A total of 1,232 patients were analyzed: mean age 30.9 ±14.0 years, 60.0% were males. 62 patients (5.0%) died during treatment, whereas the MDR-TB prevalence was 19.2%. MDR-TB increased the risk of death (HR=7.5; IC95%: 4.1–13.4) when compared to drug-susceptible cases after controlling for potential confounders. Education level (p=0.01), previous TB episodes (p<0.001), diabetes history (p<0.001) and HIV infection (p=0.04) were factors associated with mortality among 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 mortality among MDR-TB cases. New strategies for appropriate MDR-TB detection and 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 aims to: (a) compare mortality rates between multidrug-resistant and drug-susceptible cases of tuberculosis, and (b) determine independent 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 above 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 date of anti-tuberculosis treatment beginning was not available in the clinical records, patients were excluded from analysis. In addition, treatment failures were also excluded due to the risk of misclassification in the exposure of interest.

Variable definition

The main outcome of interest for both objectives was time to death. Death during follow-up was 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 censored at 180 days. Therefore, 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. If the participant was transferred or abandoned therapy, then time to event was censored accordingly.

For the first objective, type of tuberculosis was dichotomized as MDR-TB or drug-susceptible TB according to information of clinical records, based especially upon clinical assessment and the use of first- or second-line drugs, at the beginning of treatment. Thus, in the case of MDR-TB forms, diagnosis and classification was made following international standards and national guideline protocols (culture and drug susceptibility tests). This information was confirmed by checking treatment schemes as well as laboratory results. The remaining patients, those without a culture or drug-susceptibility test, were categorized as drug-susceptible TB cases.

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 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. Culture and drug-susceptibility tests are performed in order to investigate a possible MDR-TB case if any of the following risk factors are present in a patient: 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 without these risk factors are given first-line drugs. They are considered drug-susceptible TB cases for this analysis. Patients are followed during the duration of their whole treatment or censorship, accordingly.

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 (PASS) 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 who failed treatment during follow-up were excluded from analysis. Mortality curves were obtained through the Kaplan-Meier method. Each variable was evaluated with a Log-Rank test to verify potential association with mortality. Cox Regression models (crude and adjusted) were used to compare MDR-TB vs. drug-susceptible TB mortality, reporting Hazard Ratio (HR) with a 95% confidence interval (95%CI). Factors associated with mortality among MDR-TB cases were also assessed using Cox regression methods, assessing proportional hazard assumptions.

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, 10 (0.8%) were excluded due to treatment failure. Therefore, a total of 1,232 records were included in the analysis. The mean age was 30.9 ± 14.0 years, and the proportion of males was 60.0%. Of the enrolled patients, 236 (19.2%) were reported as MDR-TB cases and 62 (5.0%) died during time of follow-up. Of the total deceased, 44 (72.1%) corresponded to MDR-TB cases.

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, HIV infection, 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 = 7.5 (95%CI: 4.1 – 13.4). The survival function based on type of tuberculosis can be seen in Figure 1.

Factors independently associated with mortality within the group of MDR-TB cases were: education level ($p = 0.02$), previous TB episodes ($p < 0.001$), diabetes history ($p < 0.001$) and HIV infection ($p = 0.04$). 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 when compared to drug-susceptible cases 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 seven times the risk of death when compared to drug-susceptible TB cases during 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 approximately 20% 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 mortality among MDR-TB cases

Education level: According to our results, MDR-TB patients with lower education level have a greater risk of death during 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 TB episodes has been similarly associated with a higher 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. In addition, sample size allowed us to control for several variables in our proposed models. Nevertheless, this study has several limitations. First, non-TB related deaths such as accidents or other chronic diseases could have been included 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, it was not possible to obtain drug-susceptibility test data for non-MDR TB participants. Drug-susceptibility and cultures are performed in those with high risk and suspect of MDR-TB, yet are not done in patients without such risk factors. 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. Therefore, our results might be overestimated. Nonetheless, our findings are comparable to the investigations previously mentioned—many of which consider the beginning of treatment as their starting point of analysis. In addition, data from the ESNPCT maintains a certain level of objectivity and uniformity as it bases its clinical

records on clinical forms and notifications. Fourth, there is a possibility of misclassification of MDR-TB into the drug-susceptible group as MDR-TB is widely under-diagnosed. Nevertheless, our findings show a high proportion of MDR-TB cases (about 20%), greater than previous studies using cultures to detect resistant cases [11] and even greater than the official ESNPCT surveillance report [5]. 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

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

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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FIGURE LEGENDS

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

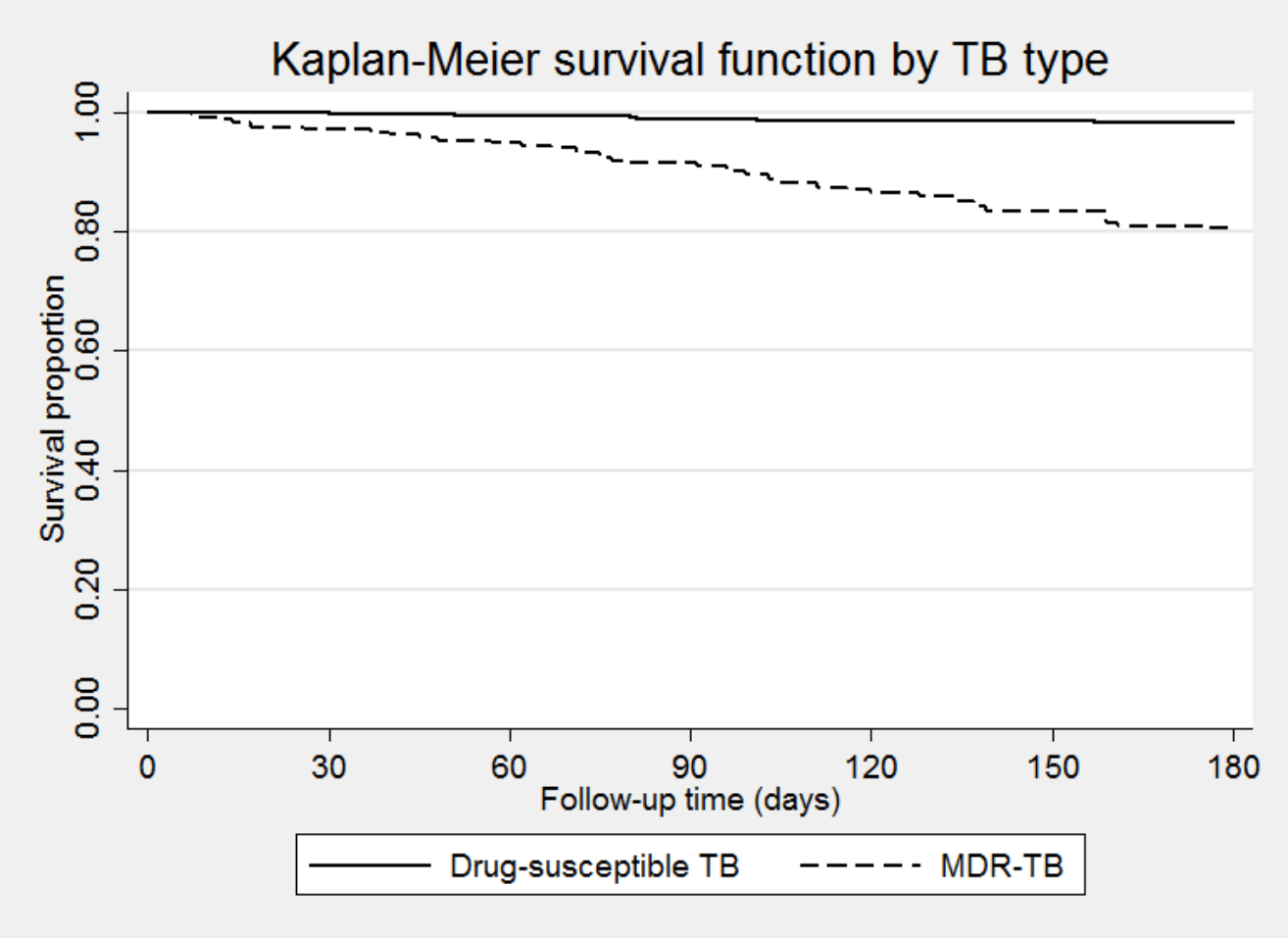

Table 1: Population characteristics according to the outcome of interest

	Alive (n = 1,171)	Deceased (n = 61)	p-value*
Sex, n (%)			
Female	472 (95.7%)	21 (4.3%)	0.29
Male	699 (94.6%)	40 (5.4%)	
Age [tertiles], n (%)			
Low tertile	451 (98.5%)	7 (1.5%)	<0.001
Middle tertile	351 (94.9%)	19 (5.1%)	
High tertile	369 (91.3%)	35 (8.7%)	
Education level, n (%)			
≥11 years	607 (97.6%)	15 (2.4%)	<0.001
7 – 10 years	364 (94.6%)	21 (5.4%)	
≤6 years	200 (88.9%)	25 (11.1%)	
Previous TB episodes, n (%)			
No previous episodes	929 (98.6%)	13 (1.4%)	<0.001
1 episode	202 (90.6%)	21 (9.4%)	
2+ episodes	40 (59.7%)	27 (40.3%)	
Diabetes history, n (%)			
No	1,143 (96.0%)	48 (4.0%)	<0.001
Yes	28 (68.3%)	13 (31.7%)	
Anemia, n (%)			
No	1,018 (95.5%)	48 (4.5%)	0.05
Yes	153 (92.2%)	13 (7.8%)	
HIV infection, n (%)			
No	1,157 (95.5%)	55 (4.5%)	<0.001
Yes	14 (70.0%)	6 (30.0%)	
Smoking, n (%)			
No	1,008 (95.6%)	47 (4.4%)	0.05
Yes	163 (92.1%)	14 (7.9%)	
Alcohol use, n (%)			
No	946 (95.5%)	45 (4.5%)	0.13
Yes	224 (93.3%)	16 (6.7%)	
Drug use, n (%)			
No	1,074 (95.6%)	49 (4.4%)	<0.001
Yes	96 (88.9%)	12 (11.1%)	
Body mass index, n (%)			
Normal	798 (96.3%)	31 (3.7%)	0.002
Overweight/obese	139 (95.2%)	7 (4.8%)	
Underweight	233 (91.0%)	23 (9.0%)	
Type of tuberculosis, n (%)			
Drug-susceptible	979 (98.3%)	17 (1.7%)	<0.001
MDR	192 (81.4%)	44 (18.6%)	

* 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)
Drug-susceptible TB	1 (Reference)	1 (Reference)	1 (Reference)
MDR-TB	11.7 (6.7 – 20.5)	9.5 (5.4 – 16.8)	7.5 (4.1 – 13.4)

** 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	1.05 (0.57 – 1.94)	
Age [tertiles]		
Low tertile	1 (Reference)	
Middle tertile	2.23 (0.80 – 6.18)	
High tertile	**3.78 (1.45 – 9.88)**	
Education level		
11+ years	1 (Reference)	1 (Reference)
7 – 10 years	1.40 (0.62 – 3.18)	2.13 (0.89 – 5.07)
6 or less years	**3.40 (1.67 – 6.92)**	**3.06 (1.43 – 6.55)**
Previous TB episodes		
No previous episodes	1 (Reference)	1 (Reference)
1 episode	2.77 (0.90 – 8.51)	**3.13 (1.01 – 9.73)**
2+ episodes	**10.23 (3.58 – 29.27)**	**7.79 (2.59 – 23.47)**
Diabetes history		
No	1 (Reference)	1 (Reference)
Yes	**4.10 (2.15 – 7.85)**	**5.42 (2.66 – 11.04)**
Anemia		
No	1 (Reference)	
Yes	0.44 (0.16 – 1.22)	
HIV infection		
No	1 (Reference)	1 (Reference)
Yes	2.33 (0.83 – 6.51)	**3.18 (1.05 – 9.69)**
Smoking		
No	1 (Reference)	
Yes	0.40 (0.12 – 1.29)	
Alcohol use		
No	1 (Reference)	
Yes	0.51 (0.21 – 1.20)	
Body mass index		
Normal	1 (Reference)	
Overweight/obese	1.14 (0.46 – 2.84)	
Underweight	1.84 (0.97 – 3.50)	

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

* This model only includes variables independently associated with mortality.