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Article

Factors associated with mortality with tuberculosis diagnosis in indigenous population in Peru 2015-2019

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Abstract: Aim. To identify factors associated with mortality with tuberculosis diagnosis in the indigenous population in Peru 2015-2019. Methods. Case-control study nested in a retrospective cohort, using the registry of persons belonging to indigenous peoples of the National Tuberculosis Prevention and Control Strategy of the Ministry of Health of Peru. A descriptive analysis was applied, and then bivariate and multiple logistic regression was used to evaluate associations between the variables and the outcome (live-deceased), the results were presented as OR with their respective 95% confidence intervals. Results. The mortality rate of the total indigenous population of Peru was 1.75 deaths per 100,000 indigenous people diagnosed with TB. The community of Kukama kukamiria - Yagua reported 505 (28.48%) individuals. The final logistic model showed that indigenous men (OR=1.93; 95% CI: 1.001-3.7), with a history of HIV prior to TB (OR=16.7; 95% CI: 4.7-58.7) and indigenous people in old age (OR=2.95; 95% CI: 1.5-5.7), are factors associated with a greater chance of dying from TB. Conclusions. It is important to reorient health services among indigenous populations, especially those related to improving the timely diagnosis and early treatment of TB-HIV co-infection, to ensure comprehensive care for this population, considering that they are vulnerable groups.

Keywords: Tuberculosis, Mortality, Indigenous, Logistic Regression

1. Introduction

Tuberculosis (TB) is an infectious disease produced by species of the Mycobacterium tuberculosis complex that can affect any tissue, mainly lungs [1], although it presents a worldwide distribution there is greater affection mainly in population groups with social vulnerabilities and high risk of transmission such as: extreme poverty, hardship, population deprived of liberty, social outcasts, street people, displaced persons and with clinical conditions that affect the immune system such as: HIV, immunosuppression status, diabetes, likewise affecting indigenous populations worldwide, among others [2].

During the year 2020, PAHO/WHO reported a total of 9.9 million people worldwide ill with TB, with an estimated 1.5 million deaths due to this infection, of which 214,000

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had HIV In the Americas, 291,000 TB cases were reported in 2020. The estimated deaths for the region was 27,000, 29% of which (7,900) corresponded to TB/HIV co-infection [3].

In 2018, 29 countries in the Americas region reported the number of TB cases diagnosed in indigenous populations. Ten of them reported that they had no TB cases in indigenous populations, and the remaining 19 reported 11 608 cases, representing 7.0% of the total number of incident TB cases reported by these countries. Brazil, Guatemala, and Mexico accounted for 75.8% of TB cases in indigenous people [4].

A systematic review by Tollefson et al. [5] reported that several countries in the Americas region had high incidences of TB in some of their indigenous peoples; for example, in the Ache people of Peru, the incidence was up to 75 times higher than in the general population. Similarly, Amazonian communities in Brazil exceeded 1,000 cases per 100,000 inhabitants.

Peru accounts for 14% of the TB cases in the Region of the Americas; Lima Metropolitan area and Callao report 64% of the country's TB cases, 79% of multidrug-resistant TB (MDR-TB) cases and 70% of extensively drug-resistant TB (XDR-TB) cases [6], even though these figures show that Peru is no stranger to this problem, a significant decrease in the notification of TB cases and other public health events has been observed during 2020, despite the efforts of health personnel to provide continuity to interventions; the reversal of this situation will not be feasible as long as the COVID-19 pandemic is not controlled.

Several studies have presented evidence that the incidence of active TB and the prevalence of latent TB are substantially higher in indigenous groups than in non-indigenous populations [5,7]; therefore, it is important to highlight the characteristics of this target population for this study.

It is estimated that there are approximately 476 million indigenous peoples around the world. Even though this figure is equivalent to only 6% of the world's population, they represent about 19% of the extreme poor [8]. Indigenous populations have higher rates of extreme poverty, morbidity, and mortality than their non-indigenous neighbors across the spectrum of low- to high-income countries [9].

In a study carried out in six indigenous populations in the U.S., Canada and Greenland, they found that child-based BCG vaccination, both detection and treatment of LTBI were associated with significant decreases in TB notification rates in these indigenous populations [10]; in Mexico, a study was conducted with indigenous populations, in which they reported that municipalities with a high proportion of indigenous people had the highest notification rates of all new TB cases [11]; in Brazil, a study reported the results of a cross-sectional survey aimed at detecting active TB in an indigenous group with a very high annual incidence of notifications, namely the Surui. According to the National Indigenous Health Service, the Suruí are among the top five indigenous groups in the country in terms of TB incidence [12]. In Colombia, an observational study was carried out in indigenous peoples of the Colombian Pacific in the department of Choco, where it was found that the incidence rate among the indigenous peoples of this region, who represent 10% of the population, was 192.1 per 100,000 inhabitants [13].

Among the studies conducted in Peru, there is one conducted in 2011 in Asháninka indigenous communities, in which it was found that in terms of gender and age, the affected indigenous population is similar to that of individuals with TB at the national level, that is. adult male, however, in terms of occupation, it is recorded that most are engaged in independent agricultural work, which is explained by the traditional lifestyle and subsistence of the Asháninka communities. It is also important to note that the majority of cases reside in communities other than where the health facility is located, which adds to the difficulty of administering and supervising TB treatment (14].

A similar study in the same year 2011 but in Quechua communities, with 211 records of patients affected by TB, showed that the proportion of TB in the sample was 93.57% (95% CI: 88.15 - 97.02). The proportion of TB cases in the Quechua population is higher than 90% from the overall and by year, 2008: 94.23% (95%CI: 84.05-98.79), 2009: 95.35% (95%CI: 84.18-99.43) and 2010: 93.57% (95%CI: 78.78-97.52). In the indigenous Quechua communities, 87.5% of the cases were pulmonary TB and 11.7% extrapulmonary TB, which is within the permitted range for this type of TB (10-15%). A higher value would probably be explained by the presence of HIV/AIDS, but no cases of HIV/AIDS have been identified, in spite of the fact that screening coverage with ELISA for HIV and confirmation with IFA or Western blot is probably low [15].

Although in recent years, in the Latin American context in general and Peru in particular, evidence has been generated on the magnitude of the problem, this focuses mainly on morbidity, generating a favorable scenario for analyzing fatal outcomes and suggesting factors that could explain it, therefore, the objective of this study was to describe mortality due to TB diagnosis in the indigenous population in Peru and its associated factors during the period 2015-2019.

2. Materials and Methods

Study design. An epidemiological design of case-control study nested to a retrospective cohort was carried out, which is characterized by analyzing all the cases of the stable cohort followed over time and for the controls the analysis was done on a sample of individuals from the same cohort [16].

Cases were defined as the indigenous population diagnosed with sensitive TB who died during the study period. In principle, the controls of the deceased cases should be alive, since they constitute a sample of the source population that gave rise to the cases [17].

Study Population and Selection. The general population with sensitive TB diagnosis of Peru were 156,406 individuals, from which 4,759 individuals belonging to the indigenous populations of Peru were selected during the period 2015-2019. After filtering and verifying the selection criteria, 2,986 records were excluded for having incomplete information especially in their exit condition, finally obtaining a database with 1,773 indigenous people of the Peruvian territory, from these 101 that correspond to cases passed away.

Selection of controls. Based on the above, the statistical power was calculated for the different scenarios with 1, 2 and 3 controls per case and an OR to detect of 2; for the ratio of one control per case and an OR of 2.0, a statistical power of 84% was obtained to estimate differences. As the number of controls increased, the statistical power decreased as shown in Figure 1.

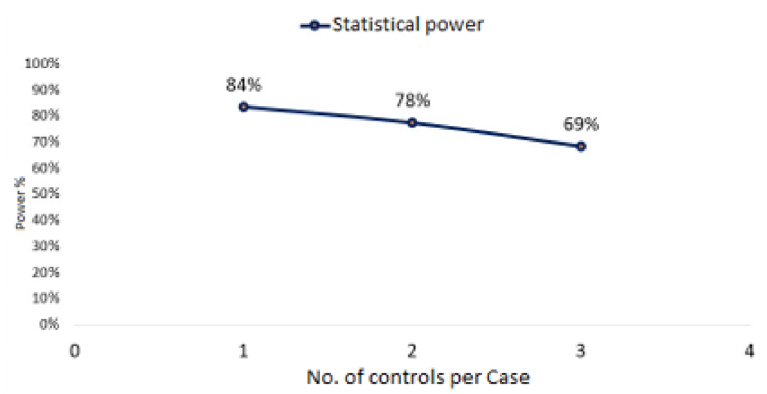

Figure 1. Relationship between number of controls per case and statistical power

The selection of an equal number of cases and controls allowed minimizing the variance of the estimated odds ratio [18], leaving a total of 101 cases (deceased) and 104 controls (alive) with which the logistic regression analyses were developed (see Figure 2).

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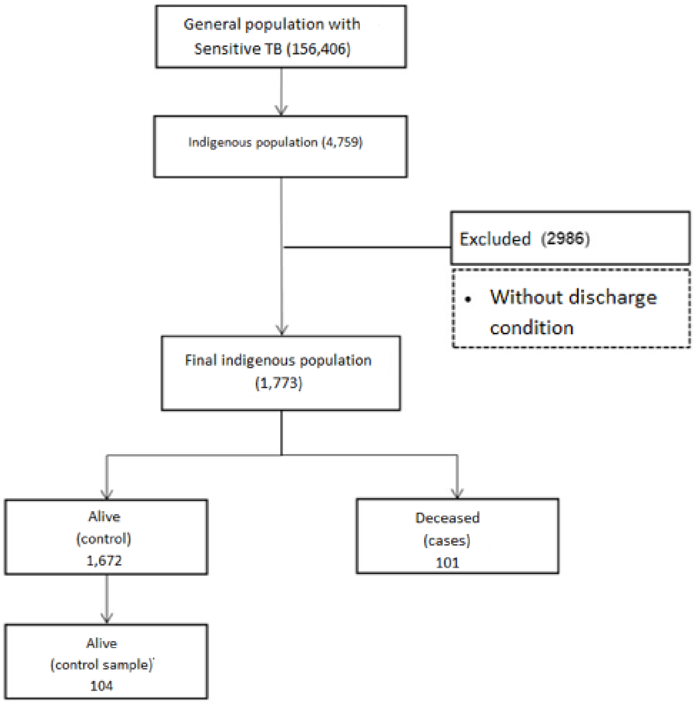

Figure 2. Flow chart of the study

Sampling design of controls (live). The selection of the controls was carried out through a systematic sampling of the 1,672 individuals of the indigenous population that were alive during the study period, then it was validated that the proportion of individuals per year and per gender was conserved according to the population distribution.

Source of information. The source of information was secondary and was obtained from the registry of persons belonging to indigenous peoples of the National TB Prevention and Control Health Strategy of the Ministry of Health of Peru.

Statistical analysis. Descriptive analysis was performed for each of the study variables, both sociodemographic and clinical, and they were presented as percentages. The normality of the quantitative variables was contrasted by means of the Kolmogorov-Smirnov test and, if the assumption was met, the mean and standard deviation were used; otherwise, the median and interquartile range were used. All results are shown in tables and graphs.

From the discharge condition, the response variable "state" (alive or deceased) was taken, and bivariate and multiple logistic regression was used to evaluate associations between the variables by means of the stepwise backward procedure; the results were presented as OR with their respective 95% confidence intervals. For the multiple model, those variables with a p-value <0.25 were selected as proposed by Hosmer and Lemeshow [19].

Finally, the goodness of fit of the model was evaluated by means of the likelihood ratio comparing the difference between the two models (saturated and adjusted) as well as the Hosmer and Lemeshow test, and thus defining that the model fits the data very well and is adequate to make predictions. The explanatory and predictive capacity of the factors in the model with respect to TB mortality was evaluated by means of the area under the curve - AUC.

The level of statistical significance was established at p<0.05 and for all analyses the Microsoft® Excel® program and the statistical package Stata corp. 17.0®.

3. Results

The estimated mortality in this study was 5.7 cases per 100 Indigenous diagnosed with sensitive TB however, the mortality rate calculated with respect to the total Indigenous population of Peru was 1.75 deaths per 100,000 Indigenous (Table 1). A similar percentage behavior was observed in all years except in 2018 where it decreased to 4% of the total indigenous diagnosed.

Table 1. TB mortality by gender.

Mortality rate	Indigenous population (2017 census)	Indigenous deceased by TB	Total indigenous d. w/ TB	Mortality % by TB	Mortality rate by TB (100,000 inhab).
General	5,771,885	101	1773	5.7 %	1.75
Men	2,801,412	76	1087	7.0 %	2.71
Women	2,970,473	25	686	3.6 %	0.84

Table 2 shows the demographic and clinical characteristics of the indigenous population studied, where a median age of 39 years was observed; 50% were between 26 and 55 years old, which corresponds to the interquartile range; 61.3% were men (1,087); within the life cycle, the majority of the indigenous population were adults (53%), corresponding to the age range between 27 and 59 years, followed by 20.6% who were in the old age stage (>=60 years). Most of the indigenous people (90%) had pulmonary TB and the remaining 10% had extrapulmonary TB.

In terms of ethnicity by community, the Kukama Kukamiria - Yagua community reported 505 individuals (28.48%), followed by the Shipibo-Konibo community with 385 individuals (21.7%) and in third place was the Asháninka community with 298 individuals, equivalent to 16.8%; these three communities account for 67% of the indigenous populations.

Most of the records of the indigenous population were new at admission (91.99%), only 4.4% were admitted for relapse; on the other hand, the most frequent condition of discharge was cured with 54.1% followed by complete treatment with 21.2%; it was also observed that the proportion of deaths was 5.7% (101). Among the habits of the indigenous population, there was a low proportion of alcohol consumption (5.4%), smoking (4.2%) and drug addiction (2.5%); the majority of the indigenous population (91.9%) received treatment for sensitive TB, and the rest received treatment for HIV-TB and extrapulmonary TB.

Table 1. Demographic characteristics of the Indigenous population with a diagnosis of Sensitive TB 2015-2019

Sociodemographic and clinical characteristics	Description	Summary measure	
		n: 1773	%
Gender	Women	686	38.7
	Men	1.087	61.3
Age (years)	Median (RIQ[1])	41 (26-55)	
Life cycle	Childhood/adolescence	140	8
	Youth	327	18.4
	Adulthood	940	53
	Old age	366	20.6
Ethnic affiliation	Kukama kukamiria - Yagua	505	28.48
	Shipibo-konibo	385	21.71
	Ashaninka	298	16.8
	Kichwa	117	6.6
	Kukama kukamiria	109	6.15
	Ticuna	52	2.93
	Shawi	47	2.65

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Sociodemographic and clinical characteristics	Description	Summary measure	
		n: 1773	%
	Harakbut	37	2.09
	Kakataibo	36	2.03
	Bora	35	1.97
	AWAJÚN	33	1.9
	Matsigenka	32	1.8
	Achuar	18	1.02
	Yagua	18	1.02
	Wampis	16	0.9
	Mestizo	14	0.79
	Quechua	12	0.68
	Kandozi	4	0.23
	Sharanahua	3	0.17
	Madija	2	0.11
Location	Extrapulmonary	176	9.9
	Pulmonary	1597	90.1
Admission condition	New	1631	91.99
	Relapsed	78	4.40
	Dropout recovered	61	3.44
	Failure	3	0.17
Discharge condition	Cured	959	54.1
	Complete treatment	376	21.2
	Dropout	158	8.9
	Deceased	101	5.7
	Failure	5	0.28
	No answer	174	9.8
Comorbidities and risk factors			
HIV	Positive	126	7.47
Diabetes	Yes	170	11.1
Alcoholism	Yes	96	5.42
Smoking	Yes	74	4.2
Drug addiction	Yes	44	2.5
Treatment regimen	2HREZ/4(HR)3	1629	91.9
	2HREZ/10HR	43	2.4
	2HREZ/7HR	101	5.7

[1] *RIQ: Interquartile range*

The bivariate logistic regression analysis (Table 3) included gender, age grouped by life cycles, location of TB, history of HIV and DM, HIV result, diagnosis of DM by glycemia test and the habits of the indigenous population: alcoholism, smoking and drug addiction. It was observed that indigenous men had 2.14 times the chance of dying from TB compared to indigenous women (p=0.012). It was evidenced that for a one-year increase in age the probability of dying from TB is 1.7% (p=0.017), when analyzing by life cycles it was found that indigenous people who are in an age group are a risk factor for dying from TB compared to indigenous minors, see Figure 3.

The indigenous population with a history of HIV prior to TB had 12.6 times the chance of dying from TB compared to those who did not have a history of HIV (p=0.00); likewise, those who tested positive for HIV had 20 times the chance of dying from TB compared to those who tested negative for HIV (p=0.000).

In the multiple model, we evaluated the collinearity between the variables, HIV history and HIV result, and performed separate analyses, finally leaving the variable "HIV history" because it presented less imprecision in the estimates, and also because of the

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total indigenous population with a history of HIV, 96% presented a positive result in the HIV test.

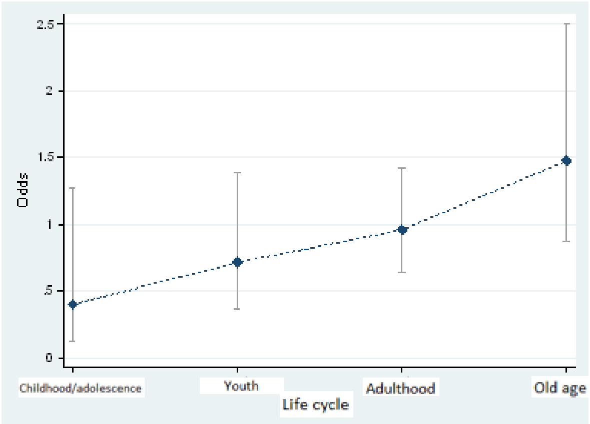

Figure 3. Association between life cycle and TB mortality.

Table 3. Association between mortality and sociodemographic and clinical factors of the indigenous community with diagnosis of Sensitive TB 2015-2019.

Characteristics		Deceased (101)	Alive (104)	OR (crude)	CI 95%		P-value
Gender	Women*	25 (24.75)	43 (41.35)	1			**0,012**
	Men	76 (75.25)	61 (58.65)	2.14	1.8	3.9	
Life cycle	Childhood/ adolescence*	4 (3.96)	10 (9.6)	1			
	Youth	15 (14.8)	21 (20.2)	1.78	0.47	6.8	0.395
	Adulthood	48 (47.5)	50 (48.1)	2.4	0.7	8.2	0.16
	Old age	34 (33.7)	23 (22.1)	3.7	1.03	13.2	**0.044**
Location of TB	Extrapulmonary*	16 (15.84)	11 (10.58)	1			
	Pulmonary	85 (84.16)	93 (89.42)	0.63	0.28	1.43	0.27
HIV history prior to TB	No*	72 (72.73)	101 (97.12)	1			
	Yes	27 (27.27)	3 (2.88)	12.6	3.7	43.2	**0,000**
HIV test result	Not Reactive*	60 (61.86)	98 (97.03)	1			
	Reactive	37 (38.14)	3 (2.97)	20	5.9	68	**0,000**
DM history prior to TB	No*	90 (94.74)	96 (96)	1			
	Yes	5 (5.26)	4 (4)	1.33	0.35	5.1	0.67
Diagnosis of DM by glycemia test	Negative*	71 (88.75)	81 (87.10)	1			0.74
	Positive	9 (11.25)	12 (12.90)	0.86	0.34	2.1	
Alcoholism	No*	91 (90.1)	98 (94.23)	1			0.28
	Yes	10 (9.9)	6 (5.77)	1.8	0.63	5.1	
Smoking	No*	97 (96.04)	101 (97.12)	1			
	Yes	4 (3.96)	3 (2.88)	1.4	0.3	6.4	0.67
Drug addiction	No*	100 (99.01)	103 (99.04)	1			0.98
	Yes	1 (0.99)	1 (0.96)	1.03	0.06	16.7	

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Characteristics	Deceased (101)	Alive (104)	OR (crude)	CI 95%	P-value

*Reference category

The adjusted or final multiple logistic regression analysis showed that in Peru, indigenous men, increasing age and a history of previous HIV are factors associated with a higher chance of dying from TB. The final model better explains the chance of dying from TB, which indicates a nice goodness of fit of the model, and the Hosmer-Lemeshow test showed that the model fits the data well (p=0.812) (Table 4). This model correctly classified 68.97% of the indigenous people with a probability of dying from TB, with a sensitivity of 51.5% and a specificity of 85.6%.

Table 4. Multiple Logistic Model and associated factors.

Characteristics		Deceased (101)	Alive (104)	OR (crude)	CI 95%		OR (adjusted)	CI 95%		P-value
Gender	Women*	25 (24.75)	43 (41.35)	1			1			0,047
	Men	76 (75.25)	61 (58.65)	2.14	1.8	3.9	1.94	1,001	3.7	
Life cycle	Childhood/ adolescence*	4 (3.96)	10 (9.6)	1						0.001
	Old age	34 (33.7)	23 (22.1)	3.7	1.03	13.2	2.95	1.5	5.7	
VIH history prior to TB	No*	72 (72.73)	101 (97.12)	1			1			0,000
	Yes	27 (27.27)	3 (2.88)	12.6	3.7	43.2	16.7	4.7	58.7	

Comparison of logistic regression models	Likelihood	P-value
Saturated Model (5 covariates)	-119.867	0.9846
Adjusted Model (3 covariates)	-120.054	
Hosmer-Lemeshow goodness-of-fit test	X^2: 0.21	0.9949

4. Discussion

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

In this research we described the sociodemographic and clinical characteristics of the indigenous population of Peru diagnosed with TB, and determined TB mortality during the period 2015-2019 and its possible associated factors.

In this study we observed that the estimated mortality was 5.7 cases (101/1,773) per 100 Indigenous diagnosed with TB, the mortality rate with respect to the total indigenous population of Peru, was 1.75 deaths per 100,000 indigenous taking into account the 2017 census[20], this rate was lower than that reported in a study also conducted in Peru where they found that the specific mortality rate for pulmonary TB, in Aymara populations was 11. 78 per 100,000 inhabitants [21]; likewise, in a study on TB in indigenous communities in Choco Colombia, a rate of 3.1 deaths per 100,000 inhabitants was reported [13] and was even much lower than that reported in studies in Chile and Brazil, which corresponded to 14.4 [22] and 13.2 [23] per 100,000 indigenous people, respectively.

The predominant gender in this study were men with 61.3% being 7.6% higher compared to the study Malacarne et al. [24] in 2016, where they found that the percentage of

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infected indigenous men was 53.7% and 4.3% higher with respect to the study of Ríos et al. [23], who reported TB mortality in indigenous men (57%); the percentage of deceased men with TB was also higher within the group of deceased indigenous men with 75% (76/101) which represented a rate of 2.7 per 100,000 inhabitants.

When observing TB mortality throughout the study period, a very slight upward trend can be observed; however, in 2016 mortality decreased by 50% compared to 2015 (6% vs 3% respectively); in Paraguay as part of the results obtained in the training of indigenous promoters for active search, a decrease in mortality from 26.5 in 2008 to 21.1/100,000 inhabitants in 2009 was achieved [25].

In the bivariate analysis, the association between gender and TB mortality was estimated, confirming the aforementioned, which shows a statistically significant association: men had 2.14 times the chance of dying from TB compared to women; this result also agrees with what was found in a study conducted in Venezuela, where it is mentioned that mortality and morbidity rates increase with age, and among the elderly, men are the most affected [26].

EIn the multivariate analysis, one of the relevant results was the evaluation of TB-HIV coinfection, where indigenous people with a history of HIV had 16.5 times the chance of dying from TB compared to those without a history of HIV; according to the literature, the risk of death from TB in a patient with HIV is 2 to 4 times higher compared to a patient with TB and without HIV [27]; this result is also similar to that reported in a study conducted in Paraguay, where TB mortality in all forms is investigated for the first time in the entire country [28].

The area under the curve (AUC) calculated showed a prediction of mortality in the indigenous population with a TB diagnosis of 73.3%; this result was similar to that reported by Alves et al, who also used a logistic model to demonstrate the ability to discriminate the risk of death from tuberculosis by 75.6%; the model proposed by the authors considered aspects such as vulnerability, extreme poverty and illiteracy in a Brazilian city with a high incidence of this disease [29].

On the other hand, it is important to mention that even though there is literature recommending the use of a certain number of controls (2, 3 or 4) for each case in order to increase the statistical power of the study [30,31], it should be noted that for a total sample size, the maximum power of a study is obtained with groups of equal size and the power decreases almost linearly with increasing unbalanced rates [32].

Initially, it was proposed in this study to perform an analysis of survival from the time of initiation of treatment to the time of death; however, as a limitation of the study, the existing database had approximately 63% underreporting in the variables related to the recording of dates, This finding is consistent with what has already been described in the study of the Quechua communities in Peru, where the quality of the information from the health facilities is not good, given that there is a loss of records and incomplete records, which does not ensure reliable information [15].

The absence of a good information system affects the quality of the data, and this was reflected in some laboratory results where the percentage of tests not performed, such as culture, was above 30%, part of this was also evidenced in the study of Ashaninka communities where there is loss of relevant information due to poorly filled out medical records and records, absence of information up to 20% [14]; it was also evidenced in the study of Quechua communities, where there are no adequate diagnostic methods: a little more than 50% perform only BK; if you want to do culture you have to send the sample to the hospitals and if you want to do drug sensitivity you must send it to the health region or to the National Institute of Health. Since these communities are remote and the health facilities do not have the budget to transport the sample, these procedures are omitted, which confirms why laboratory data are scarce [15].

Another important variable that could not be evaluated in this study was schooling. Nájera et al. (33] in their study on demographic and socioeconomic factors associated with pulmonary mortality, explain that low schooling can favor the occurrence of TB deaths because it is a determinant that increases the social vulnerability of the population.

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In this study it was not possible to evaluate the timeliness of care in the medical service because many of the variables related to this aspect had incomplete information (63% approximately), in this sense it is necessary to conduct prospective studies to ensure the collection of these variables.

5. Conclusions

Our study showed that indigenous men, with a HIV history, and in old age, were more likely to die from TB. These factors could be used to reorient health services in indigenous populations, incorporating parameters related to the improvement of timely diagnosis and early treatment, in order to ensure comprehensive care for this population, taking into account that they are vulnerable groups that require institutional responses through a differential approach that incorporates their worldview on the health-disease process.

In accordance with PAHO's guidelines for the prevention and control of TB in indigenous peoples, comprehensive care is explained as follows: "It is indispensable that in the indigenous populations, traditional doctors -who are respected figures of authority and represent comprehensive care (physical, emotional and spiritual) from traditional practices- are broadly linked with treatment support and adherence of patients to comply with pharmacological therapy, starting from a dialogue of knowledge to the construction of joint care routes where they and Western medicine are reflected together (general guideline 2)" [34].

Likewise, to maintain the strengthening of collaborative actions on TB-HIV coinfection, it is advisable to improve the registry used to follow up TB cases, the respective application of Directly Observed Treatment - DOT, and to strengthen the quality of data on important variables such as barriers to access and treatment of TB.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee) of WIENER UNIVERSITY (protocol code 146-2020, 26 august 2020.) for studies involving humans.

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Conflicts of Interest: The authors declare that they have no conflicts of interest.

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