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RESEARCH ARTICLE

Effect of COVID- 19 Period Compared to Non COVID-19 Period on the Odds of Pulmonary Tuberculosis at Ndola Teaching Hospital in Zambia

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Abstract

Introduction: There is a belief by researchers that COVID-19 pandemic threatens to reverse recent progress in reducing the global burden of TB disease. This is as result of extreme pressures on health systems, exacerbated by COVID-19, people with TB are likely to face decreased access to diagnostic and treatment services, which might also result in adverse outcomes.

Objective: To estimate the odds of Pulmonary Tuberculosis before and during COVID- 19 period at Ndola Teaching Hospital using the effect size of the odds ratio.

Design and Methods: This was an analytical cross-sectional study on the secondary data from Ndola Teaching Hospital Information system data base. We estimated the odds of Pulmonary Tuberculosis among patients with respiratory tract infections who were referred to Ndola Teaching Hospital during non-COVID-19 period compared to COVID-19 period (2020 March, to 2021 March). The Wilcoxon rank sum test for continuous variables and the Chi squared test for categorical variables were applied to compare the study population by Tuberculosis status. The main research question was addressed by establishing the association between the periods in which the patient was reviewed and the Pulmonary Tuberculosis diagnosis status, adjusted for potential confounders using the logistic regression model.

Results: The results revealed that COVID-19 period compared to non-COVID-19 period reduced the odds of Pulmonary Tuberculosis (OR:0.649, 95% CI 0.448, 0.940, p-value= 0.022).The results further showed that a unit increase in age was associated with reduced odds of Pulmonary Tuberculosis(OR: 0.983,95% CI:0.972, 0.994, p-value= 0.002), equally, there was an indication that being female compared to being male reduced the odds of Pulmonary Tuberculosis(OR:0.987, 95% CI: 0.689,1.413, p-value= 0.942) albeit the estimates were not statistically significant and staying in an urban area compared to living in the sub-urban area had a protective effect against Pulmonary Tuberculosis (OR: 0.358,95% CI: 0.220, 0.583, PV: <0.0001).

Conclusion: Period in which the patient was reviewed is significantly predictive of the odds of Pulmonary Tuberculosis at univariate analysis however at multivariable analysis the effect was insignificant. The reduced effect of the COVID-19 period may be a manifest of screening efforts for TB being reduced to deal with the effects of the pandemic by health providers.

Keywords: Odds, Pulmonary Tuberculosis, COVID-19 period, Non-COVID-19 period.

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Working Definitions

1. odds of pulmonary Tuberculosis (pTB) is the probability of being diagnosed with pTB divided by the probability of not being diagnosed with pTB.
2. non-COVID-19 period in our case is defined the period from March 2019 to March 2020 before Zambia recorded the first case of COVID-19.
3. COVID-19 period in our case is the period from March 2020 to March 2021 during which there was COVID-19 cases being recorded.

1. Introduction

1.1 Background

The history of Tuberculosis (TB) is as old as humanity with provincial prevalence in Zambia ranking as; Copperbelt at 41%, Lusaka at 36%, and the rest of the provinces account for 23% and an incidence rate of 319 cases per 100,000 population in Zambia (1). Tuberculosis is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (2). Tuberculosis can affect anyone anywhere, but most people who develop the disease are the elderly, malnourished, diabetics, or who have some other chronic disease or are immune-compromised, there are more cases among men than women (3). TB is a disease of poverty, and economic distress, vulnerability, marginalization, stigma and discrimination are often faced by people affected by TB (4). It is hypothesized that the acquisition of Coronavirus increases the probability of victims being infected with Pulmonary Tuberculosis due to a weakening of the host immune system (5). The use of corticosteroids for managing COVID-19 may also carry the risk of exogenous TB infection or reactivation of old endogenous infection. Likewise, those with active TB or who have structural lung disease secondary to healed pulmonary Koch's disease are probably at a greater risk of developing COVID-19. The interactions between the two agents are reported in a meta-analysis by Sheerin D et al, 2020 (5)in which an overlapping of genetic signatures between TB and COVID-19 were identified.

It was found that both Angiotensin Converting Enzyme 2 (ACE2) and Trans-membrane protease serine type 2 (TMPRSS2) over gene-expression in males, may raise the hypothesis of male predominance in pandemic disease, along with the higher severity and worse outcome (6). As both ACE2 and TMPRSS2 are expressed in the testes and in the prostate, thus, zinc supplementation for males will provide an additional benefit besides its antiviral effect by protecting the male reproductive system from the possible viral attack (7). Additionally, different genomes leading to human beings' variations as a result of different genes expressions, populations' behaviors and their clinical presentation of different diseases and therefore patients' response to management protocols used (8). The importance of COVID-19 signalome was demonstrated by describing various pathways involved in SARS-CoV-2 infection and their impact on COVID-19 comorbidity.(9)

Zambia is among other countries in Africa and globally have been affected by the outbreak of COVID-19. The first 2 cases of COVID-19 in Zambia were reported in March 2020, involving a couple who had traveled to France on holiday for 10 days (10). The COVID-19 pandemic was prioritized over every other health issue throughout the world. There may be grave consequences for existing and undiagnosed TB patients globally, particularly in low- and middle-income countries (LMICs) where TB is endemic and health services poorly equipped (5). The researchers in this study hypothesized that during COVID-19 pandemic, it's likely that TB control programs would be strained due to diversion of resources, and an inevitable loss of health system focus, such that some activities could not or would not be prioritized. On the other hand, the researchers also asserted that it could be reasonably expected that the prevention and control strategies against COVID-19 may also positively impact the odds of Tuberculosis infections (11). This study sought to investigate the odds of Pulmonary Tuberculosis infections among medical patients presenting to Ndola Teaching Hospital during the COVID-19 and non-COVID- 19 period based on case records using the odds ratio as the effect size measure.

1.2 Statement of the Problem

In Zambia provincial Tuberculosis prevalence ranking is Copperbelt at 41%, Lusaka at 36%, and the rest of the provinces account for 23% (1). With the advent of COVID-19, it was likely that TB control programs would be strained due to diversion of resources, and an inevitable loss of health system focus, such that some activities could not or would not be prioritized. The London School of Hygiene and Tropical Medicine asserted that this resource diversion and loss of health

system focus would likely lead to a reduction in quality of TB care and worse outcomes consequently raising the incidence and prevalence of TB (11).

The relationship between COVID -19 and Tuberculosis is not clear because logically intensified health promotion measures to prevent the spread of COVID-19 are expected to have an extended benefit on Tuberculosis being a respiratory tract infection too. It is for this reason that we developed interest in estimating the odds of Pulmonary Tuberculosis at Ndola Teaching Hospital during and before COVID-19 period.

1.3 A Brief Review of What Other Studies have Done

It is estimated that 8.4 million people globally develop tuberculosis (TB) each year, and nearly 2 million deaths result from the disease(5). Overall, one-third of the world's population is currently infected with the Tuberculosis bacillus, over 90% of them in developing countries (5). It is the poorest people from the poorest countries that are most affected by Tuberculosis. Not only are they more vulnerable to the disease because of their living and working conditions, they are also plunged deeper into poverty as a consequence of tuberculosis. Researchers have hypothesized that a person with TB loses, on average, 20-30% of annual household income due to illness (12). The situation warrants urgent action to fight the epidemic. Examining the gender dimensions of TB is important for overcoming barriers to effective prevention, coverage and treatment of tuberculosis. Gender dynamics are key factors affecting an individual's risk of becoming infected with and developing tuberculosis (TB), his or her access to health information and health-seeking behavior, and ultimately the outcome of treatment (4).

The COVID-19 pandemic threatens to reverse recent progress in reducing the global burden of TB disease(2). The global number of TB deaths could increase by around 0.2–0.4 million in 2020 alone, if health services are disturbed to the extent that the number of people with TB who are identified and treated falls by 25–50% over a period of 3 months. In India, Indonesia, the Philippines and South Africa, four countries that account for 44% of global TB cases, there were large drops in the reported number of people diagnosed with TB between January and June 2020 compared with the same 6-month period in 2019, overall reductions in India, Indonesia and the Philippines were in the range 25–30% (2).

Researchers from the London School of Hygiene & Tropical Medicine (LSHTM) and Lancaster University estimated additional TB deaths and cases in China, India and South Africa over the next five years as a result of COVID-19 pandemic (11). They examined the impact of various reductions in social contacts and impacts on health services due to COVID-19. The researchers hypothesised that social distancing and masks might reduce TB incidence as Mycobacterium tuberculosis, the bacteria which causes the disease, is transmitted via droplets in the air similar to the coronavirus. However, even after considering this potential reduced TB transmission, the most likely scenario was estimated to result in more than 110,000 additional TB deaths. In the worst-case scenario where the impact of COVID-19 on health services is severe, this number could rise to up to 200,000 additional deaths (11**).**

The coronavirus pandemic which has negatively impacted global affairs has seen most of the gains in medical care which were achieved over the past decades under the threat of being wiped out within a short period of time. The COVID-19 pandemic has disturbed ordinary health services in more than 90% of the countries (13). This disruption of health service delivery has led to a reduction in hospital visits for other reasons. South African scientists feared that as a result of COVID-19 pandemic restrictions, fewer TB diagnoses, less attention to adherence and support during TB treatment, poorer treatment outcomes and consequently increased transmission will increase the TB burden and TB-related mortality(14**).**

Tuberculosis continues to be a major public health problem in Zambia with an incidence of 319 per 100,000 population, Zambia is ranked among the 30 countries with the highest per capita burden of TB in the world. Minister of Health Sylvia T Masebo, said the COVID-19 pandemic had a disruptive effect on the implementation of tuberculosis (TB) interventions in Zambia (15). Copperbelt Province has the highest prevalence of TB (41%), followed by Lusaka Province (36%) (15). It is for this reason that we developed interest in estimating the odds of Pulmonary Tuberculosis at Ndola Teaching Hospital during and before COVID-19 period.

2. Research Design and Methods

2.1 Study Design

The study was analytical cross-sectional design in which quantitative methods were used to ascertain the

association between explanatory variables with the primary outcome variable through statistical analyses. In this analysis, the explanatory variables are; Period in which patients were reviewed (priori explanatory variable), age, sex, and residence of patients while the effect size was the estimated odds of Pulmonary Tuberculosis measured by comparing the odds of pTB in the COVID-19 period with the odds in the non-COVID-19 period.

2.2 Study Setting

The study was conducted at Ndola Teaching Hospital's medical records department. Ndola Teaching Hospital is the largest referral Hospital in Copperbelt Province also catering to referral cases from 4 provinces (Luapula, Northern, Muchinga, and Northwestern provinces) of the Northern region of Zambia. Its status as a referral and teaching hospital entails appropriateness for human and material resource capacity towards the achievement of quality health care services.

2.3 Study Population

The target populations were adult patients with respiratory tract infections referred to Ndola Teaching Hospital, whose records where used in the study. A total of 800 participants' records were selected through a simple random sampling technique using a lottery method were recruited for the study as shown in the study flow chart below. The checklist with the variables of interest was used to derive information on TB status, period in which the patients were reviewed, age, sex, and residence of the patients.

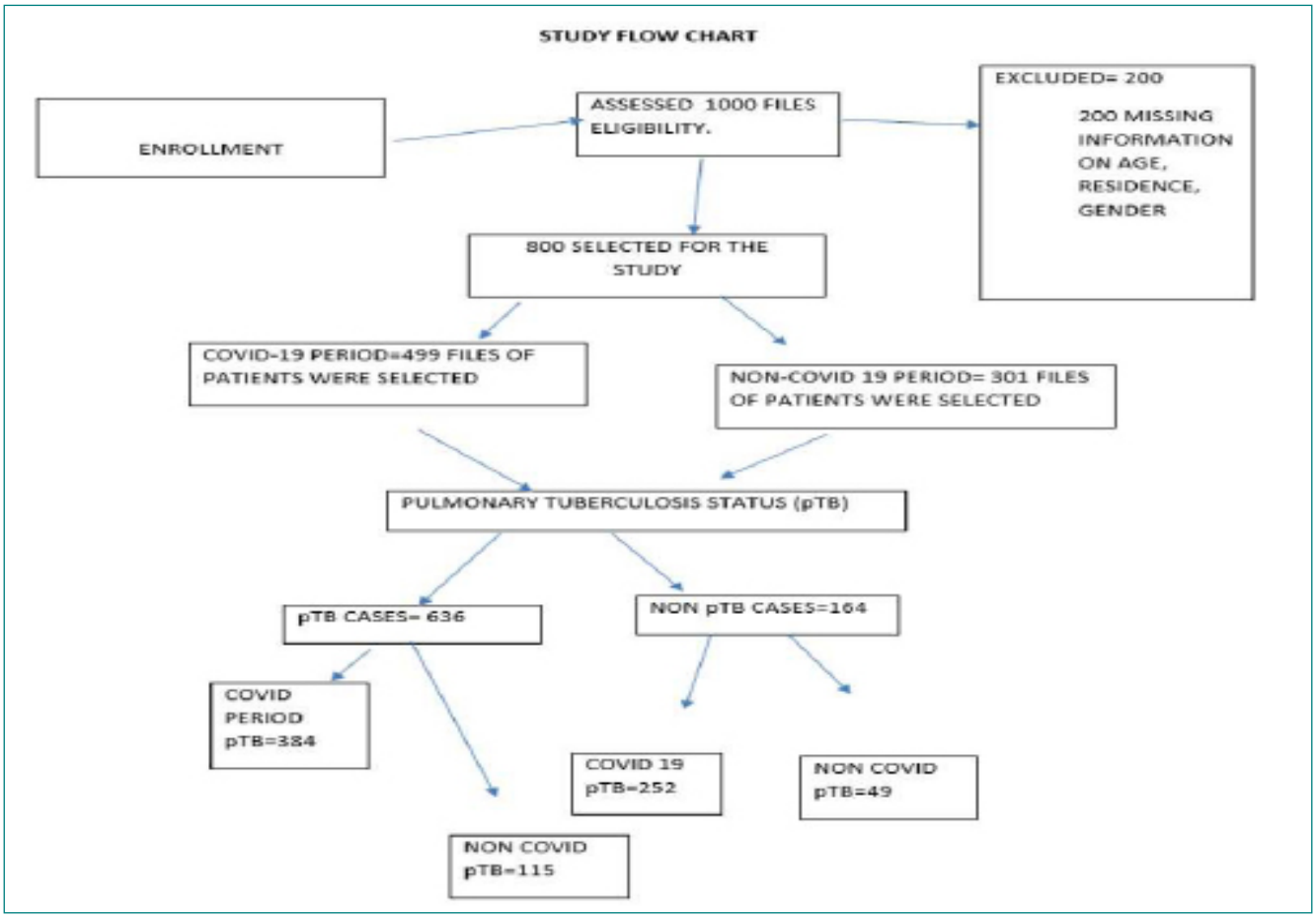

Figure 1. *Study flow chart*

Inclusion Criteria: The study inclusion criteria included cases diagnosed with Respiratory tract infections during COVID and non-COVID- 19 periods as eligible participants.

Exclusion Criteria: The study excluded all cases with the most missing information on Respiratory tract infections during the COVID and non-COVID-19 period at Ndola Teaching Hospital.

3. Sample Size Calculation and Sampling

This study will involve a population of approximately 372 medical records for the case as well as for the control groups. The sample size estimate was derived based on the Cochran formula as follows:

$$n = \frac{z^2 pq}{d^2}$$

Equation 1: Sample size calculation

where n= sample size,

p= 41% (representing the known prevalence for Tuberculosis Copperbelt),

q= 1-p,

z= 1.96

d= 0.05 at 95% confidence interval.

$$\frac{1.96^2(0.41)\ x1-\ 0.41}{0.05^2}$$

=371.71,= 372

This gave a n= 372, as the minimum sample size required to address each objective. A total of 800 patients' files were reviewed. The researchers searched for patients' records during the period of interest on Ndola Teaching Hospital data base (March 2019 to March 2021) for patients diagnosed with respiratory tract infections. The files with most of the information missing on variables of interest were left out the sampling procedure according to set out inclusion and exclusion criteria. Then simple random sampling using the Lottery method was performed to select eligible files.

3.1 Data Analysis

The baseline characteristics of participants by Tuberculosis status were analyzed using Wilcoxon rank sum assessment for continuous variables and chi-squared test for categorical variables. The main research question was addressed by establishing the relationship between period in which the patient was reviewed and Pulmonary Tuberculosis status. Logistic regression model was used to adjust for potential confounders. The statistical software package used to analyze the data was STATA version 16. Ethical approval was sought and granted by the University of Zambia Biomedical Research Ethics Committee (ref: UNZA-2110/2021) and the National Health Research Authority in Lusaka (ref: NHRA00021/7/12/2021), Zambia.

4. Results

The total number of subjects whose results were available for analysis in the study was 800. Of the 800 subjects, 281 (35.13%) were female and 519 (64.88%) were males. Out of these 800 subjects, 636 were Pulmonary Tuberculosis cases, 164 were free of Pulmonary Tuberculosis. Out of 636 TB cases 252(39.62%) were diagnosed during COVID 19 period, 384 (60.38%) during Non COVID-19 period. Table 1 below gives details of descriptive statistics in the study.

Table 1. *Baseline characteristics between patients with Pulmonary Tuberculosis and without Pulmonary Tuberculosis*

Characteristic	Pulmonary Tuberculosis		Total N (%)	P-Value
	Yes N =636	No N =164		
Age in Years				
Median (IQR)	39(31-49)	43(32-60)	39(31,50)	0.0218[W]
Period Non-COVID-19 Period	252(83.7)	49(16.3)	301(100)	0.022x2
COVID-19 Period	384(77.0)	115(23.05)	499(100)	
Sex				
Male	413(79.58)	106(20.42)	519(100)	0.942[x2]
Female	223(79.36)	58(20.64)	281(100)	
Residence				
Suburban	587(81.5)	133(18.5)	720(100)	<0.0001[x2]
Urban	49(61.25)	31(38.75)	80(100)	

X2= Chi-square, W= Wilcoxon rank sum

Table 2 below shows the results of the univariable and multivariable logistic regression models. The age, period, and residence of the participants at the time of review showed significant associations between these explanatory variables and the odds of Pulmonary Tuberculosis, as indicated by the p-values that are statistically significant. On the other hand, results show no significant difference between sex and odds of pulmonary Tuberculosis with an insignificant p-value**.** We note that COVID-19 period reduced the odds of having Pulmonary Tuberculosis by a factor of 0.649 at univariate analysis and 0.702 at multivariable analysis respectively. This reduction could be as low as 0.445 and 0.480 to as high as 0.940 and 1.026 respectively

with p-values equal to 0.022 and 0.067. The age of a participant (AOR; 0.986, 95% Cl; {0.975, 0.996}, p=0.009) and being female compared to being male (AOR; 0.961, 95% Cl; {0.669, 1.402}, p=0.866) both decreased the odds of having Pulmonary Tuberculosis controlling for all covariates, and we could rule out random chance finding in the estimates for age. There was very strong evidence of an association between the odds of Pulmonary Tuberculosis and residence of the patients came from (p=<0.0001).

Table 2. *Univariable and Multivariable Analysis*

	Unadjusted			Adjusted		
Variable	**OR**	**95%CI**	**P-value**			
Period						
NON-COVID PERIOD	**Ref**			**Ref**		
COVID-PERIOD	0.649	(0.448, 0.940)	0.022	0.702	(0.480,1.025)	0.067
Age	0.983	(0.972, 0.994)	0.002	0.986	(0.975, 0.996)	0.009
Sex						
Male	**Ref**			**Ref**		
Female	0.987	(0.689, 1.413)	0.942	0.969	(0.669, 1.402)	0.866
Residence						
Suburban	**Ref**			**Ref**		
Urban	0.358	(0.220, 0.583)	<0.0001	0.376	(0.229, 0.616)	<0.001

OR=Odds ratio, CI=Confidence interval, Ref=Reference category

5. Discussion

This study estimated odds of Pulmonary Tuberculosis at Ndola Teaching Hospital during the COVID-19 period compared to non-COVID-19 period. The factors that were used to estimate the odds of Pulmonary Tuberculosis are; Period in which the patient was reviewed (COVID-19 or Non COVID-19 period), age of the patient at a time the patient was reviewed, and residence where the participant was coming from at the time of review.

5.1 Period variable

The odds of Pulmonary Tuberculosis during COVID-19 period was 0.657 (AOR) (95% CI: 0.452, 0 .955,) indicating a reduced effect on the odds of Pulmonary Tuberculosis, this is consistent with World Health Organisation (WHO) report in 2020(2) where researchers made predictions that logically it could be reasonably expected that the prevention and control strategies against COVID-19 may also positively impact on the odds of Tuberculosis infections by reducing TB cases during the period of interest. It may be argued that the reduced effect of the COVID-19 period maybe a manifest of screening efforts of TB being reduced to deal with the effects of the pandemic by health providers. However, we do not have data to conclusively make this claim. But a more logical explanation is that as found by the WHO (2) report that found that the prevention and control strategies against COVID-19 may also positively impact on the reduction of TB cases.

On the other hand, WHO survey said, ‘’*It was reasonable to anticipate that even a simple disruption in essential health services could lead to an increase in Tuberculosis morbidity and mortality from causes other than COVID-19 in the short to medium and long-term (9)”*. London School of Hygiene and Tropical Medicine researchers also predicted that TB cases would rise during COVID-19 period as a result of strained TB programs due to diversion of resources, and an inevitable loss of health system focus, such that some activities would not be prioritized (11). Literature has also shown that the economic impact of the COVID- 19 pandemic was predicted to worsen at least some of the key determinants of TB incidence like; Gross Domestic Product (GDP) per capita and undernutrition consequently raising the incidence of Tuberculosis. Modeling has suggested that the number of people developing TB could increase by more than 1 million per year in the period 2020–2025 (2). The impact on livelihoods resulting from lost income or unemployment could also increase the percentage of people with TB and their households facing catastrophic costs. The results in this study to

the contrary have shown that the COVID-19 period was characterized by decreased odds of Pulmonary Tuberculosis contrary to the predictions by World Health Organization and London School of Tropical hygiene researcher's predictions.

5.2 Residence Variable

The results from this study showed that staying in an urban area reduced the odds of Pulmonary Tuberculosis compared to staying in a suburban area. This is consistent with Wang's study in China which concluded that residents in suburban areas and families with lower income were found to be at high risk of catching Pulmonary Tuberculosis (15). Wang's study showed that the poorest people from the poorest parts of the country are most affected by Tuberculosis (sub-urban areas). Not only are they more vulnerable to the disease because of their living and working conditions, but they are also plunged deeper into poverty as a consequence of Pulmonary tuberculosis disease. A person with pTB loses, on average, 20-30% of annual household income due to illness worsening poverty status and later on living conditions (12).

5.3 Age Variable

Studies have shown that elderly people (especially those≥60 years) are both susceptible to new TB infection, and at high risk for reactivation of latent TB. So, the elderly population represents a large reservoir of TB infection (16). Elderly pTB patients have a low positive rate of sputum smears, making diagnosis difficult, and more likely to have delayed diagnosis. We found that a unit increase in age had a decreasing effect on the odds of Pulmonary Tuberculosis contrary to the majority of studies on the topic, and this could be a result of the age group of participants in the study. The median age of the study population is 39 years with an interquartile range of 31 to 50 years old, this indicates that the majority of the participants were below 60 years old and could be an explanation for why the age variable in our study reduced the odds of Pulmonary Tuberculosis because this age group is characterized with good immunity.

5.4 Sex Variable

The study has shown that the female gender is associated with a reduction of the odds of Pulmonary Tuberculosis compared to the male gender. The results are similar to the recently available meta-analysis study on three of the studies from the United States of America, Poland, and Brazil(17). The findings of the meta-analysis regarding the epidemiological characteristics of Pulmonary Tuberculosis revealed that TB afflicted males more than females. The trend of male and female Pulmonary Tuberculosis diagnosis among elderly patients was consistent with the overall trend, the proportion of male patients in elderly patients was significantly greater than that of female patients. The other study in South Africa also showed that Pulmonary Tuberculosis prevalence was higher in men than in women, with a large difference in the prevalence to case notification ratio between sexes; a finding that is consistent with the literature (17). This bias of males being prone to Tuberculosis can be explained by a number of factors among which occupation stands out, Zambia is a mining country and TB is a common disease for miners where the majority are males.

5.5 Study Limitations

The use of secondary data may have affected the completeness and accuracy of the data we collected. In cases where some variables were missing from files, we dropped the variables with a lot of missing information and unobserved data.

6. Conclusion

From the results, we can deduce that in this sample, a unit increase in age predicts less odds of having Pulmonary Tuberculosis. We have noted too that being reviewed during COVID-19 period and staying in the urban area at the time of review or diagnosis reduces the odds of having Pulmonary Tuberculosis.

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Author Contributions

The concept, design, analyses, and translation of study findings were managed by Catherine Maliko. All co-authors contributed to the content, review, editing and ultimate write-up of the manuscript.

Conflict of Interest

All authors declared no conflict of interest.

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