

Delay to initiate treatment is associated with unsuccessful treatment outcome among new pulmonary tuberculosis patients in Tigray, Northern Ethiopia: a follow up study

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Abstract

Background : Previous studies in Ethiopia indicated that tuberculosis (TB) patient's elapse long time before treatment initiation. However, there is very limited evidence on the association of delay to initiate treatment with treatment outcome. **Objective :** To investigate the association of time to treatment initiation delay with treatment outcomes of new adult TB patients in Tigray region of Ethiopia. **Methods :** We conducted a follow up study from October 2018 to April 2020 by recruiting 875 newly diagnosed Pulmonary Tuberculosis (PTB) patients from 21 randomly selected health facilities. Study participants were selected using simple random sampling technique during treatment initiation from October 1/2018 to October 30/2019. Delay to initiate treatment and treatment outcome were collected using standardized questionnaire and laboratory investigation. Adherence of TB patients to their treatment was collected using a 10 points linear visual analogue scale (VAS) at the end of treatment. The association of delay to initiate treatment with treatment outcome was modeled using log binomial regression model. Statistical significance was reported whenever p-value was less than 0.05. Data was analyzed using SPSS software version 21. **Result :** The median total delay to treatment initiation was 62 days with inter-quartile range of 16-221 days. A unite increase in a day to initiate treatment results in increment of risk of unsuccessful treatment outcome by 2.3. Other factors associated with unsuccessful treatment outcomes were being less adherent to the treatment, HIV co infection, being smear positive at initiation of treatment and after 2 months of treatment initiation. **Conclusion :** delay in a day to initiate treatment is associated with increased risk of unsuccessful treatment outcome. Any effort targeted towards reducing the negative effects of PTB should target on strategies that reduces the length of delay to initiate treatment and strengthen community engagement to improve treatment adherence of patients that have started treatment.

Introduction

In 2018, an estimated 10 million people developed TB disease and 8.6% of these individuals were HIV positive. In the same year there were about half a million new cases of rifampicin-resistant TB and 78% of them were multidrug-resistant TB (1). In 2019 there were 161,000 new TB cases, 27,000 deaths and 1,600 drug resistant TB cases making Ethiopia one of the 30 high-TB -burden countries (2).

To halt the burden attributable to TB, WHO developed the End TB Strategy which includes ending the TB epidemic by eliminating catastrophic expenses due to TB, reducing deaths by 95% and by attaining 90% reduction in the incidence TB by 2035 (1, 3). Early detection of TB cases and initiating treatment for the detected cases are main pillars for the End TB strategy (4). Nonetheless, patients elapse very long time to initiate care for their illness and to start treatment in different parts of the world (5–7) and in Ethiopia (8–10). For example median number of days to initiate treatment is 60 days in Tigray (11, 12), 97 days in Bale (13) and 64 days in Addis Ababa (10). Delayed treatment intuition results in more serious clinical illness, increased length of infectiousness and poor treatment outcomes including mortality and drug resistance (14, 15). The increased length of infectiousness also increases disease transmission within the community and creates a favorable condition for TB epidemic (9, 15). In contrast to these findings, in

Israel successful treatment outcome was not associated with patient delay and health system delay to initiate treatment (16).

Achieving high treatment success enables to reduce TB related mortality, prevalence of drug resistant TB and transmission of TB in the community (2). In the year 2017 successfully treated TB cases globally was 85% and it was 89% in Ethiopia (2, 17). However, compared to the treatment success, cure rates of TB patients is still low at 81% in Ethiopia which ranges from 38–92% in different parts of the country (18)

In previous studies patient related, socio-demographics, lifestyle and behavioral, clinical, and bacteriologic profile were significantly associated with unsuccessful TB treatment outcomes (19, 20). Despite of the long time elapsed to initiate TB treatment and poor treatment outcomes in different parts of Ethiopia, there is very limited evidence that investigated the effect of delay to initiate treatment on the outcome of TB treatment provided to the TB patients. This study investigated association of delayed treatment initiation with treatment outcomes of TB patients. Findings from this study will be an evidence for program people in designing interventions that reduce new TB infection and improve treatment success.

Methods And Materials

Study setting

Tigray is one of the nine Regional States of Ethiopia with an estimated 5.3 million population (21). There are 712 health posts, 214 health centers and 38 hospitals (1 specialized hospital, 15 general hospitals, 22 primary hospitals) in the region. The study was conducted in 21 health facilities (five hospitals and 16 health centers) in two zones of Tigray, Northern Ethiopia. The two study Zones (Eastern and Mekelle) harbor an estimated 2 million people (21). During the data collection period almost all health facilities were providing directly observed short-course tuberculosis treatment by trained health workers (TB focal persons). The program was introduced in all hospitals, health centers and in most of the health posts (21).

Diagnosis and treatment of all forms of TB across Ethiopia has been based on the national TB control guidelines that specify case definitions, diagnostic and treatment standards (18). Thus all TB cases enrolled for this study were diagnosed using Genexpert, sputum smear microscopy or clinical signs aided with x-ray (18). The treatment regimens for all new adult cases of TB were treated with combination of Ethambutol(E), Rifampicin(R), Isoniazid(H) and pyrazinamide(Z) for the first two months (2ERHZ) followed by Rifampicin(R) and Isoniazid (H) combinations for the remaining six months (4RH) (18).

Study design, aim and period

A follow-up study with the aim of investigating the effect delayed treatment initiation of PTB on treatment outcome was conducted from October 2018 to April 2020 in 21 health facilities (five hospitals and 16 health centers) in Eastern and Mekelle zones of Tigray Regional State of Ethiopia that harbor an estimated 2 million people.

Reference population

All newly diagnosed PTB patients and initiated treatment in all health facilities in Tigray Regional State of Ethiopia.

Study population

All newly diagnosed PTB cases who initiated treatment from October 2018 to April 2020 in the 21 health facilities selected for the current study.

Inclusion criteria

All newly diagnosed PTB patients whose age is 18 years or more, with no previous treatment history of TB, were eligible for the study. All Patients who were diagnosed and initiated treatment within the study settings but moved to another place inside the study area were eligible. However; patients diagnosed and started treatment out of the study area but transferred in to the study area were not eligible.

Sample size and sampling technique

The sample size was computed using StatCalc program of Epi-Info at 95% significance level, 80% power, considering design effect of 1.5. This is assuming that a unit change in time to initiate PTB treatment results in increment of risk of unsuccessful treatment outcome by 2.02 (risk ratio) and 5.8% of the patients with unsuccessful treatment outcome (22), the required sample size at the end of the follow-up was 489. However, the sample size for assessing predictors of delay computed using 95% significance level, 80% power, expected frequency of exposure (visit to non-DOTS center) among controls of 43% and odds ratio (OR) 1.63 (11) with design effect of 1.5 and 4% non-response rate; provided a total of 875 new cases. Hence, the same cases were followed for the outcome; the larger sample of 875 was taken the final sample size.

The total sample size was proportionally allocated to each health facility based on the average number of TB cases reported by the facility in the previous 2 years. List of eligible patients extracted from daily list of TB patient clinic in each facility was used as our sampling frame to select study participants allocated to that facility (8, 15). Each TB patient's registration numbers of TB patients written on the TB registration book in clinical management was used in the random sampling process and the patients were recruited prospectively during treatment initiation. The number of patients selected from each health facility was obtained by dividing the number of study participants allocated to each of health facility to the total number of data collection time (one year).

Data collection

A structured questionnaire was used to collect the data which was adapted from tools used elsewhere (22–24) and standard TB register book (25). Besides, eligible cases were interviewed for socio-demographic, health care seeking, and lifestyle. The following data were also collected from the study participants:

Exposure and outcome data

The main exposure variable was delay to initiate treatment (total delay) measured by number of days elapsed between onsets of illness and time to initiation of anti-TB treatment. This delay was computed as a sum of patient and health system delay. The main outcome variable was treatment outcome which was ascertained based on standard definitions (26, 27). For the purpose of this paper this outcome was categorized as binary (favorable versus non-favorable outcome)

Treatment adherence data

was collected using a 10 points linear visual analogue scale (VAS) (ranging from 0%= no single dose taken; to 100%= no single dose missed) at the end month of treatment, where patients were asked 'How much of your prescribed TB medications have you taken until now in the course of your treatment?' The VAS method was chosen because I) it can be used to assess TB treatment adherence for the whole duration of anti-tuberculosis treatment rather than at a specific time. II) VAS was used to assess adherence to anti-tuberculosis treatment in another study conducted in the same study area, and was found to be accurate (29). Study participants with adherence level above 90% were considered as adherent based on the World Health Organization (WHO) adherence definition (30) and national guideline (27).

Clinical data

symptoms (respiratory symptoms, constitutional symptoms, or both), and the time duration from onset of symptom up to treatment initiation. Respiratory symptoms included dyspnea, hemoptysis, cough, or expectoration while constitutional symptoms included malaise, loss of appetite, weight loss, fatigue, fever, chills, chest pain or night sweats.

Laboratory investigation

Smear status of all study participants was determined. This was done during treatment initiation, 2nd and 6th month of treatment initiation. One spot sputum specimen (about 5 ml) was collected. Two direct smears were prepared from the specimens for Ziehl-Nielsen (Z-N) staining. The smear preparation and Ziehl-Nielsen (Z-N) staining were performed according to the standard operating procedure (25, 26).

Data quality and management

A total of 18 nurses with BSc degrees collected the data and 3 Senior BSc degree nurses supervised the field data collection process. These data collectors and supervisors were trained on the objectives of the study, the importance of the findings and on how to collect the data from study participants. The training also included description of questionnaire, interviewing techniques. Pretest was done at nearby health facilities not included in the study. The PI cross checked the interview for 10% of the study participants. Efforts were made to minimize recall bias by using local calendars listing main religious and national days to define the perceived date of onset of cough (TB symptoms) and time of first health seeking. The questionnaire was translated into regional language (Tigrigna) spoken by almost all residents in the study area.

Data analysis

Data was entered, cleaned and analyzed using SPSS software version 21 (29). The data were described using frequency, proportions, measures of location and dispersion (to calculate the mean and median. As total delay was not normally distributed; the data was transformed before analysis. During analysis delay was considered as continuous variable. Association between the exposure and outcome (unsuccessful vs successful) was determined by log binomial regression model. Accordingly, both simple and multiple log-binomial models were fitted to estimate crude and adjusted relative risk (RR) of the outcome variables. The goodness of fit of the model was assessed using Pearson chi-square and Deviance tests. In all the statistical tests, statistical significance was judged at $p < 0.05$.

Operational definitions

Total delay

is the time from the onset of TB symptoms to the first start of anti-TB treatment.

Treatment outcomes

were categorized into successful or favorable and unsuccessful or unfavorable treatment outcomes.

Successful treatment outcome

includes treatment completed with or without the evidence of cure.

Unsuccessful treatment outcome

includes treatment failure cases, patients who died and defaulted patients.

Cured

if he/she became smear or culture negative in the last month of treatment and on at least one previous occasion; including, a patient with a positive Xpert MTB/RIF test at baseline can be declared cured if a negative smear result is recorded at the end of treatment.

Treatment completed

if he/she completed treatment with resolution of symptoms (26).

Treatment failure

a patient, who becomes smear or culture positive at five months or later during treatment or harbors a multi-drug resistant (MDR) strain at any point of time during the treatment.

Died

a patient who died for any reason while he/she were on treatment for TB.

Defaulter

a defaulter is a patient who has been on treatment for at least four weeks (26).

Results

Socio-demographic, clinical characteristics and accessibility to health facilities of study participants

A total of 875 newly diagnosed adult pulmonary tuberculosis patients were enrolled from 16 health centers and 5 hospitals. The median age [inter-quartile range (IQR)] of the study participants was 35 (25–45) years, 58.1% were males, and 54.5% were from urban areas. Regarding to educational status, 390 (47.5%) were lower than secondary school, 314 (39.9%) were secondary school and the remaining 93 (12.6%) college and above. Participants with 28.7% and 26.6% had a BMI of below 18 and below 16, respectively. Similarly, 39.6% had MUAC below 220mm and 23.5% had MUAC measurement of below 200mm. Among the study participants 57% were living within the distance of less than 10KM from the nearest health facility.

Tuberculosis treatment initiation delay

The median total delay of the study participants were 62 days with inter-quartile range of 16–221 days. The mean total delay of the study participants were 125 ± 256 (sd) days. TB patients with age of more than 45 years old had the highest median delay to initiate TB treatment compared to the other age groups. Similarly, rural residents, house wives and those TB patients who made more than one visit to health facility had higher median time of delay to initiate TB treatment compared to their counter parts. Furthermore; TB patients with MUAC measurement of lower than 200mm and who traveled for more than 10 KM had delayed longer to initiate TB treatment (Table 1).

Table 1
 median delay results of the different delay categories among TB cases in two zones of Tigray, Northern Ethiopia, 2020

Variable		Patient delay		Health system delay		Total delay	
		Median	p value	Median	p value	Median	P value
Sex	Male	30	0.854	17	0.669	62	0.854
	Female	30		20		62	
Age	18–25	30	0.007	9	0.474	46	0.007
	26–44	30		19		62	
	>45	35		25		73	
HIV result	Positive	30	0.554	19	0.81	63	0.6
	Negative	30		22		54	
Residence	Urban	22	0.000	11	0.000	33	0.000
	Rural	72		33		117	
Marital status	Single	30	0.000	8	0.004	46	0.000
	Married	57		21		67	
	Divorced/Widowed	30		31		73	
Educational status	Lower than secondary school	30	0.053	21	0.008	65	0.053
Occupation	Secondary	31		9		68	
	College and above	30		7		41	
	Farmer	30	0.001	22	0.01	69	0.001
	Housewife	35		23		72	
	Employed	28		14		64	
	Daily laborer	30		14		42	
	Student	23		5		33	
	Unemployed	30		25		65	
First action taken	Visited HF	30	0.000	16	0.000	52	0.000
	Other actions ^a	51		24		118	

^aself treatment, consult traditional healer, used holy water

Variable		Patient delay		Health system delay		Total delay	
		Median	p value	Median	p value	Median	P value
Distance to the nearest health facility	≤ 10km	28	0.2	16	0.244	58	0.115
	> 10km	34		22		67	
Knowledge on TB	Poor	30	0.892	16	0.8	62	0.1
	Good	29		18		62	
Visited > 1HCF	Yes	40	0.000	32	0.000	63	0.000
Distance to the nearest health facility (in KM)	No	23	0.000	12	0.000	30	0.000
	≤ 10	23		12		58	
	> 10	40		25		67	
MUAC (in MM)	> 220	47	0.000	23	0.000	52	0.000
	200–220	30		7		64	
	< 200	40		32		74	

^aself treatment, consult traditional healer, used holy water

Association of treatment initiation delay with TB treatment Outcomes

Overall, 797(91.1%) study participants had successful treatment outcome (cured and treatment completed) and 78 (8.9%) study participants had unfavorable treatment outcome (treatment failure, death and defaulter) (Fig. 1). The overall cure rate and treatment complete was 69.2% and 21.9%, respectively. On the other hand, 5.5% of TB patients were died and 2.3% with treatment failure. TB patients with successful treatment outcome had initiated treatment with a median delay of 54 days with 31 to 71(IQR) whereas TB patients with unsuccessful treatment outcome had initiated TB treatment after a median delay of 256 days with 112 to 264 (IQR).

Regarding treatment adherence, from the total 875 study participants, treatment adherence was measured for 94.4% (817/875) and treatment adherence was not documented for the remaining 58 study participants. Seven hundred seventy three (94%) study participants had complete treatment adherence or adherent above 90%, while the remaining 45 (6%) had incomplete treatment adherence or non-adherent.

The result of log binomial regression model showed that a unite increase in a day to initiate treatment results in an increase of risk of unsuccessful treatment outcome by 2.3 (Adjusted relative risk (ARR) = 2.3, 95% CI; 1.32–3.38) (Table 1). Being non-adherent to treatment, (ARR = 2.1,95% CI; 1.18–2.94), HIV co-

infection (ARR = 2.5,95% CI; 1-5.8), being smear positive at initiation of treatment (ARR = 3.6,95% CI; 1.2–10.7), being smear positive after 2 months of treatment initiation (ARR = 5.7,95% CI; 2.7–18.5) and being secondary school (ARR = 2.1, 95% CI;1.14–4.33) are significantly associated with higher risk of unsuccessful treatment outcomes.

Table 1

Associations of treatment initiation delay with risk of attaining unsuccessful treatment outcomes among newly diagnosed PTB patients in selected health facilities of Tigray, Northern Ethiopia (n = 875)

Measures of Effect	Treatment success		Risk ratio(95% Confidence Interval)
	Successful	Unsuccessful	
Crude effect	797	78	3.4(2.69–4.17)
Partially adjusted effect	797	78	2.4(1.36–3.43)
Fully adjusted effect	797	78	2.3(1.32–3.38)
*adjusted for Treatment adherence, Residence, Education, HIV status, Forms of TB; ; **adjusted for Treatment adherence, Residence, Education, HIV status, Forms of TB, Smear status after 2 months, X-ray cavitations, Age, Distance to health facility(KM) ; + the reported figures are numbers			

Table 2

Associations of selected characteristics and risk of attaining unsuccessful treatment outcomes among newly diagnosed PTB patients in selected health facilities of Tigray, Northern Ethiopia (n = 875)

Variables	Categories	Treatment success		Crude Relative Risk (CRR)	Adjusted Relative Risk (ARR)
		Successful	Unsuccessful		
Treatment adherence score	Non-adherent	37	8	2.1(1.18–2.94)	2.4(1.26–3.51)*
	Adherent	760	21	1.00	1.00
Age	18–25	211	17	0.63(0.34–1.2)	1(0.37–2.8)
	26–44	360	32	0.69(0.41–1.2)	0.5(0.21–1.2)
	≥ 45	226	29	1.00	1.00
Education	Lower than secondary school	390	27	2.1(0.85–7.1)	4.1(0.45–36)
	Secondary school	314	35	3.8(1.2–11.7)	2.1(1.14–4.33)*
	College and above	93	16	1.00	1.00
Residence	Rural	338	61	4.9(2.8–8.5)	1.9(0.81–4.5)
	Urban	459	17	1.00	1.00
HIV status	Positive	86	13	1.7(0.88–3.1)	2.5(1–5.8)*
	Negative	711	65	1.00	1.00
Forms of TB	Smear positive	251	69	16.7(8.2–33.9)	3.6(1.2–10.7)*
	Smear negative	546	9	1.00	1.00
Smear status after 2 months	Positive	19	15	9.8(4.8–19)	5.2(2.7–18.5)*
	Negative	778	63	1.00	1.00
X-ray cavitations	Present	327	71	14.6(6.6–32.1)	2.1(0.59–7.1)
	Absent	470	7	1.00	1.00
Distance to health facility	≤ 10	459	40	0.78(0.49–1.24)	0.75(0.44–1.29)
	> 10	338	38	1.00	1.00

Discussion

In this cohort study we have investigated treatment initiation delay and its association with TB treatment outcome of PTB patients. Hence, here listed below are the main discussion points from the follow up study summarized under two subthemes as association of treatment initiation delay with treatment outcome and other factors affecting treatment outcome.

Association of treatment initiation delay with TB treatment outcome

A unite increase in a day to initiate treatment results in increment of risk of unsuccessful treatment outcome. This finding is in line with studies from Ethiopia (24) and China (30). The reason for increased risk of unsuccessful treatment outcome with increasing the time to initiate TB treatment could be (i), those TB patients might have severe clinical presentation which is a previously reported predictor of unsuccessful treatment outcomes (14). In this study, those who had not delayed initiating treatment and those who have initiated treatment after a delay of 30 to 60 days had 4% and 17% lower risk to develop severe clinical presentation compared to those who have initiated treatment after two and more months (15). (ii), studies had indicated that none formal medication sources (traditional medication, prescribed and self-treatment) are associated with delayed treatment initiation which might lead to poor treatment outcome (8). In the current study, the majority (64.8%) of the cases had visited at least two times until the actual diagnosis of TB is made at which time both self and prescribed medicines had been used (8).

Other factors associated with TB treatment outcome

In the current study HIV co-morbidity increase risk of unsuccessful outcome which is similar with other studies in Ethiopia (24, 31, 32). The increased risk of unsuccessful outcome among the HIV co infected could be due to the complex and overlapping drug interactions, toxicities, and TB-associated immune reconstitution inflammatory syndrome (33). Furthermore, this increased risk might also be associated with lower uptake of TB/HIV collaborative interventions.

Being smear positive at initiation of treatment is associated with higher risk of unsuccessful treatment. This study result is supported by previous reports in Ethiopia (20) and elsewhere (34). This might be due to the reason that patients with smear-positivity have more advanced disease which leads to lower tuberculosis treatment response. This might also be due to the heavy initial bacillary load which is associated with delay in smear conversion leading to treatment failure and death (35).

Similar to other studies in Ethiopia (36, 37) and elsewhere (35) being smear positive after 2 months of treatment initiation was associated with poor treatment outcome. This could be related with patient attitude and behavior towards the disease (36). Patients may feel better and assume they are cured by the subsidence of symptoms after completing the initiation phase. On the other hand, patients may also loss interest in continuing treatment if symptoms persist and no improvements are seen after the initial phase of treatment. The other reason might be related with partly emergence drug resistance.

But this research had limitations like measurement of the exposure relied on patient self-report which is liable to recall bias. However, we tried to minimize this bias through interviewing patients soon after diagnosis and helping them to recall using local events like national holidays, religious days, and dates of some events. Second, we studied only new PTB and adult cases so that the findings cannot be generalized to all forms of TB cases among all age groups. On the other hand, relatively large sample, geographic coverage (include all levels of the health care system), reduced selection bias through random enrolment, able to measure treatment adherence, being prospective design, direct estimation of risk and use of standard outcome ascertainment could be mentioned as strength of the study. Therefore, the study is valid and could be applied to new TB cases in similar settings.

Conclusion And Recommendation

Patients experience long time to initiate treatment in Tigray, northern Ethiopia. A unite change in a day to initiate TB treatment is associated with increased risk of unsuccessful treatment outcome. Similarly, patients with poor treatment adherence, being HIV positive, being smear positive at initiation of treatment, being smear positive after 2 months of treatment initiation and being or completed secondary school independently predicted higher risk of unsuccessful treatment outcomes. Hence, multiple interventions are needed to halt the long time taken to initiate treatment like health education about TB, making those advanced diagnostic tools more accessible to the local community mainly to the rural areas, introducing universal screening for those who have cough regardless of the time of cough starts. Delayed treatment initiated TB patients should be identified early or during treatment initiation and should be closely monitored throughout the course of treatment. Community engagement in the treatment package of direct observed treatment strategy (DOTS) to improve tuberculosis patients' treatment adherence. Further study is needed on the role of this long delay on emergence of drug resistance and the mechanisms or interventions needed to halt this high rate of unsuccessful treatment outcome.

Abbreviations

TB.....Tuberculosis

PTB.....Pulmonary Tuberculosis

WHO.....World Health Organization

HIV..... human immunodeficiency virus

MUAC..... Mid-Upper Arm Circumference

RIF..... Rifampicin

RR.....Relative Risk

Declarations

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Authors' contributions

KT wrote the proposal, participated in data collection and drafted the manuscript. AM, GB, GM and NB commented the proposal with great revisions, participated in data analysis and revised drafts of the manuscript. All Authors revised and approved the final manuscript.

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Availability of data and materials

All data is contained in the manuscript and other raw data will be provided to readers upon the request to the corresponding author.

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Research and Ethical Committee of Addis Ababa University, Aklillu Lemma Institute of Pathobiology. A formal permission letter was also obtained from the regional health bureau of Tigray to the selected district health office. Each health facility selected for the study was contacted with a permission letter from the district health office. Each case diagnosed as TB according to the national guideline was consented in a written form before the interview. To assure confidentiality interview with TB case was held in a private room and the information collected was recorded anonymously. All patients were treated according to the national guideline and there was no any interference during the treatment.

Consent for publication

Not applicable.

Competing interests

There is no financial and non-financial conflict among the authors.

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Figures

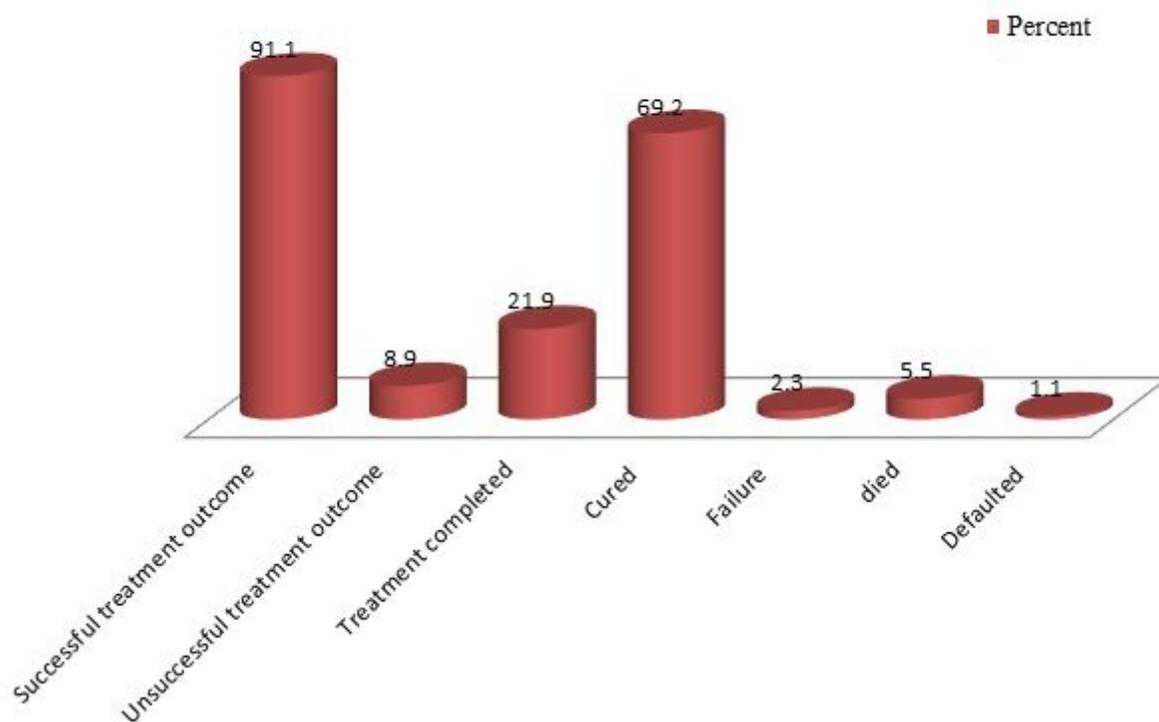


Figure 1

Treatment outcome of pulmonary tuberculosis patients attending in selected health facilities of two zones of Tigray, Northern Ethiopia, April 2020 (n=875)