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Evaluating determinants of treatment outcomes among tuberculosis patients in the mining district of Butha Buthe, Lesotho

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ABSTRACT

Background: Before the COVID-19 pandemic, tuberculosis (TB) was the leading infectious cause of death globally. In low- and middle-income countries (LMIC) including Lesotho, treatment outcome is lower than the recommended rate and poor TB treatment outcomes remain a programmatic challenge. The aim of this study was to determine unfavourable treatment outcomes and associated risk factors among TB patients in Butha Buthe district.

Methods: This was a retrospective record review of TB patients registered between January 2015 and December 2020. Data were collected from TB registers and patients' files and entered Microsoft Excel 2012. Analysis was conducted using R and INLA statistical software. Descriptive statistics were presented as frequencies and percentages. The differences between groups were compared using Pearson's X^2 test in bivariate analysis. Frailty Cox proportional hazards model was used to determine the risk of unfavourable outcomes among the variables.

Results: A total of 1792 TB patients were enrolled in the study with about 70% males (1,257). Majority (71.7%) of the patients were between 20 and 59 years old, with 48% of the patients being unemployed. Almost a quarter of the patients (23.1%) had unfavourable outcomes with death (342 patients) being the most common unfavourable outcome. Our study has shown that patients older than 59 years, and unemployment increased the risk of having unfavourable treatment outcomes. Death was the most common unfavourable outcome followed by lost-to-follow up. We also observed that the patients in the initiation phase of treatment died at a faster rate compared to those in the continuation phase (p=0.02).

Conclusion: TB treatment programs should have efficient follow-up methods geared more toward elderly patients. Active case finding to identify population at risk should be part of a TB program which would improve early diagnosis and treatment initiation. Patients in the intensive phase of the treatment program should be monitored more closely to determine adverse drug effects and nutritional requirement to prevent death during this phase of treatment.

Background

Prior to the Covid-19 pandemic, tuberculosis (TB) was the leading infectious cause of death worldwide despite the fact that it is a preventable and curable disease [1,2]. An estimated 100 000 more deaths from TB were reported during the 2019/2020 period [1,3]. This increase could be attributed to the interruption of TB care services due to lockdown measures during the peak of the Covid-19 pandemic [1,4]. Globally there was a decline in the incidence of TB disease in 2020 (127 cases per 100 000 population), with the World Health Organization (WHO) Pacific South-East Asia region having the highest percentage (43%) of TB incident cases [1]. This is followed by the WHO Africa region with 25% of incident cases[1]. However, this decline was minimal compared to previous years, and as such the world did not meet the 2020 milestone of the End TB strategy.

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In sub-Saharan Africa, TB control remains one of the key public health challenges where treatment success rate is lower than that recommended by the WHO [5,6]. In this region, TB treatment outcome is still a problem, with studies showing poor outcomes being positively associated with lower social-economic status and health system factors within these countries [7–9]. A study conducted in Karamoja, Uganda at 10 different TB diagnostic and treatment units showed that drug stockouts contributed to failure in treatment success [7]. Another study showed that the distance travelled by patients to get to the health clinic was a significant factor for unfavourable outcome as poor accessibility increased risk of missed treatment [9]. Drug resistant TB is another factor affecting treatment outcome. The continuous mutation of the *Mycobacterium tuberculosis* (Mtb) requires different innovative diagnostics and treatment techniques [10]. This poses a burden on the health system due to cost, and adverse effects associated with drug resistant medication [11,12].

The WHO Africa region carries the highest number of high TB burden [1,2]. Lesotho is one of the 16 high TB burden country in sub-Saharan Africa, with a recent national TB incidence rate of 660 per 100 000 population [2]. It is classified as a lower middle income country with a per capita income of US$967.23 [13], and with mining as one of its major sources of economic activity and the main source of employment for the adult males and females. TB studies conducted in Southern Africa showed that the mining industry contributes heavily to the burden of TB disease in these countries [14–16].

Studies conducted in Lesotho have focused on drug resistant TB treatment regimens [17,18], as well as the burden, diagnosis and treatment of TB [19–21]. Other studies have looked at the knowledge, attitudes and practices among patients and healthcare workers [22,23]. However there has been no study focusing on treatment outcomes, specifically unfavourable outcomes in a mining population in the last five years. This study aimed to model the unfavourable TB treatment outcomes in Butha Buthe district, Lesotho. The results of this study would inform on the improvement of TB treatment programs in Lesotho.

Methods

Study design

This was a retrospective record review of patients on TB treatment registered between January 2015 and December 2020.

Study setting

The study was conducted in Butha Buthe, a district found in the northern part of Lesotho. It has a total population of around 110 000 inhabitants covering an area of 1767 km^2. It houses two diamond mines, Kao and Liqhobong. The study was conducted in all of the 12 health facilities found in the Butha Buthe district. This included two district hospitals which served as referral hospitals (Butha Buthe Government Hospital and Seboche Hospital] and 10 primary health clinics [Boiketsiso Clinic, Linakaneng Clinic, Makhunoane Clinic, Motete Clinic, Muela Clinic, Ngoajane Clinic, St Paul Clinic, Tsime Clinic, St Peters Clinic, and Rampai Clinic).

Population of study

The study population consisted of the patients in Butha Buthe who were diagnosed with tuberculosis during the period of January 2015 to December 2020. Active and passive case finding through symptomatic patients reporting to the health facility and contact tracing were used to identify TB patients during this period. To be included in the study, patients should have started TB treatment. Patients with incomplete records that could not be traced, such as dates of treatment commencement or end, were excluded from the analysis.

Data collection

Data were abstracted from TB patients' registers and medical records. Research assistants trained in data collection visited all 12 health facilities gathering data. The following variables were considered important for this study: demographic information (age, sex, occupation), type of TB diseases (pulmonary and extra-pulmonary TB), phase of treatment (initiation/phase 1 and continuous/phase 2), drug resistance, treatment contact, treatment outcome (cured, completed, failure, defaulted/interrupted, lost to follow-up, death) and employment status (unemployed, employed non-mine workers, mine workers). For this study ex-mine workers were grouped together with mine workers. This is because ex-mine workers were assumed to have the same level of exposures to mining as mine workers hence might have similar risk to TB. We further classified employment as a binary variable [employed vs unemployed] when determining the risk factors associated with unfavourable outcomes. Data collected were entered into a MS Excel 2010 spreadsheet, cross-checked for errors, and validated.

Treatment outcomes

TB treatment outcomes are defined per WHO TB treatment guidelines as: "i) Cured: Patient who is sputum smear-negative in the last month of treatment and on at least one previous sputum test; ii) Treatment completed: Patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure; iii) Treatment failure: Patient who is sputum smear-positive at 5 months or later during treatment, iv) Death: Patient who dies for any reason during the course of treatment; v) Defaulted/interrupted: Patient whose treatment was interrupted for two consecutive months or more; Lost to follow-up: Patient whose treatment has been interrupted and cannot be traced [24]. For this study, treatment outcomes were classified as "favourable" (Cured and completed) and "unfavourable outcomes" (failure, death, defaulted/interrupted and lost to follow up).

Statistical analysis

Data processing and analysis were conducted using R, and INLA software packages [25]. Descriptive statistics was done with data expressed as frequency and percentages. The differences between groups were compared using Pearson's X^2 test in bivariate analysis. Variables with $p< 0.05$ were considered statistically significant. To determine the probability of unfavourable outcomes among variables, frailty Cox proportional hazards model was conducted. The frailty model was used because this model considers within-group variability and accounts for heterogeneity as well as the time factor. We accounted for variability at the 12 different health facilities. We further conducted a sub-analysis for death as this was seen to be the most unfavourable outcome. Survival analysis for the unfavourable outcome death was conducted as a secondary analysis for phase of treatment variables.

Results

Sociodemographic characteristics

Table 1 provides characteristics of the patients that were enrolled in TB treatment. A total of 1,792 TB patients were enrolled in TB treatment in 12 health facilities with 70.1% (1,257) being males. The mean age of the patients was 45.8 years, with an age range of 2 years to 94 years. We categorized the patients into three age groups of 19 years and below (71, 4.0%), 20 to 59 years (1285, 71.7%), 60 years and above (436, 24.3 %). Less than half of the patients were unemployed (n=817, 45.6%) while 568 (31.7%) were mine workers and 407 (22.7%) had other occupations. More than three quarters of the patients had pulmonary TB (n=1,381, 77.1 %). Most patients were registered as being in the initiation phase of treatment (phase 1) (n=1,157, 64.6%). Half

Table 1
Distribution of socio-demographic characteristics

Characteristics	N=1,792	(%)
Sex		
Female	535	29.9
Male	1,257	70.1
Age category		
≤19Yrs	71	4.0
20-59Yrs	1,285	71.7
≥60Yrs	436	24.3
Occupation Category		
Employed (non-mine workers)	407	22.7
Employed (mine workers)	568	31.7
Unemployed	817	45.6
Tuberculosis category		
Extrapulmonary TB	411	22.9
Pulmonary TB	1,381	77.1
Phase of treatment		
Phase 1	1,157	64.6
Phase 2	635	35.4
Treatment contact		
Community Health Worker	274	15.3
Family Member	887	49.5
Friend	162	9.0
Unreported	469	26.2
Drug Resistance		
Resistance	218	12.2
Susceptible	1,574	87.8

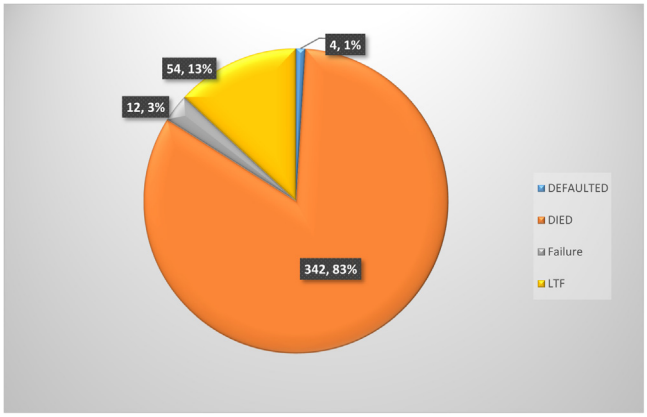


Figure 1. Distribution of unfavourable treatment outcomes

of the patients had a family member as their treatment contact person (n=887, 49.5%), and 26.2% (469) of the patients did not provide information on their treatment contact. Less than 10% of the patients had a friend as their treatment contact (n=162), and 274 (15.3%) reported having a community health worker as their treatment contact.

Treatment outcomes

Treatment outcome data were available for 1,781 patients. Eleven patients (0.6%) were transferred out from the 12 health facilities in Butha Buthe, and we could not trace their treatment outcome data. These patients were excluded from overall analysis of outcomes. Of the 1,781 patients, 1,369 (76.9%) patients had favourable treatment outcomes. Among those with favourable outcomes, 655 (48.1%) of them completed their treatment and 714 (52.5%) were cured. Unfavourable TB treatment outcomes were reported in 412 (23.1%) patients. Of this number 4 (1%) patients defaulted treatment, 12 (2.9%) had treatment failure and 54 (13.1%) were lost-to-follow up (LTF). The most common unfavourable outcome was death with 342 patients dying after starting TB treatment, making up 83% of the unfavourable outcomes (figure 1).

Association between demographic characteristics and treatment outcomes

Table 2 depicts the differences between the outcome measures among the demographic characteristics of the patients. There was no statistically significant difference between male and female with regard to the treatment outcomes (p=0.38). Patients who were 60 years and above had significantly higher proportion of unfavourable outcomes (p<0.001). There was no statistically significant difference in outcomes among the different occupation categories (P=0.50). Patients who had pulmonary TB had better favourable outcomes (79.8%) as compared to patients who had extrapulmonary (20.2%) (p<0.001). There was a statistically significant difference in outcomes between patients who had pulmonary TB and patients who had extrapulmonary TB (p<0.001). Patients in phase 1 had better favourable outcomes as compared to patients in phase 2. There was a statistically significant difference in outcomes between patients who were in phase 1 and phase 2 (p<0.001). Patients who had their treatment contacts as family members had better treatment outcomes as compared to other groups: community health worker, friend and unknown (p<0.001). Patients with drug resistant TB had more favourable outcomes than patients susceptible to treatment (p<0.02).

Determinants of unfavourable TB treatment outcomes

Table 3 shows the hazard ratios of unfavourable treatment outcomes. Variables with increased hazards of unfavourable outcomes included being 60 years and older (HR=2.81, 95%CI 1.82 – 4.33), unemployment (HR=1.25, 95%CI 1.03 – 1.51) and susceptibility to TB treatment (HR=1.93, 95% CI 1.36 – 2.74). Patients with pulmonary TB (HR 0.57, 95%CI 0.47 – 0.70), having a close relation as their treatment contact (family member or friends) (HR=0.58, 95%CI 0.46 - 0.74) and those in the second phase of treatment (HR=0.13, 95%CI 0.09 - 0.19) significantly decreased the risk of unfavorable treatment outcomes. Although males were less likely to have unfavourable outcome, this was not statistically significant (HR=0.8, 95%CI, 0.70 – 1.06).

Survival probability of outcome death between phases of treatment

Patients in phase 1 of treatment are seen to die at a very fast rate compared to patients in the second phase of treatment right from day 0 of treatment. Patients in phase 1 had a 50% survival rate at about 30 days (1 month) of treatment while patients in phase two had a 50% survival rate at about 120 days (4 months) of treatment (p=0.002).

Discussion

This study determined unfavourable treatment outcomes and its associated factors among TB patients in Butha Buthe. We further conducted a survival analysis for the unfavourable death outcome between the phases of TB treatment. Our study found that almost a quarter of the patients, 23.1%, had unfavourable outcomes with death being the most common unfavourable outcome. Our study has shown that patients 60 years and older, unemployment and drug susceptibility are factors that show an increased risk of having unfavourable treatment outcomes. We also observed that the risk of dying was higher in patients who were in the initiation phase of the treatment.

About 70% of the patients were men. A higher proportion of male TB patients has also been reported in other studies internationally [26–28]. Many more men may be diagnosed with TB in this population, probably because this is a mining district with many migrant workers that are men who move into the district to work in the mines or worked in South African mines. Other studies have shown that mines produce favourable conditions for TB infection and disease [16]. The majority of our patients were aged between 20 and 59 years, which is the working age group also known as the productive age group. This is in line with other reports from other sub-Saharan countries [26,29]. The greater proportion of

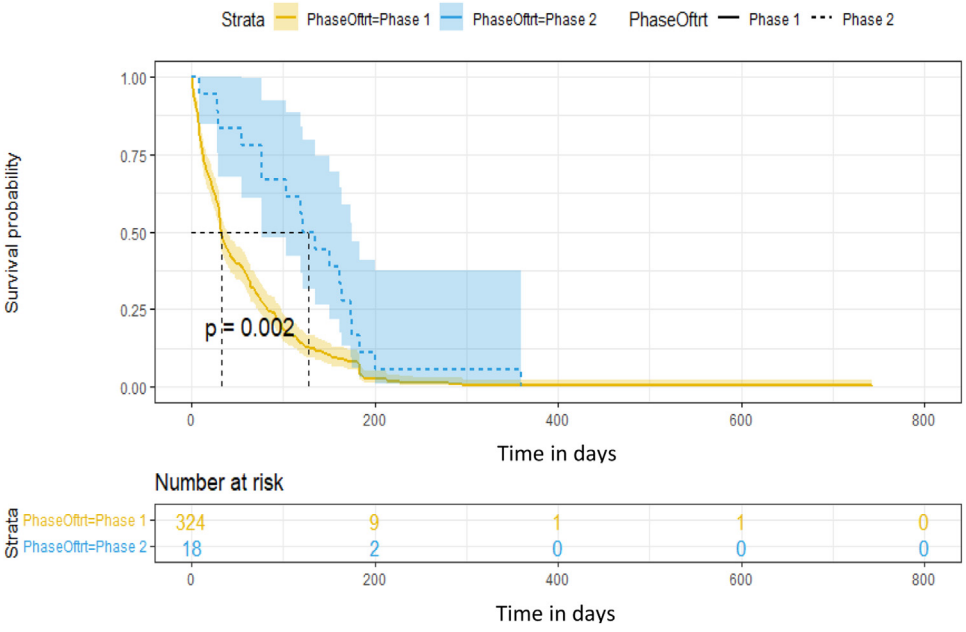


Figure 2. Survival probability plot between phases of treatment among patients who died

Table 2
Bivariate analysis of TB outcomes among demographic characteristics

Characteristics	Favorable outcome N=1369 (%)	Unfavorable outcomes N=423 (%)	P value
Sex:			0.381
Female	401 (29.3)	134 (31.7)	
Male	968 (70.7)	289 (68.3)	
Age category			<0.001
≤19 years	49 (3.6)	22 (5.2)	
20 – 59 years	1180 (86.2)	105 (24.8)	
≥ 60 years	140 (10.2)	296 (70.0)	
Occupation category			0.506
Employed non-mine workers	317 (23.2)	90 (21.3)	
Mine worker	438 (32.0)	130 (30.7)	
Unemployed	614 (44.9)	203 (48.0)	
Tuberculosis category			<0.001
Extrapulmonary TB	277 (20.2)	134 (31.7)	
Pulmonary TB	1092 (79.8)	289 (68.3)	
Phase of treatment			<0.001
Phase 1	767 (56.0)	390 (92.2)	
Phase 2	602 (44.0)	33 (7.8)	
Treatment contact			<0.001
Community Health Worker	177 (12.9)	97 (22.9)	
Family Member	674 (49.2)	213 (50.4)	
Friend	137 (10.1)	25 (5.9)	
Unreported	381 (27.8)	88 (20.8)	
Drug Resistance			0.018
Resistance	181 (13.2)	37 (8.75)	
Susceptible	1188 (86.8)	386 (91.3)	

patients in this age group could be explained due to influx of persons in search for better economic opportunities.

Unfavourable treatment outcomes were reported in 23.1% of the patients, which is higher than the 13.1% stipulated by the WHO [5]. This equates to a favourable outcome of 76.9%. This favourable rate is lower than the 95.1% and the 87.8% reported in Mozambique and Southeast Ethiopia respectively over a five year period [28,30]. An approximate rate to that in our study of 78.1% over five years was reported in Nigeria [26], and a lower pooled estimated rate of 74.4% from 13 European countries reported over 5 years [31].

Patients who were 60 years and above had a higher risk of unfavourable outcomes. Advanced age has been shown to be a significant risk factor for poor TB treatment outcomes [27,32–34]. A study in China specifically reported patients older than 60 years having up to four times the odds of unfavourable treatment outcomes compared to younger patients [27]. Older patients would be more susceptible to unwanted treatment outcomes such as treatment failure and death because of the gradual degeneration of their bodies including a waning immune system [34]. The lack of family support among older persons living on their own and the inability to access health services would enable treatment defaults and/or loss to follow-up [33].

Patients who were unemployed were observed to have a higher risk of unfavourable treatment outcomes. Similar findings have been reported internationally [35–37]. A six year retrospective study conducted in Thailand reported that unemployed pulmonary TB patients were about 3 times significantly more at risk of unsuccessful treatment outcomes [37]. Unemployed patients do not have a stable source of income, which is an indicator of poverty. Patients in our study with no

Table 3
Frailty Cox proportional hazard model for unfavourable TB outcomes

Characteristic	Hazard Ratio	(95% CI)
Age category		
<20yrs	reference	
20-59 yrs.	0.24	0.15 - 0.38
≥60 yrs.	2.81	1.82 - 4.33
TB Category		
Extrapulmonary	reference	
Pulmonary TB	0.57	0.47 – 0.70
Gender		
Female	reference	
Male	0.86	0.70 – 1.06
Treatment Contact		
Community health worker	reference	
Close relations	0.58	0.46 – 0.74
Employment status		
Employed	reference	
Unemployed	1.25	1.03 – 1.51
Phase of treatment		
Phase 1	reference	
Phase 2	0.13	0.09 – 0.19
Drug Resistance		
Resistance	reference	
Susceptible	1.93	1.36 – 2.74

stable source of income would probably not be able to afford nutrition to sustain TB treatment, which can lead to poor treatment adherence, or worse, dying from the side effects of the treatment. They also encounter challenges with funds for transport to treatment on a monthly basis, which leads to treatment defaulting.

An interesting finding in our study was that patients without drug resistant TB had almost twice the risk of unfavourable outcomes compared to patients with drug resistant TB. The treatment of drug resistant TB is complex, long, and can sometimes lead to treatment failure or in worse cases death when the treatment becomes too toxic [12,38]. Our findings are therefore contrary to other findings [39,40]. The explanation for these results could be because a majority of the patients in our study did not have drug-resistant TB [87.8%]. As such, most of the patients with unfavourable outcome were probably those without drug resistant TB.

Although more than 70% of our patients were diagnosed with pulmonary TB, they were shown to have a significantly decreased risk of unfavourable outcomes compared to those with extrapulmonary TB. Extrapulmonary TB is very complex to diagnose and most times there is a misdiagnosis or late diagnosis when the symptoms are already advanced [41,42]. Late diagnosis and/or misdiagnosis could explain our findings. Contrary to our findings a retrospective cohort study in Benin of the national TB program for one year showed that patients with pulmonary TB had significantly higher odds of treatment failure and death compared to those with extrapulmonary TB [43].

Death was recorded among 342 [83%] of 412 patients with unfavourable treatment outcomes. This finding is in line with several other studies conducted in sub-Saharan Africa in which death was reported as the most common unfavourable outcome [9,28,30,44]. It was observed that patients seemed to die at a faster rate during the initiation phase of TB treatment. Higher rate of death at the start of treatment could be due to late diagnosis, when the disease is already at an advanced stage. This would be common in the case of extrapulmonary TB, which is difficult to diagnose. The initiation phase of TB treatment is quite intense and could be harsh on some patients, especially on those with poor nutrition. Given that most patients in our population are unemployed, they probably lack the proper nutrition for their bodies to cope with the treatment. This could be another reason for the high death rate during this phase of treatment. The other reason could be side effects of the treatment considering that the immune system of such patients might have been too weakened by other comorbidities.

Our findings are not without limitations. Although data was collected by trained data captures and measures were taken to ensure data entry was as accurate as possible, this was a retrospective review of data from hospital records. As such, the reliability of the data cannot be 100% validated. Data on level of education, marital status, smoking, and alcohol consumption are socio-economic variables that were not available in patient's records. These could introduce bias when assessing risk factors associated with unfavourable conditions. A strength of our study was that we were able to obtain over 95% of all data with very minimal missing data. As such we can conclude that our finding of unfavourable outcomes seemed to occur across clinics in the Butha Buthe district and is useful for future TB programs in this district.

Conclusion and recommendations

To our knowledge, this is the first study evaluating unfavourable TB treatment outcomes and its associated risk factors in the mining district of Butha Buthe, Lesotho. Our study reports an unfavourable outcome rate higher than that set forth by the WHO. The study also revealed that patients 60 years and older are at a higher risk of unfavourable outcomes and that a majority of patients died during the initiation phase of the treatment. We therefore recommend that for TB treatment programs, older persons should be prioritized and be assigned a treatment contact that will follow up with them throughout the course of their treatment. Contact tracing should be intensified and scaled up to identify patients at risk and assess them for TB signs and symptoms. This would improve early diagnosis for prompt treatment and reduce death in the initiation phase of treatment. The follow up of patients on treatment should also be prioritized in the TB program. Community members should be trained as community health workers who will be dedicated to follow up with patients on treatment to reduce loss to follow up. From our findings, it is unclear how service delivery is organized and provided to patients who are unemployed. Further research on delivery of services would be advantageous in improving TB treatment programs for the unemployed.

Declarations

Ethical Approval: This study was approved by the Human Research Ethics Committee of Stellenbosch University, and the Ministry of Health Lesotho. Written permission was obtained from the health facilities. Data was analysed anonymously as patient identifiers were not collected

Author Contributions: V.D.N, M.R. and PSN.: conceptualization and study design; V.D.N., M.R., L.M., S.M., M.M. and R. R.: data acquisition. V.D.N, M.R, PSN and I.F: statistical analysis. N.V.D., M.R., I.F., M.O. and P.S.N: drafting of manuscript. V.D.N., M.R., I.F., M.O., J.D. and P.S.N. review and revision the manuscript. All authors read and approved the final version of the manuscript.

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Consent for publication: Not applicable

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