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Weight variation over time and its relevance among multidrug-resistant tuberculosis patients

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SUMMARY

Objectives: We aimed to assess the variation in patient body weight over time according to the treatment outcome among multidrug-resistant tuberculosis (MDR-TB) cases.
Methods: This was a retrospective cohort study. The data of patients commencing MDR-TB therapy were analyzed. Data were collected from different public TB treatment facilities located in peri-urban areas to the south of Lima, Peru. The outcome was patient body weight (kilograms) from treatment commencement, measured monthly. A random effects model was fitted using robust standard errors to calculate 95% confidence intervals.
Results: Of a total of 1242 TB cases, 243 (19.6%) were MDR-TB. Only 201 cases were included in the analysis; 127 (63.2%) were males and the mean patient age was 33.6 (standard deviation 16.2) years. Weight changes over time among the patients who were cured differed from changes in those who died during therapy ($p < 0.001$). Weight curve divergence was important at the end of the third, fourth, and fifth treatment months: on average, the weight difference was 2.18 kg ($p < 0.001$), 3.27 kg ($p = 0.007$), and 3.58 kg ($p = 0.03$), respectively, when cured patients were compared to those who died.
Conclusions: Our results show that weight variation during treatment can be a useful surrogate for the treatment outcome, specifically death during therapy. MDR-TB patients with weight loss should be followed more closely, as they are at greater risk of death.

1. Introduction

According to the World Health Organization (WHO), multidrug-resistant tuberculosis (MDR-TB) is present in 3.7% of new TB cases and 20% of previously treated TB cases, with an estimated total of 630 000 cases worldwide.[1,2]

The treatment of MDR-TB cases is complex because it requires the use of second-line TB drugs,[3] which are associated with a greater probability of adverse effects,[4,5] longer treatment duration, as well as increasing costs.[6,7] Mortality is also increased among MDR-TB patients. Two recent systematic reviews reported that around 11% of patients on MDR-TB treatment died at the end of follow-up, whereas only 62% had a successful outcome.[8,9]

Body weight variation has been identified as a potential predictor of TB treatment outcome, especially in drug-sensitive TB.[10–13] A previous study reported that patients under DOTS (directly observed treatment, short course) had gained 3.2 kg on average at the end of treatment.[11] A further two studies found a cutoff of 5% weight gain to predict the TB treatment outcome.[12,13] A study reporting a longitudinal analysis established that differences in weight could be found from the first month of therapy.[14] In several countries with standardized schemes of treatment, patients are weighed routinely during follow-up to assess the treatment response. Thus, body weight might be a helpful test to predict the TB treatment outcome; however, to our knowledge, no information regarding this potential association is available for MDR-TB cases.

The objective of this study was to evaluate variation in patient body weight over time according to the treatment outcome among MDR-TB cases. We hypothesized that the weight variation that

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occurs during follow-up among those who die during treatment differs from the variation that occurs among those who are cured at the end of treatment.

2. Methods

2.1. Study design, setting, and participants

A retrospective cohort study was carried out using the data of patients commencing therapy for MDR-TB from January 2000 to December 2012. Data were collected from different public TB treatment facilities located in peri-urban areas to the south of Lima (DISA II – Lima Sur). The medical records were obtained from the National Health Strategy for Prevention and Control of Tuberculosis (ESN-PCT) and were reviewed for sociodemographic data, TB treatment history, treatment scheme, weight measures, and outcomes.

Patients included in the analysis were at least 18 years old and had been diagnosed with pulmonary MDR-TB, confirmed by a positive culture and appropriate drug susceptibility testing.[15] Those abandoning therapy or failing during follow-up were excluded from the statistical analysis. We decided to exclude data for treatment failure patients because of the small number of cases ($n = 7$) and hence a lack of appropriate power to detect differences. See Figure 1 for detailed information regarding participation.

2.2. Outcomes and variables of interest

The main outcome of the study was patient body weight, recorded in kilograms (kg), from treatment commencement, and measured monthly. The ESN-PCT staff usually assess patients at the end of every month of treatment and the data available were used for this analysis. The main exposure was overall mortality, defined as those patients who died during the first 6 months of MDR-TB treatment. We specifically used data from the first months of therapy because deaths could be directly attributable to TB.[16]

Other variables of interest included in the analysis were: age (categorized in tertiles), sex (male or female), education level (primary school, incomplete secondary school, or complete secondary school or higher), number of previous TB episodes (none, one, or two or more), baseline body mass index (BMI; categorized as underweight (<18.5 kg/m^2), normal (≥ 18.5 and <25 kg/m^2), or overweight/obese (≥ 25 kg/m^2) based on the World Health Organization definition[17]), HIV infection status (positive or negative), sputum result at baseline (positive or negative), treatment scheme (individualized or standardized), and enrollment year (before 2005, from 2005 to 2009, or from 2010 onwards).

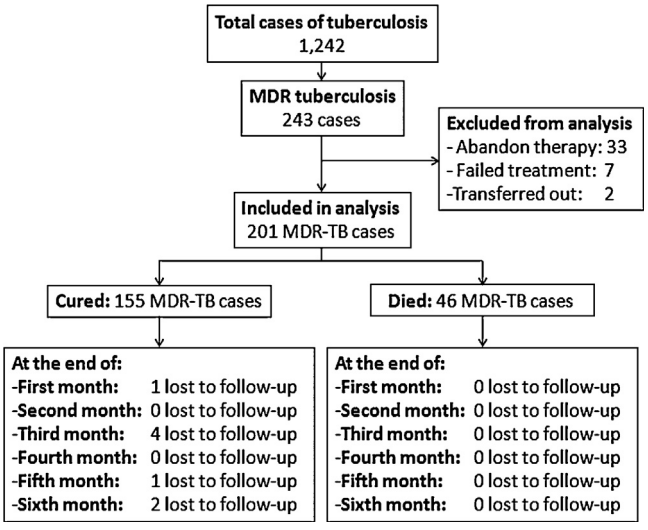

Figure 1. Flowchart of enrollment and inclusion of patients in the study.

2.3. Procedures

All MDR-TB patients were treated by the ESN-PCT using individualized or standardized treatment schemes. The ESN-PCT uses monthly food packages as an incentive for adherence, and these are given to all patients. Before receiving treatment, MDR-TB cases are assessed by an expert committee based on clinical records, previous TB treatment history, sputum cultures, TB drug susceptibility testing, HIV infection status, and pulmonary X-rays. The usual management of MDR-TB cases includes programmatic monitoring with monthly sputum cultures and weight measures. Weight data are usually recorded using clinic scales with established programmatic training for their use.[15] The accuracy of the scales used was not systematically confirmed, but repeat measurements made for each patient were done using the same scales, and weights were generally recorded to the nearest 0.1 kg.

2.4. Data management and statistical analysis

Data were entered into a database using Microsoft Excel by double data entry and were then transferred to Stata 11.0 for Windows (StataCorp, College Station, TX, USA) for the statistical analysis. Initially, a brief description of the demographic and clinical characteristics according to the outcome was tabulated and compared using the Chi-square test or Fisher's exact test, as appropriate. Next, the weight average was calculated for each outcome group according to our exposure of interest and the month of follow-up. Although total follow-up data were available, information for the first 6 months was used in the analysis because of the small number of deaths reported after that time. Finally, a longitudinal analysis was carried out to assess weight variation over time. A random effects regression model was fitted to assess average body weight changes of the patients according to outcome results.[18] Random effects models are needed when the observations (i.e. patient weights in this analysis) are not obtained by simple random sampling, but come from a cluster or multilevel sampling design (i.e., a patient being followed-up during treatment). Thus, this type of design induces additional sources of variation that need to be taken into account by the model. The crude model was specified as follows: $Y_{ij} = \beta_0 + \beta_1.\text{Outcome} + \beta_2.T_{ij} + \beta_3.T_{ij}.\text{Outcome}$, where Y_{ij} is the mean weight (kg) of patient '*i*' at time '*j*', β_0 is the intercept, i.e. weight in kilograms among those cured at baseline, β_1 is the difference in weight at baseline in patients who died compared to those who were cured, β_2 quantifies the change in weight between baseline and one selected month for patients who were cured, and the sum of β_2 and β_3 (interaction term) represents the change in weight between baseline and one selected month for participants who died.[18] In this model, the time variable was included as a categorical variable, because weight over time did not show linearity in patients who died during follow-up.

Additionally, the model was controlled for potential confounders including age, sex, education level, number of previous TB episodes, baseline BMI, HIV infection status, treatment scheme, and enrollment year. The Wald test was used to report *p*-values, especially for the interaction term, whilst robust standard errors, in the case of misspecification of the variance correlation structure, were used to calculate 95% confidence intervals for coefficients in the model.

2.5. Ethics

Institutional review board approval for this project was granted by the Universidad Peruana de Ciencias Aplicadas (UPC), Lima,

Peru. Informed consent was not necessary because of the use of routine and programmatic data from the National Health Strategy for the Control and Prevention of Tuberculosis.

3. Results

3.1. Population characteristics

From a total of 1242 cases of TB recorded by the ESN-PCT during the study period, 243 (19.6%) were MDR-TB. Of these, 42 were excluded: 33 (13.6%) defaulted, seven (2.9%) failed, and two (0.8%) were transferred out. Thus, only 201 MDR-TB cases were included in the analysis; 127 (63.2%) were males with a mean age of 33.6 (standard deviation 16.2) years. Detailed characteristics of the study population according to the outcome are shown in Table 1.

3.2. MDR-TB deaths and weight during follow-up

A total of 46 (22.9%) deaths were reported during an average of 12.2 (interquartile range 5.8–16.5) months of follow-up. Of these deaths, 43 (93.5%) occurred during the first 6 months of follow-up, whereas three deaths occurred in the subsequent months. Table 2 shows a detailed description of weight changes during treatment follow-up as uncorrelated data. Of note, weight among the patients who were cured increased consistently during the 6 months of follow-up, whereas in the group who died, weight also increased but potentially as a selection of patients with better health status (i.e., those with a greater weight at the start of treatment had a higher probability of surviving after 6 months of treatment).

Table 1
Characteristics of the study population at the beginning of MDR-TB treatment according to outcome[a]

	Cured (n = 155)	Died (n = 46)	p-Value
Sex (%)			
Female	58 (78.4%)	16 (21.6%)	0.75
Male	97 (76.4%)	30 (23.6%)	
Age (%)			
Lower tertile	59 (83.1%)	12 (16.9%)	0.02
Middle tertile	53 (82.8%)	11 (17.2%)	
Higher tertile	43 (65.2%)	23 (34.8%)	
Education level (%)			
Primary school	33 (61.1%)	21 (38.9%)	0.004
Incomplete secondary school	49 (81.7%)	11 (18.3%)	
Complete secondary school or higher	73 (83.9%)	14 (16.1%)	
Number of previous TB episodes (%)			
None	61 (93.9%)	4 (6.1%)	<0.001
One	66 (82.5%)	14 (17.5%)	
Two or more	28 (50.0%)	28 (50.0%)	
Baseline BMI (%)[b]			
Normal (<25 kg/m^2)	101 (82.8%)	21 (17.2%)	0.06
Overweight/obese (≥25 kg/m^2)	18 (69.2%)	8 (30.8%)	
Underweight (<18.5 kg/m^2)	36 (67.9%)	17 (32.1%)	
HIV infection (%)[b]			
Negative	149 (78.0%)	42 (22.0%)	0.24
Positive	6 (60.0%)	4 (40.0%)	
Treatment scheme (%)[b]			
Individualized	129 (77.3%)	38 (22.7%)	0.99
Standardized	26 (76.5%)	8 (23.5%)	
Sputum result (%)[b]			
Negative	42 (84.0%)	8 (16.0%)	0.24
Positive	113 (74.8%)	38 (25.2%)	
Enrollment year (%)			
Before 2005	19 (70.4%)	8 (29.6%)	0.63
2005–2009	60 (76.9%)	18 (23.1%)	
From 2010 onwards	76 (79.2%)	20 (20.8%)	

MDR, multidrug-resistant; TB, tuberculosis; BMI, body mass index.
[a] Proportion calculations are presented in rows.
[b] p-Values were calculated using Fisher's exact test.

Table 2
Weight (kg) variation over time during follow-up according to outcome status

	Treatment outcome			
	Cured		Died	
	n	Mean (SD)	n	Mean (SD)
Baseline	155	56.6 (10.7)	46	54.8 (9.4)
First month	153	57.8 (11.2)	44	54.3 (10.3)
Second month	154	58.2 (11.1)	33	57.1 (9.7)
Third month	150	59.2 (11.2)	25	57.2 (9.6)
Fourth month	148	59.9 (11.3)	11	62.5 (8.7)
Fifth month	149	59.9 (11.7)	8	62.6 (8.6)
Sixth month	147	60.5 (11.9)	3	69.7 (11.0)

SD, standard deviation.

3.3. Weight variation during treatment and its association with death among MDR-TB cases

Results of crude and adjusted random-effects model are shown in Table 3. Of interest, the adjusted coefficient for death variable was not significant ($p = 0.47$), indicating that the difference in weight at baseline (about 0.8 kg) among cured patients and those who died was not statistically different. The interaction terms together were statistically significant (Wald test for interaction, $p < 0.001$), indicating that changes in weight over time among cured patients differed from those of patients who died during therapy (Figure 2). According to the graph, weight curve divergence was more important at the end of the third, fourth, and fifth months of treatment: on average, the weight difference was around 2.18 kg ($p < 0.001$), 3.27 kg ($p = 0.007$), and 3.58 kg ($p = 0.03$), respectively, when cured patients were compared to those who died. In addition, using this model, between-subject differences (intra-class correlation) explained 96.9% of the total variance of the model.

4. Discussion

This study demonstrates the relevance of weight variation during the first 6 months of treatment to predict death among MDR-TB patients, after controlling for several potential confounders including age, sex, education level, number of previous TB episodes, baseline BMI, HIV status, and treatment scheme. The weight progression curve among cured MDR-TB patients was found to differ from that of patients who died during follow-up.

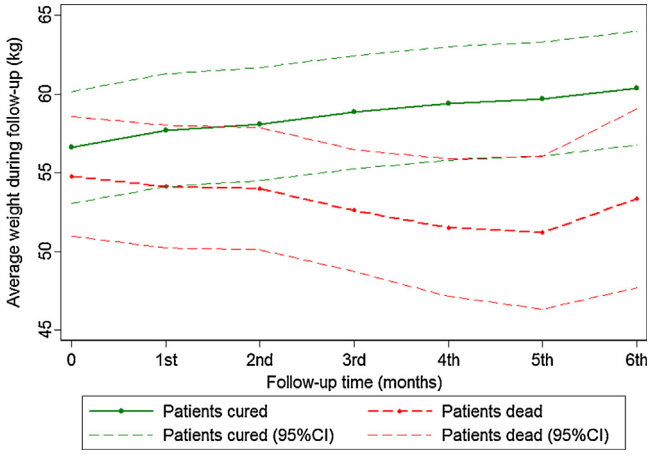

Figure 2. Weight change during the first 6 months of MDR-TB therapy according to the treatment outcome. Predicted lines were adjusted for age, gender, education level, number of previous TB episodes, baseline body mass index, HIV status, treatment scheme, and enrollment year.

Table 3
Crude and adjusted random-effects models assessing weight change over time according to outcome

	Crude model			Adjusted model[a]		
	β	95% CI	*p*-Value	β	95% CI	*p*-Value
Intercept	56.60	54.91; 58.29	<0.001	54.91	50.42; 59.40	<0.001
Death	−1.83	−5.02; 1.36	0.26	−0.78	−2.92; 1.36	0.47
Time (1st month)	1.10	0.68; 1.53	<0.001	1.10	0.67; 1.53	<0.001
Time (2nd month)	1.49	0.99; 2.00	<0.001	1.49	0.98; 2.00	<0.001
Time (3rd month)	2.25	1.70; 2.80	<0.001	2.25	1.70; 2.80	<0.001
Time (4th month)	2.80	2.22; 3.39	<0.001	2.80	2.21; 3.38	<0.001
Time (5th month)	3.09	2.43; 3.75	<0.001	3.09	2.43; 3.75	<0.001
Time (6th month)	3.78	3.08; 4.48	<0.001	3.78	3.07; 4.48	<0.001
Death * time (1st month)	−1.75	−2.38; −1.11	<0.001	−1.75	−2.39; −1.11	<0.001
Death * time (2nd month)	−2.24	−3.07; −1.40	<0.001	−2.28	−3.11; −1.44	<0.001
Death * time (3rd month)	−4.37	−5.43; −3.31	<0.001	−4.42	−5.48; −3.35	<0.001
Death * time (4th month)	−5.95	−8.43; −3.48	<0.001	−6.06	−8.53; −3.58	<0.001
Death * time (5th month)	−6.55	−9.88; −3.23	<0.001	−6.66	−9.99; −3.33	<0.001
Death * time (6th month)	−5.04	−9.56; −0.53	0.03	−5.19	−9.68; −0.70	0.02

CI, confidence interval.
[a] Adjusted by age, gender, education level, number of previous TB episodes, baseline body mass index, HIV status, treatment scheme, and enrollment year.

For instance, and using information from the adjusted model shown in Table 3, patients who were cured had gained on average 1.10 kg at the end of the first month compared to the baseline, whereas at the end of the third month, weight had increased by around 2.25 kg. In contrast, patients who died had lost about 1.75 kg at the end of the first month compared to the baseline, and continued losing weight, 4.42 kg on average at the end of the third month. Of note, patients who died did not gain weight during the first 6 months of therapy.

This finding may be relevant in public health, especially in resource-constrained settings: weight can be used as a surrogate of the TB outcome and how patients progress during treatment. Moreover, changes in weight could be observable from the first month of therapy. Some previous studies have reported that weight can be clinically relevant in the prediction of the treatment outcome. Two of these studies found a cutoff of 5% weight gain to predict the TB treatment outcome.[10,12,13] Other studies have reported different results. For example, Kennedy et al. found that weight gain was an unreliable indicator of the treatment response;[19] nevertheless, they used only information from baseline and 12 months of follow-up for their analysis. Schwenk et al., in a study involving only 30 participants, found that patients gained 10% in weight from baseline to month 6 of follow-up, particularly due to fat mass and not protein mass.[20] Additional reports have utilized survival analysis techniques to assess the effect of weight or BMI at baseline on the TB treatment outcome.[21,22] Our study expands on previous findings to demonstrate that the change in weight during treatment can also be a helpful surrogate for the treatment response among MDR-TB cases using an appropriate longitudinal analysis. Our results suggest that appropriate strategies to avoid patient deaths must be implemented as early as the end of the first month. Of note, weight loss might be indicative of a greater risk of death: 50% of those who died during treatment follow-up had lost 1 kg at the end of the first month (data not shown).

Programmatic assessment of MDR-TB patients involves monthly weight, sputum, and culture evaluations during treatment. The quality of sputum results is low and can be insensitive, especially for relapse and failure.[23] Also, in resource-poor settings, the time associated with obtaining culture results might be several weeks because of the use of the Lowenstein–Jensen technique.[15,24,25] Recently, rapid-culture techniques, such as the microscopic observation drug susceptibility (MODS) assay, have become widespread;[26] however, their use is limited to diagnosis and drug susceptibility testing rather than patient follow-up. As a consequence, the assessment of weight might be an easy, rapid, and inexpensive method to predict death among patients receiving specific therapy.

TB is the archetypal wasting disease that, 2400 years ago, Hippocrates termed phthisis, derived from the ancient Greek word for 'a wasting away'.[27] Present-day patients and clinicians also associate weight changes with TB and the treatment response.[19,28] Surprisingly, however, this easily assessed clinical measure has received relatively little rigorous evaluation with regard to its value in predicting treatment outcomes.

The strengths of this study include the use of programmatic data to evaluate weight variations among MDR-TB patients initiating therapy and the use of random effects modeling to assess the death-related prediction ability of weight, and also its change during the first 6 months of treatment. To our knowledge, no previous study has assessed the relevance of the change in weight during therapy follow-up.

This study also has several limitations. First, data from only the first 6 months of MDR-TB patient follow-up were used for the analysis. Since more than 90% of patients died during the study period, the follow-up data after 6 months were not included because of a lack of appropriate power to detect differences. Second, the sample size of the cohort was not based on a priori power calculations; nevertheless, all the main study conclusions are based on findings that were strongly statistically significant. Third, some confounders might not have been included in the analysis. For example, socioeconomic status, a very important variable associated with weight and death, was not available from the data. However, cohort patients for this study lived in a poor, peri-urban area. In addition, we adjusted our model for education level, a well-recognized proxy of socioeconomic status.[29] Fourth, deaths reported in this analysis may not have been attributable to TB. We used all-cause mortality, as information regarding cause of death was not available. And finally, results might not be applicable to other countries. Thus, we recommend that new prospective studies be performed to verify our results.

In conclusion, our results reveal that weight change during treatment follow-up can be useful to determine how the patient will progress during therapy as well as being a surrogate of the treatment outcome, specifically death during therapy. MDR-TB patients with weight loss should be followed more closely, as they are at greater risk of death.

Conflict of interest: No conflict of interest to declare. No funding to declare.

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