ORIGINAL ARTICLE

Determinants of Multi-drug Resistant Tuberculosis Treatment Failure in a prevalent region in Peru

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ABSTRACT

Background: Multi-drug resistant tuberculosis (MDR-TB) treatment failure is becoming a growing concern among health managers, clinicians, epidemiologists and health workers worldwide. Patients in this situation have a high probability of increasing drug resistance and extremely resistant forms of the disease, which put their health and their contacts' at risk.
Aim: To identify factors associated with multi-drug resistant tuberculosis (MDR-TB) treatment failure in a region of high prevalence in Peru.
Methods: Analytical unpaired case-control study with a 1:2 ratio, including 90 cases and 199 controls. The evaluated factors were selected taking components of social determinants of health as references. The Odds Ratio (OR) was defined through bivariate and multivariate analysis.
Results: Multivariate analysis showed four factors associated with treatment failure that corresponded to the human biological dimension: presence of cavities (AOR: 10.0, 95% CI: 1.3 -17.6); fibrous tracts in chest radiography (OR: 3.9, 95% CI: 1.1-10.9); pattern of resistance to five or more drugs in sensitivity test results (AOR: 4.1; 95% CI 2.9-5.7) and having received a second line treatment between seven and twelve months prior to the start of individualized treatment (AOR: 1.5; 95% CI 1.4 -1.6).
Conclusions: These findings suggest, regarding MDR-TB case management, the need to direct efforts to promote early diagnosis and timely administration of highly effective treatment based on resistance patterns regarding MDR-TB case management.
Keywords: Tuberculosis, Drug Resistance, Treatment Outcome, Risk Factors. (source: DeCS BIREME)

INTRODUCTION

Nowadays, multi-drug resistant tuberculosis (MDR-TB), defined as resistance to isoniazid (H) and rifampicin (R), is one of the most serious public health issues facing the world. According to the World Health Organization (WHO), Peru is the country that reports the highest burden of MDR-TB in The Americas: by 2012, 1,225 confirmed cases through sensitivity test were reported and, in 2017, this rose to 1,508 cases; however, the estimated number of cases for these periods was 2,200 and 2,100, respectively[1,2].

By 2018 in Peru, MDR-TB "therapeutic success" was 55% and failures were 6%, in contrast to the success rate in patients with drug-sensitive pulmonary tuberculosis which was 87%, with a failure rate of 1.0% (1.3). Lima and Callao have 83% of MDR-TB cases, with 1,028 and 101 MDR-TB cases reported respectively (1). Considering the high burden of MDR-TB in the country, the need to develop strategies to improve treatment outcomes arises and an essential step in that process involves the identification of factors associated with treatment failure in patients with MDR-TB.

There are many factors that can influence the outcome of MDR-TB treatment. Many of these are social determinants of health (SDH) that may act at the individual or structural level. Predictive factors of poor MDR-TB outcomes at patient level include HIV[4-7], alcohol and substance use[8,9], smoking[10], low body mass index[8,9,11,12]. Programmatic determinants have included treatment duration, access to drug sensitivity testing as well as individualized treatment regimens and use of directly observed therapy (DOT)[8,13-16].

In MDR-TB, SDH play an important role in TB control because they improve living conditions and, thus, the circumstances in which the population is born, grows, lives, works and ages. Therefore, SHDs contribute to the reduction of inequalities that affect health the most, such as poverty[15,16].

MDR-TB patients with treatment failure have a high probability of amplifying resistance and acquiring extremely resistant forms of the disease, which puts their health and their contacts' at risk as the prognosis is poor and the treatment difficult due to complications during use and the cost of care[5,6].

This research aims to identify the factors that are associated with MDR-TB treatment failure in Callao, a region of Peru.
The identification will allow the design of effective interventions that will contribute to the improvement of treatment outcomes, which will impact the control of the disease.

MATERIAL AND METHODS

We undertook an analytical observational study with an unpaired case-control type, using a 2:1 ratio.
The study included new patients diagnosed with MDR-TB who were admitted for treatment from the period January 1, 2010 to December 31, 2012 and who completed their treatment by December 31, 2015 at health facilities in Callao, a region of Peru, including 48 primary health care facilities, grouped into three Health Networks (Bonilla,

BEPECA and Ventanilla) and four hospitals (Daniel Alcides Carrión, San José, Alberto Sabogal and Naval Medical Center).

The data were collected from the tuberculosis control records of the patients of the health strategy in the Callao region. The data collection technique was documentary analysis of clinical files and treatment control card, using a data collection sheet that was validated by expert judgment.

The clinical file was in accordance with a format pre-established by the country's national tuberculosis control program, and included relevant data obtained from the patients' clinical history with multi-drug resistant tuberculosis that health facilities in the jurisdiction send to the Regional Health Directorate of Callao for consolidation and analysis of the information. The treatment control card for patients receiving second-line drugs was also regulated by the national program, and health facilities in the Callao region periodically send a copy to the regional directorate to follow up cases of multi-drug resistant tuberculosis under treatment. As for therapy response, this was evaluated by means of monthly smears and cultures.

To reduce information and selection bias, data were crossed between the clinical file and the treatment control card to ensure that the information was accurate. In addition, we used the operational definitions of cured and failure according to the national technical regulation, which is mandatory for all health facilities in the country.

Case was defined as those subjects who met the definition of failure: *patients who, having received regular and strictly supervised treatment, do not achieve bacteriological conversion in their culture after the sixth month of treatment, or when bacteriological reversion occurs in the culture after that period, or when amplifying resistance to a fluoroquinolone and/or a second line injectable is demonstrated*[17].

Regarding controls, subjects who met the definition of cured were included: *patients who completed the treatment scheme and whose ten consecutive monthly cultures are negative in the last twelve months of the scheduled treatment for MDR-TB.*

Both the definitions of failure and cured are established in the technical health standard for comprehensive care of persons affected by tuberculosis, which is strictly enforced at all health facilities[17].

According to records of the tuberculosis control program for the period 2010-2012, 600 cases of MDR-TB were reported in the Callao region, of which 90 patients were reported as failures and 510 as cured.

The selection of both cases and controls was also based on the following criteria:

Inclusion criteria: patients admitted to individualized and supervised MDR-TB treatment between 2010 and 2012, at health facilities of the Regional Health Directorate of Callao; age over 15 years and having conventional first- and second-line sensitivity tests.

Exclusion criteria: presence of patients with incomplete information in their clinical file and/or treatment control card and/or who had not completed their treatment by December 31st, 2015. Of those cured, 199 patients met the inclusion criteria for control and all of them were included. Therefore, the study had 90 cases (failures) and 199 controls (cured).

Variables: The variable of interest was failure, as a condition for admission to multi-drug resistant tuberculosis treatment in the study period. Explanatory variables were used for risk factors, based on the *Lalonde* model of health determinants, which took into account the following dimensions: Human biology (age, gender, characteristics of the pattern of resistance and adverse reactions to treatment), Health status (diabetes, hematocrit, duration of treatment with second-line drugs prior to the current scheme and radiological findings), Social environment (schooling, marital status, occupation and family support) and Lifestyles (alcohol consumption, smoking and use of psychoactive drugs)[18].

Data analysis: A database was created using Microsoft Excel v16.0 (Windows 2016 version) and a quality control of the collected information was performed, taking 10% of the surveys and verifying the data with the clinical file and treatment card, which resulted in no discrepancies. The statistical program Stata 14.0 (Stata Corporation, Computing Resources Center, College Station, Texas) was used for data analysis. An exploratory analysis of the data was performed to determine the frequency of presentation of each variable and its distribution. For continuous variables, central tendency measures (means) and dispersion measures were obtained according to the nature of the data. The process of describing categorical variables was complemented with frequency tables.

Subsequently, a bivariate analysis was performed, in which the statistical association between the outcome variable and the categorical explanatory ones were evaluated using 2x2, 2xC tables using the odds ratio (OR) with its corresponding 95% confidence interval and the p values, using the Chi-square test or the Fisher's exact test when necessary.

The presence of confusion and possible modifications of the effect between the final variables and variables such as bacillary load in smears, bacillary load in cultures and health facilities were assessed, using stratified analysis through the Mantel-Haenszel method.

Then, a multiple logistic regression analysis was performed using the Stepwise method, where, step by step, the indicators that showed a value of $p < 0.05$ in the bivariate analysis are added. These indicators were entered, elaborating regression equations until there were no more indicators that contributed to the model. The advantage of this method is that there is a continuous evaluation of the predictors included in the model, so the eliminated indicator is explained by the one(s) not eliminated.

Ethical aspects: For the development of the study, the ethical considerations stipulated in the Declaration of Helsinki and Law No. 26842, the General Health Law of Peru, were taken into account. The study was reviewed and approved by the research ethics committee of the Regional Health Directorate of Callao, Peru.

RESULTS

The study included 289 participants (90 cases and 199 controls). Sixty-one percent of the participants were male. In addition, 4.1% of the participants had diabetes and 51% had a low hematocrit level (lower than 30%); 15.2% of the patients said they had been treated for seven to 12 months with second-line drugs prior to the current scheme

(individualized). Bivariate analysis of the human biological dimension allowed us to find these factors associated with treatment failure: having a pattern of resistance to 3-4 drugs (OR: 25.6, 95% CI: 5.9-109.9); to more than five drugs (OR: 77.3, 95% CI: 17.8-335.6), having adverse drug reactions (dermal, angioedema, hepatic, gastrointestinal) (OR: 9.8, 95% CI: 5.4-17.7) (table 1).

In the health status dimension, we found factors such as diabetes (OR: 4.7, 95% CI: 1.4-16.2), low hematocrit levels (OR: 2.4, 95% CI: 1.4-4.1), treatment duration with second line drugs between 7 and 12 months (OR: 10.5, 95% CI: 4.7-23.8), radiological findings such as: cavities (OR: 116.5; 95% CI: 39.8-340.7), extensive fibrous tract (OR: 265; 95% CI: 8.1-9.6), bilateral alveolar infiltrate (OR: 4.9; 95% CI: 2.4-10.5), pleural empyema (OR: 19.5; 95% CI: 7.8-48.8), miliary pattern (OR: 24.9; 95% CI: 10.5-59.3) (Table 2).

In table 3, we found factors regarding marital status such as married (OR: 2,71; IC 95%: 1,4-5,1), cohabiting partner (OR: 2,2; IC 95%: 1,2-3,9). In addition, protective factors such as family support were evidenced (OR: 0,1; IC 95%: 0,1-0,2)

Table 4 reflects protective factors in treatment failure such as not using tobacco (OR 0.2, 95% CI 0.1-0.5) and not using psychoactive drugs (cocaine, heroin) (OR 0.3, 95% CI 0.2-0.7).Multiple logistic regression analysis (Table 5) showed four risk factors determining therapy failure: cavities (OR: 10.0, 95% CI: 1.3-17.6); fibrous tracts in chest radiography (OR: 3.94; 95% CI:1.1 -10.9); pattern of resistance to five or more drugs in sensitivity test results (OR:4.1; 95% CI: 2.9-5.7) and MDR-TB treatment duration between seven and twelve months prior to the start of individualized treatment (OR: 1.5; 95% CI: -1.4-1.6).

Table 1: Characteristics of the population and factors associated with treatment failure in the human biological dimension

Characteristics		**Case (N=90) (%)**	**Control (N=199)(%)**	**OR IC 95 %**	**P value**
Age	15 a 29	41 (45,5)	102 (51,2)	1	0,18
	30 a 44	35 (38,8)	61 (30,6)	1,4 (0,8;2,4)	
	45 a 59	13 (14,4)	30 (15,1)	1,0 (0,5;2.2)	
	60 or older	1 (1,1)	6 (3,0)	0.04 (0,01;0,31)	
Gender	Female	30 (33,4)	82 (41,2)	1	0,22
	Male	60 (66,6)	117 (58,8)	0,71 (0,40;1,23)	
Resistance pattern	2 drugs	2 (2.2)	97 (48.7)	1	
	3-4 drugs	37 (41.1)	70 (35.1)	25,6 (5,9;109,9)	<0,21
	More than 5 drugs	51 (56.6)	32 (16,1)	77,3 (17,8;335,6)	<0,01
Adverse drug reaction	No	19 (21)	144 (72)	1	
	Yes	71 (79)	55 (28)	9,8 (5,4;17,7)	<0,001
Dermal reaction	No	53 (59)	170 (85)	1	
	Yes	37 (41)	29 (15)	4,1 (2,3;7,3)	<0,001
Angioedema	No	79 (88)	197 (99)	1	
	Yes	11 (12)	2 (1)	13,7 (2,9;63,3)	<0,001
Hepatic	No	83 (92)	194 (97.5)	1	
	Yes	7 (8)	5 (2.5)	3,2 (1,0;10,6)	<0,001
Gastrointestinal	No	26 (29)	164 (82)	1	
	Yes	64 (71)	35 (18)	11,5 (6,4;20,7)	<0,001

Table 2: Characteristics of the population and factors associated with failure in the health status dimension

Characteristics	**Cases (N=90) (%)**		**Control(n=199)(%)**	**Or ic 95 %**	**P value per category**
Diabetes	No	82 (91,1)	195 (98)	1	
	Yes	8 (8,9)	4 (2)	4,7 (1,4;16,2)	0,04
Hematocrit level	Normal (31-54%)	31 (34)	112 (56)	1	
	Low (≤30%)	59 (66)	87 (44)	2,4 (1,4;4,1)	<0,01
Treatment duration with second-line drugs prior to the current schema	From 3 to 6 months	20 (22.2)	0	-	-
	From 7 to 12 months	30 (33.3)	14 (7.0)	10,5 (4,7-23,8)	<0,01
	From 13 to 18 months	22 (24.4)	96 (48.2)	1,1 (0,6-2,2)	0,72
	From 19 to 24 months	18 (20)	89 (44.7)	1	-
Radiological findings					
Cavities	No	4 (4)	168 (84)	1	
	Yes	86 (96)	31 (16)	116,5(39,8;340,7)	<0,001
extensive bilateral fibrous tracts	No	3 (3)	95 (48)	1	
	Yes	87 (97)	104 (52)	26,5 (8,1;9;6)	<0,001
bilateral alveolar infiltrate	No	9 (10)	71 (36)	1	
	Yes	81 (90)	128 (64)	4,9 (2,4;10,5)	<0,001
pleural empyema	No	56 (62)	193 (97)	1	
	Yes	34(38)	6 (3)	19,5 (7,8;48,8)	<0,001
miliary pattern	No	47(52)	192 (97)	1	
	Yes	43(48)	7 (3)	24,9 (10,5;59,3)	**<0,001**

Table 3: Characteristics of the population and factors associated to treatment failure in the social environment dimension

Characteristics		Case(n=90)(%)	Control(n=199)(%)	Or ic 95 %	P value per category
Schooling	Without formal education	2 (2)	5 (3)	1	-
	Primary	22 (24)	67 (34)	0,8 (0,14;4,5)	0,82
	Secondary	50 (56)	110 (55)	1,1 (0,2;6,0)	0,87
	University	11 (12)	11 (5)	2,5 (0,4;15,7)	0,32
	Higher technical	5 (6)	6 (3)	3,1 (0,4;25,5)	0,28
Marital status	Single	28 (31)	103 (52)	1	-
	married	28 (31)	38 (19)	2,71 (1,4;5,1)	**< 0,01**
	Cohabiting partner	33 (37)	56 (28)	2,2 (1,2;3,9)	**0,01**
	Divorced/separated	1 (1)	2 (1)	3,6 (0,2;60,7)	0,36
Occupation	worker	20 (22)	17 (9)	1	-
	employee	22 (24)	45 (23)	0,41 (0,18;9,46)	**0,03**
	Sales person	4 (4)	6 (2)	0,56 (0,13:0,23)	0.43
	housewife	7 (8)	33 (17)	0,18 (0,06;0,51)	< 0,01
	Dependent worker	11 (13)	3 (1)	9,35 (1,09;80)	**0,04**
	Independent worker	0	5 (2)		**-**
	student	19 (21)	59 (30)	0,27 (0,11;0,62)	**< 0,01**
	Unemployed	7 (8)	31 (16)	0,19 (0,06;0,54)	**< 0,01**
Family support	No	43 (48)	19 (10)	1	**-**
	Yes	47 (52)	180 (90)	0,1 (0,1;0,2)	**<0,001**

Table 4: Characteristics of the population and factors associated with failure treatment in the lifestyle dimension

Characteristics		Case(n=90)(%)	Control(n=199)(%)	Or ic 95 %	P value Per category
Alcohol	Current consumption	14 (16)	20 (10)	1	-
	Past consumption	34 (38)	56 (28)	0,9 (0,4;1,9)	0,72
	No consumption	42 (47)	123 (62)	0,5 (0,2;1,1)	**0,07**
Tobacco	Current consumption	17 (19)	13 (7)	1	-
	Past consumption	36 (40)	50 (25)	0,5 (0,2;1,3)	0,16
	No consumption	37 (41)	136 (68)	0,2 (0,1;0,5)	<0,01
Other psychoactive drugs(Cocaine, heroin)	Current consumption	16 (18)	15 (7,5)	1	
	Past consumption	9 (10)	7 (3,5)	1,2 (0,3;4)	0,76
	No consumption	65 (72)	177 (89)	0,3 (0,2;0,7)	<0,01

Table 5: Risk factors associated with MDR-TB treatment failure according to multiple logistic regression analysis

Characteristics		Adjusted or ic 95 %	P value
Fibrous tracts	Low (≤30%)	9 (0,1;22)	0,26
	No	1	-
	Yes	3,94 (1,1;10,9)	**0,04**
Alveolar Infiltrate	No	1	-
	Yes	434 (0,2;754)	0,11
Cavities	No	1	-
	Yes	10,0 (1,3;17,6)	**0,04**
Family support	No	1	**-**
	Yes	0,2 (0,1;0,5)	**0,04**
Treatment duration	From 19 to 24 months	1	-
	From 13 to 18 months	0,1 (0-47)	0.47
	From 7 to 12 months	1,5 (1,4-1,6)	**0,03**
Resistance pattern	2 drugs	1	
	3-4 drugs	34 (0,2-44,0)	0,16
	5 or more drugs	4,1 (2,9-5,7)	**0,02**
Previous use of psychoactive substances (cocaine, heroin)	Current consumption	1	
	Past consumption	0,2(0,1-60,2)	0,55
	No consumption	0,3 (0,2-0,5)	0,04

DISCUSSION

MDR-TB treatment failure has become a public health challenge, as well as a threat to the economy of communities because patients continue being a focus of infection since they spread resistant forms among the population, and complicate the clinical course of the disease[7].

It is a priority to find guidelines for the early identification of patients who could fail second line therapeutic schemes. Therefore, it is understood that considering factors such as human biology, health status, social environment and lifestyles can predict treatment failure, and that would allow health services to develop strategies to avoid such an eventuality[13,16,18].

Conventional risk factors, reported in other studies, such as age, gender and schooling level, did not show significant data in this research, although, as mentioned in a meta-analysis by Johnston et al. (19), being male was a protective factor (OR: 0.61; 95% CI: 0.31 - 0.91).

It can be inferred that an early diagnosis, a highly effective therapeutic arsenal that is available in a timely manner, and adequate follow-up of cases under treatment are key components in confronting MDR-TB, since they become an important barrier to prevent the presence of patients with greater clinical radiological issues and amplification of resistance, elements that favor treatment failure[9,19,20,21].

Some findings in this research are consistent with other studies, such as those by Toczek et al[22] and Aibana et al[6], who stated that good treatment results are attributed, partly, to early diagnosis, resistance to fewer drugs, not being multi-treated patients and the availability of drugs for treatment. Hence, we can highlight that the therapeutic arsenal is very important for treatment success, and drugs with high efficacy should be included according to the susceptibility test results.

In relation to the association between alcohol and treatment failure, this research does not prove it despite the fact that other studies describe that some inappropriate lifestyles, such as alcoholism, smoking and drug addiction, are associated with treatment failure because they are related to some social determinants such as conditions of poverty, unemployment and/or living on streets which influence that situation[21]. A possible explanation why that was not evidenced in the study is that the patients probably abandoned the treatment or died, before being categorized as failures.

Regarding radiological findings, we found that the existence of extensive bilateral fibrous tracts and cavities had an association with treatment failure through multivariate analysis. Although some authors such as Naidoo et al[23] indicated that radiological manifestations of MDR-TB are varied and unspecific and, regardless of the radiological presentation, treatment is the most important factor within the prognosis of patients; others such as Rodriguez et al[24] and Zhang et al[25], coincided with what was found in this research, demonstrating the association of treatment failure with the existence of cavities. In that perspective, Velázquez et al[26] and Mitnick et al[27], found that not having an extensive disease is a factor associated with a favorable response.

There are populations of Mycobacterium tuberculosis in the cavities that are metabolically active and continuously growing, which can cause pharmacological failure and resistance if they are not homogeneously eliminated with an adequate treatment[13,16]. The presence of a cavity is a continuous source of germ elimination. Essentially, drug resistance is more likely in cavernous pulmonary tuberculosis because of the large number of bacilli that multiply rapidly in it[6,16,28].

It is described that treatment success is determined by many factors, so the treatment scheme plays an important role. Studies suggest that patients benefit when treatment contains a minimum of four drugs[26,29,30].

Another aspect that deserves attention is related to comorbidity with diabetes mellitus and anemia that in logistic regression did not reach statistical significance, which is similar to other published studies. However, it cannot be assured that they are not risk factors for MDR-TB treatment failure, although Bastos et al[31] found that not having diabetes mellitus was a protective factor for MDR-TB treatment failure, (OR: 0.6; 95% CI: 0.4 -0.8).

The support received from family members was a factor in reducing the probability of treatment failure, which would contribute to improvement of adherence and cure of MDR-TB treatment. It is important to mention that indicators such as family context and the support offered to the patient during treatment have not received adequate importance in health services management process as a strategy to decrease treatment failure[30-32].

People do not get sick or fail treatment because they want to. There are associated risk factors that will determine the increase of their vulnerability and this situation is associated with the social determinants of health. However, the biological perspective in health care that predominates in many health systems does not consider other dimensions related to the environment of the patient with tuberculosis and his/her family, underestimating the value of this knowledge to make a control program more effective[33-35].

However, the concept and purpose of participation in addressing the social determinants of health is not always fully understood. This requires interactive processes that need to be consolidated based on lessons learned, hence the need to consider the plurality of social, political, economic and cultural realities, as well as the clinical-social-sanitary and epidemiological profile of each reality.

CONCLUSIONS

Multiple logistic regression analysis demonstrated four determinant risk factors in MDR-TB treatment failure: presence of cavities, fibrous tracts in chest x-ray, pattern of resistance to five or more drugs in sensitivity test results, and having received a second-line treatment for MDR-TB between seven and twelve months prior to the initiation of individualized treatment.

There are still questions about the best therapeutic approaches for patients with drug resistance; however, there is a consensus on the need to treat them early and avoid the risk factors that contribute to failure; hence the importance of providing evidence to help improve good care practices through this study, allowing the establishment of strategies for a better operational and social clinical approach to prevent new cases and cure patients with this disease.

These findings suggest the need to focus efforts on MDR-TB cases' early diagnosis with more effective, rapid and simple laboratory techniques, in addition to the administration of timely and highly effective treatment. If these elements are not addressed, society would be exposed to the serious situation of the expansion and emergence of cases of extreme drug resistance.

Limitations of the study: The limited size of the study population may restrict the power of binary logistic regression analysis to evaluate associations of interest. Similarly, the research did not include cases from all over the country; however, we considered the Callao region, which reports the largest number of cases nationally along with Lima, the capital of Peru, hence, the results could be representative of the national situation.

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