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PREDICTOR FACTORS FOR MULTIDRUG-RESISTANT TUBERCULOSIS AMONG PATIENTS WITH PULMONARY TUBERCULOSIS IN HUÁNUCO, PERU. 2010-2015

PREDICTORES CLÍNICOS DE TUBERCULOSIS MULTIDROGORRESISTENTE EN PACIENTES CON TUBERCULOSIS PULMONAR EN HUÁNUCO, PERÚ. 2010-2015

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ABSTRACT

Introduction: In the city of Huánuco and around the world, there is a progressive increase in cases of tuberculosis and multidrug-resistant tuberculosis, for this reason it was necessary to identify predictors to develop multidrug-resistant tuberculosis. **Objective:** To determine if persistent fever, cavitary radiographic pattern and positive smear microscopy at the first month of treatment, are predictors of multidrug-resistant tuberculosis in patients with pulmonary tuberculosis, in four health facilities in the city of Huánuco, between January 2010 and December 2015. **Methods:** Case and control study. We considered 37 cases and 111 controls. Data were collected from medical records. **Results:** The predictive factors found in the bivariate analysis were persistence of fever at 2 weeks (p = 0.001, OR 0.05, CI 0.01-0.5), cavitary radiographic pattern (p = 0.000, OR 11.6, 95%IC 4.6-26.5), and smear microscopy positivity at the first month of treatment (p = 0.00, OR 13.5, 95%CI 4.1-44.6). These were confirmed by multivariate analysis (p = 0.012, p = 0.00, p = 0.00 respectively). **Conclusion:** The persistence of fever at two weeks, cavitary radiographic pattern and positive smear microscopy at the first month of treatment were predictive factors associated independently for the diagnosis of multidrug-resistant Tuberculosis.

Key words: Tuberculosis; Multidrug – resistant tuberculosis; Case and control studies (source: MeSH NLM).

RESUMEN

Introducción: En la ciudad de Huánuco se observa un crecimiento progresivo de casos de tuberculosis y cada vez más frecuente la tuberculosis multidrogorresistente, por esta razón fue necesario identificar factores predictores para desarrollar tuberculosis multidrogorresistente. **Objetivo:** Determinar si la fiebre persistente, el patrón radiográfico cavitario y la baciloscopía positiva al primer mes de tratamiento son predictores de tuberculosis multidrogorresistente en pacientes con tuberculosis Pulmonar en cuatro establecimientos de salud de la ciudad de Huánuco, entre enero 2010 y diciembre 2015. **Métodos:** Estudio observacional, casos y controles. Se consideraron 37 casos y 111 controles. Los datos se recolectaron de las historias clínicas. **Resultados:** Los factores predictores encontrados en el análisis bivariado fueron la persistencia de la fiebre a las dos semanas (p=0,001; OR 0,05; IC 0,01-0,5), el patrón radiográfico cavitario (p=0,000; OR 11,6; IC 4,6–26,5), y la positividad de la baciloscopía al primer mes de tratamiento (p=0,00; OR 13,5; IC 4,1-44,6 al 95%). Estas fueron confirmadas con el análisis multivariado (p=0,08; p=0,002; p=0,00 respectivamente). **Conclusión:** La persistencia de la fiebre a las dos semanas, el patrón radiográfico cavitario y la baciloscopía positiva al primer mes de tratamiento mostraron asociación predictiva en forma independiente para el diagnóstico de tuberculosis multidrogorresistente.

Palabras clave: Tuberculosis; Tuberculosis farmacoresistente; Estudios de casos y controles (fuente: DeCS BIREME).

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as simultaneous resistance to isoniazid and rifampicin, and is now considered a major public health problem, mainly in developing countries where there are high rates of poverty[1]. According to WHO, in 2016 approximately 490 000 people worldwide developed MDR-TB, of which almost 50% were in India, the People's Republic of China and the Russian Federation[1]. In the countries of the Americas, the overall rate of new cases in 2011 was 28 per 100,000 inhabitants, with Haiti and Bolivia being the countries with the highest incidence; however, the cases reported by Brazil and Peru accounted for more than half of all cases in the region[2]. In Peru, according to data published by the Ministry of Health and the WHO, 5% of all TB cases in Peru are MDR-TB and 82% of these are concentrated in the areas of Lima and Callao[3,4]. In Huanuco, 22 new cases confirmed MDR-TB were registered during 2014, of which 59% corresponded to the province of Huánuco, being Huánuco, the city where most of the MDR-TB cases are concentrated[5].

Sensitivity tests, both molecular and culture, are essential markers for the proper diagnosis and management of MDR-TB; Unfortunately, some of these tests are expensive, others have late results and are not available, especially in areas with limited resources such as Huánuco, which is located in the central-eastern part of Peru, is the second poorest region in Peru with 30% of people in extreme poverty, a quarter of its population does not have sewage service, 9.2% of the inhabitants do not have access to drinking water, and where a significant burden of tuberculosis cases is currently concentrated; Therefore, it is imperative to develop new, faster and more affordable methodologies to facilitate the identification of patients with MDR-TB[6].

In this context, a series of studies have been carried out worldwide using clinical, radiology, laboratory tests and even immunogenetics, to establish predictive factors for MDR-TB, among whose results the association with HIV infection, the presence of hilar or mediastinal adenopathies in chest radiography and the absence of infiltrates in chest radiography stand out[7]; Similarly, other associated factors are being young, abandoning treatment and the presence of cavitary lesions in the chest X-ray[8]; while in Peru another study found that contact with a patient with MDR-TB within the family, an abnormal lung exam and the cavitary pattern in the chest X-ray are factors related to presenting MDR-TB[6].

Under these considerations, we can observe how important it is to identify predictive factors in MDR-TB that can be accessible in our reality, being this necessary to carry out an active and reasoned search of patients with potential risk, decrease the time of diagnosis and offer an adequate and timely treatment; achieving in this way better control of tuberculosis, avoiding the transmission of the disease and consequently providing adequate secondary prevention. All these actions will have a greater impact on the population with fewer economic resources, who are the most vulnerable to this disease in Huánuco, Peru and other parts of the world[9,10].

In such a scenario, the objectives of our study were to establish predictors for developing MDR-TB from clinical, radiological and laboratory parameters that are easily accessible in limited-resource areas.

METHODS

Design

An observational, analytical, longitudinal, retrospective, case-control study was carried out between January 2010 and December 2015; it included records of patients with pulmonary tuberculosis from four health facilities in the city of Huanuco: health center (CS) Aparicio Pomares, CS Las Moras, Essalud Huánuco Hospital II and Hermilio Valdizán Regional Hospital.

Population and sample

During the study period, 200 clinical histories of patients with pulmonary tuberculosis were found, of which 37 patients were TB-MDR and 111 TB sensitive, of which 52 stories were excluded from the study due to incomplete data needed for research.

Procedures and variables

Clinical, radiographic and bacilloscopy evaluations were carried out at the beginning of treatment and then monthly until treatment was completed in the Tuberculosis Control Program (TCP) services from each of the establishments included in the study, which had a pulmonologist or infectologist, a licensed nurse, and technical staff; and where patients with pulmonary tuberculosis, both sensitive and MDR, received specific treatment under direct observation.

All patients who had rapid and/or conventional tests resulting in resistance were defined as MDR tuberculosis (case), and all patients diagnosed by rapid tests or conventional tests as sensitive TB (controls), or

those who were receiving anti-tuberculosis treatment for sensitive TB and had adequate clinical progress.

Non-probabilistic type sampling was performed on all patients diagnosed with tuberculosis.

The data were obtained by reviewing clinical records, using a collection sheet, which was validated by expert judgement.

Statistical analysis

Data processing was carried out using the software SPSS v. 15.0, using Fisher's test for the variables diabetes mellitus, drug use and persistent fever after two weeks of treatment; Mann Whitney's U-test for the age variable and for qualitative variables was used the chi-square statistical test.

Multivariate analysis was performed with the variables that obtained statistical significance in bivariate analysis. A predictive model was constructed using multivariate logistic regression with goodness-of-fit test to evaluate predictivity. The generated table presents only the variables that maintain the statistical significance, besides considering age and sex as confusing variables and controlling bias.

Ethical considerations

The data were confidential and the identity of the patients was protected by unique code assignment and the ethical principles of the Helsinski Declaration of the World Medical Association were respected. The research protocol, prior to its execution, was reviewed and approved by the research ethics committee of the Faculty of Medicine of the Universidad Nacional Hermilio Valdizán de Huánuco.

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RESULTS

During the years 2010 to 2015 in the four health facilities that were included in the study, a total of 200 cases of Pulmonary Tuberculosis were registered, 90% of which were complete and with adequate follow-up. Thirty-seven cases were included that were diagnosed as MDR-TB, to which 111 controls were assigned, whose epidemiological characteristics are shown in Table 1.

The bivariate analysis found that the association between MDR-TB and alcohol use was statistically significant, but not with drug or tobacco use. The presence of contacts with tuberculosis in patients with pulmonary tuberculosis was only 1% in controls and 0% in the cases of MDR-TB patients, and no association was found. A significant association was found with the regularity of treatment of patients with sensitive TB, as a protective factor for the development of MDR-TB.

The most frequent radiographic patterns in the diagnosis of patients with MDR-TB were the cavity pattern and the reticular one, showing a statistically significant association with the cavity radiographic pattern. The relationship between MDR-TB and positive bacilloscopy at diagnosis and the first month of treatment was statistically significant, the rest of the analysis can be seen in table 2.

In the multivariate analysis shown in Table 3, the association of MDR-TB with persistent fever, the cavity radiographic pattern, positive bacilloscopy at the first month of treatment, productive cough at diagnosis and lung crackles at diagnosis were statistically significant.

Table 1. Epidemiological characteristics of patients with pulmonary tuberculosis in Huánuco from 2010 to 2015 (n = 148).

Characteristics	Frecuency	Porcentage
Hospital / Healthcare Facility		
Health Center Aparicio Pomares	61	41.2%
Helath center Las Moras	50	33.8%
Regional Hermilio Valdizán Medrano Hospital	22	14.9%
EsSalud Hospital II	15	10.1%
Year of medical history		
2010	12	8.1%
2011	25	16.9%
2012	24	16.2%
2013	30	20.3%
2014	36	24.3%
2015	21	14.2%
Gender		
Female	62	41.9%
Male	86	58.1%
Level of education		
No education	8	5.4%
Primay	29	19.6%
Seconday	82	55.4%
Superior	29	19.6%
Marital Status		
Married	32	21.6%
Single	111	75.0%
Widower	5	3.4%
Ocupation		
Estudient	48	32.4%
No Health Professional	88	59.5%
Health Professional	2	1.4%
Without ocupation	10	6.8%
Place of origin (District/ Province)		
Amarilis (Huánuco)	26	17.6%
Ambo (Ambo)	2	1.4%
Chinchao (Huánuco)	1	0.7%
Huánuco (Huánuco)	116	78.4%
Panao (Pachitea)	1	0.7%
Pillcomarca (Huánuco)	1	0.7%
Rondos (Lauricocha)	1	0.7%
Age (años)		
(X + DS)	**30.85 + 16.20**	

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Table 2. Bivariate analysis of MDR-TB in patients with pulmonary tuberculosis in Huánuco from 2010 to 2015 (n = 148)

Characteristics	Tuberculosis				X2	p	OR	IC 95%	
	MDR n=37	%	Sensible n=111	%				Inf	Sup
Marital status									
No single	14	40.5	22	19.8	4.89	0.027	2.46	1.09	5.55
Single	23	59.5	89	80.2					
Alcohol consumption									
Yes	16	43.2	19	17.1	10.49	0.003	3.69	1.63	8.35
No	21	56.8	92	82.9					
Diabetes Mellitus									
Yes	4	10.8	1	0.9	5.59	0.014 *	13.33	1.44	123.45
No	33	89.2	110	99.1					
Regularity of treatment									
Yes	27	73.0	101	91.0	6.244	0.0125	0.27	0.10	0.71
No	10	37.0	10	9.0					
Productive caough st diagnosis									
Yes	31	83.8	48	43.2	16.73	0.000	6.78	2.62	17.56
No	6	16.2	63	56.8					
Crackles at diagnosis									
Yes	11	29.7	9	8.1	9.32	0.002	4.79	1.79	12.78
No	26	70.3	102	91.9					
Fever after 2 weeks of treatment									
Yes	5	9.0	1	1.4	8.34	0.004*	17.19	1.94	152.48
No	32	91.0	110	98.6					
X-ray pattern at diagnosis									
Cavity pattern	22	59.5	13	11.7	35.04	0.000	11.06	4.60	26.52
No cavity pattern	15	40.5	98	88.3					
Baciloscoy at first month of treatment									
Positive	23	52.9	8	7.7	47.35	0.000	21.15	7.94	56.31
Negative	14	47.1	103	92.3					
Age (X + DS)	34.05 + 14.45		29.78 + 16.67		1531.00 #	0.021			
BMI at diagnosis (X + DS)	21.74 + 2.37		20.53 + 2.92		1561.50 #	0.029			

* Fisher´s exact test / # U de Mann Whitney.

Table 3. Logistic regression of MDR TB with predictive factors in patients with pulmonary tuberculosis in the city of Huánuco from 2010 to 2015 (n = 148)

Characteristic	Z	p	OR	IC 95%	
				lower	Higher
Gender	-0,04	0,969	0,97	0,3	3,4
Age	0,68	0,741	1,0	1,0	1,1
Cavity radiographic pattern	3,90	0,000	18,02	4,2	77,1
Fever at two weeks	2,50	0,012	61,8	2,4	1570,0
Positive basiloscopy at the first month of treatment	4,85	0,000	47,4	9,9	225,8
Productive cough at diagnosis	2,43	0,015	5,48	1,4	21,6
Crepitus at diagnosis	2,38	0,017	8,4	1,4	48,1

Goodness-of-fit test:
Hosmer-Lemeshow chi2(10) = 3,49
Prob > chi2 = 0,9675

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DISCUSSION

Tuberculosis is a huge public health problem worldwide and in Peru, despite a reduction in its incidence in recent years, it still mainly affects the population with fewer economic resources[2]. One of the objectives of our study was to find the association between MDR-TB and persistent fever, defined as fever lasting more than 2 weeks after starting treatment with first-line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol); this was statistically significant, which means that the persistence of fever despite starting treatment with anti-tuberculosis drugs predicts the presence of MDR-TB. This is similar to what was found by Solomon et al, who, when evaluating the response of fever to anti-tuberculosis therapy, found that the decrease or disappearance of fever was less likely in patients with MDR-TB than in those with sensitive tuberculosis[7].

Chest X-ray is considered a mainstay in the diagnosis of pulmonary tuberculosis since a normal chest X-ray decreases the likelihood of active disease. Pulmonary tuberculosis can manifest itself in different radiological patterns, depending on the age group and the patient's immune status, among other factors. The cavity pattern is produced when liquefied caseosal material is expelled from the center of the lesion into the bronchial tree. It can vary in size and can be single or multiple. In our study, we found a significant association of MDR-TB with the cavity radiographic pattern. In countries with high prevalence and incidence of TB, studies have been conducted to look for the association between MDR-TB and different radiographic patterns. Chuchottaworn et Cols. carried out a study in Thailand to determine the risk factors associated with MDR-TB, finding, as we did, an association with the presence of cavities in the chest x-ray; additionally, they found statistical significance with certain particular characteristics of the cavities such as: the number of cavities from 3 to more, the maximum diameter greater than 30 mm and more than 2 affected lung areas[11]. Lai et Cols in 2010, found that patients with XDR-TB (Extremely Resistant) had a significantly higher prevalence of cavitary lung lesions on chest radiography than patients with MDR-TB ($p < 0.05$)[12], suggesting that the presence of cavitary pattern is associated with increased resistance. A simple laboratory predictor, routinely obtained in every patient diagnosed with pulmonary tuberculosis, is baciloscopy. In the case of our study, the clear association between persistently positive baciloscopy at the first month of treatment and the subsequent diagnosis of MDR-TB is evident; it coincides with the results obtained in a Peruvian investigation in which it is concluded that of 1545 patients studied, 145 of them had positive baciloscopy during the first 60 days of treatment, and 21.8% of these patients had some type of resistance[13]. In contrast, a study by Kumar et al. found positive baciloscopy at two, four, five and six months after the start of treatment, however, when cultures were taken from these patients they were negative by more than 60%, concluding that starting empirical treatment for MDR-TB based on persistently positive baciloscopy is incorrect and would have

dangerous consequences[14].

Our study found no association between sex and the possibility of developing MDR-TB, similar to research conducted in Peru, where despite the higher frequency of male sex in the control group, when the statistical analysis was performed, no significant differences existed[15]; however, research conducted in China showed that male sex was more likely to develop MDR-TB than female sex (8.3% vs. 3.3%; X2 = 8.69, p < 0.001)[16]. The age groups in which MDR-TB can occur are varied and depend on several factors. In our study, the mean age for cases was 33.12 + 11.66 years, and for controls, 29.82 + 16.69 years, without being statistically significant. These findings are consistent with the results of the Mekonnen study, which assessed the prevalence and risk factors of MDR-TB in Ethiopia, where the mean and median age was 32 and 29 years respectively, but no age group was statistically significant[17]. Conversely, some research has found a statistically significant association between specific age groups and the risk of developing MDR-TB, however, the results of the studies are not uniform because they differ by age group. For example, Avalos-Rodriguez et Cols studied the factors associated with primary MDR-TB in Callao, Peru, finding that age greater than 40 years was a protective factor against MDR-TB, that is, the greatest risk was found in younger patients[18]. Zhao's group, on the other hand, developed a meta-analysis in China, finding a statistically significant association with an older group, between 40 and 60 years of age[19].

The present study considered three social factors associated with pulmonary tuberculosis: alcohol, tobacco and drug use. The frequency of use of these was low in both MDR-TB and sensitive patients. In multivariate analysis, no statistically significant association was found with tobacco or drug use, but an association with alcohol use was evidentSimilarly, Odone et Cols. conducted a cohort study in Lima, on the role of social determinants in MDR TB, which included tobacco use among its studied variables and, like our study, found no significant association with having been or currently being a smoker[20]; likewise, Martinez's group conducted a prospective cohort study in 37 health centers located in poor areas of Lima, finding a significant association between MDR TB and alcohol use[11]. Concerning drug use, other research finds an association of MDR-TB with drug use, but only with some types of drugs. Young in his study of social and clinical predictors of resistant TB in Monterrey, Mexico, found a significant association of resistant TB (which included MDR-TB) with cocaine use, but not with marijuana, methamphetamine or intravenous drug use[21].

The comorbidities assessed in our study were HIV infection and diabetes mellitus. Concerning HIV, no seropositive patients were found within the sample, while the frequency of diabetes mellitus in patients with sensitive TB was only 0.9%, and 10.8% in patients with MDR-TB, data that resulted in a statistically significant association in the bivariate analysis, but due to the very small sample size it requires further study in this regard, since a study conducted in 2014, evidence that diabetes mellitus in the multivariate analysis was not significantly associated with any drug resistance[22].

Contact with TB patients is considered a risk factor for MDR-TB according to the Peruvian Ministry of Health's guidelines; which is supported by some research as a meta-analysis developed in New York in which 25 studies were found that evaluated a median of 111 family contacts of drug-resistant patients, the combined yield was 7.8% (95% CI, 5.6% -10.0%) for active tuberculosis and 47.2% (95% CI, 30.0% -61.4%) for latent tuberculosis, although there was significant statistical heterogeneity (P<0.0001), This study concludes that household contact research on anti-tuberculosis drug resistance is a high-performance intervention for the detection of tuberculosis and the prevention of MDR-TB[23], contrary to the findings of our study, in which no significant association was found, perhaps due to the low number of contacts with sensitive TB patients and the lack of contacts with MDR-TB patients; Such evidence is also seen in a study in Thailand, where similarly to ours, no statistical association is evident[24].

Our study identified regularity and adherence to treatment in patients with sensitive TB as a protective factor against MDR-TB. Irregularity of treatment is considered by many researchers as a risk factor for MDR-TB, as demonstrated by a meta-analysis conducted in China, which in assessing poor adherence to treatment, found that it was a risk factor for developing MDR-TB[19].

Limitations

We found that during the development of our study the most important limitation was the source of information used, since a percentage of the clinical histories used were found to be incomplete, and therefore excluded from the research resulting in fewer patients for the study. Also, our design, being

retrospective, presents biases typical of this type of research, so its extrapolation may be limited.

CONCLUSION

In our study the predictors independently associated with MDR-TB in patients with pulmonary tuberculosis were persistent fever at two weeks after initiation of treatment, productive cough at diagnosis, lung crackles at diagnosis, cavity radiographic pattern and persistently positive baciloscopy test at the first month of treatment.

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