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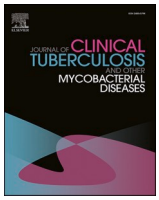

High variability in tuberculosis treatment outcomes across 15 health facilities in a semi-urban area in central Ethiopia

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ABSTRACT

Background: Despite reported tuberculosis (TB) treatment success rate of 86%, TB remains a leading cause of death in Ethiopia. We investigated patient and provider-specific factors associated with unfavorable treatment outcomes in Ethiopian health facilities providing TB care.

Methods: Data on characteristics and treatment outcomes of patients registered for TB treatment at 15 public health facilities (4 hospitals and 11 health centres) were collected from clinic registers. Proportions of unfavorable outcomes (defined as deaths, loss-to-follow-up [LTFU] and treatment failure), were compared across facilities using multivariable logistic regression, with separate analyses for death and LTFU.

Results: Among 3359 patients (53.5 % male, median age 28 years, 19.6 % HIV-positive), 296 (8.8 %) had unfavorable treatment outcome. Proportions of unfavorable outcomes across facilities ranged from 2.0 % to 21.1 % (median 8.3 %). Median proportions of death and LTFU among facilities were 3.3 % (range 0–10.9 %) and 2.6 % (range 0.6 %-19.2 %), respectively. Three facilities had significantly higher rates of LTFU, whereas two facilities had higher rates of death. The two facilities with full-time TB-nurses had higher proportions of successful outcomes (95.2 % vs 90.1 %, adjusted odds ratio 2.27, $p < 0.0001$).

Conclusion: Substantial variability of TB treatment outcomes was observed across the assessed health facilities providing TB care, independently of age and HIV co-infection, reflecting possible differences in service structure and related quality of care.

1. Introduction

In 2021, an estimated 10.6 million new cases of tuberculosis (TB) and 1.6 million TB-related deaths occurred globally [1]. The World Health Organization (WHO)'s End TB Strategy promotes adherence support and directly observed treatment to improve individual patient outcomes, as well as to minimize emergence of drug resistance and interrupt transmission. Standardized reporting of treatment outcomes is recommended for monitoring of TB program performance [2]. Both adherence support and treatment monitoring is challenging, especially in low-resource settings [3]. While patient-level risk factors for unfavorable treatment outcomes have been identified [4], patterns of health care delivery and relationships between health providers and patients could also influence TB treatment outcomes [5].

Ethiopia, with a population of around 100 million and 143 000 new TB cases annually, is one of the 15 countries with the highest number of TB cases in the world. In 2021, the reported TB treatment success rate in Ethiopia was 86 %, higher than the average among low-income, high-burden countries [1]. In the last decade, the Ethiopian TB prevention and control program has been updated based on the WHO's End TB strategy [2]. Previous studies of TB treatment outcomes in Ethiopia have identified higher age, HIV co-infection and previous treatment for active TB to be associated with unfavorable treatment outcome [6–10]. Furthermore, variations in TB treatment outcomes related to geographical location, residential area, or type of health facility have been observed in several studies from Ethiopia [8–12].

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In this study, we aimed to assess differences in rates of adverse TB treatment outcomes across health facilities providing outpatient TB care in a semi-urban area in Central Ethiopia, and to explore factors that might explain such differences.

2. Methods

2.1. Study setting and design

This study was a register based cohort study of patients undergoing treatment for active TB at 15 public health facilities (4 hospitals and 11 health centres) providing TB care in the Oromia region, Central Ethiopia. All health facilities are located in towns along the commercial route connecting Addis Abeba to Djibouti [13]. Patients receiving care at the following urban facilities were included: in Adama (ca. 300.000 inhabitants), Adama Hospital and 7 health centres; in Bishoftu (ca. 100.000 inhabitants) one zonal hospital and one health center; in Mojo (ca 50.000 inhabitants) one district Hospital and one health center; in Welenchiti (ca 20.000 inhabitants) one district Hospital and one health center.

At both hospitals and health centres, nurses are in charge of TB care [14].

All patients initiating treatment for active TB between September 2015 and September 2018 were included. Individuals with confirmed drug-resistant TB are managed at separate departments and were not considered for this study. Patients with transfer of care to facilities not included in the study were also excluded. Study data were collected from registers kept at each facility, containing information on age, sex, residence, clinical TB manifestation, results of sputum microscopy and Gene Xpert MTB/RIF testing (for pulmonary TB), previous TB treatment history, start date of anti-TB treatment (ATT), HIV test result and treatment outcome.

Data from the TB registers were directly entered into an encrypted REDCap database (https://www.project-redcap.org) [15], hosted by Armauer-Hansen Research Institute (AHRI), Addis Ababa, Ethiopia.

Study outcomes were based on the WHO definitions [16], with the following exceptions: cases with recorded transfer of care were not considered, and cases with no assigned treatment outcome as well as those having lost at least two consecutive months of therapy were defined as loss to follow-up (LTFU). Unfavorable treatment outcome was defined as a composite of death, LTFU and treatment failure. TB manifestations were categorized following the National TB Program (NTP): smear-positive pulmonary TB (PTB+), smear-negative pulmonary TB (PTB-), and extrapulmonary TB (EPTB) [14].

2.2. Statistical analysis

Descriptive statistics using proportions were presented. The primary outcome was unfavorable treatment outcome, with death and LTFU as secondary outcomes. To test the over-all heterogeneity of outcomes across health facilities, Chi2 tests were performed pairwise for unsuccessful outcome, LTFU and death compared with successful outcome. The following independent variables were analyzed for association with these outcomes: age, sex, TB manifestation, previous TB treatment, HIV serostatus and specific health facility, using *Hospital facility A* as reference facility. Univariable associations were described using odds ratios (OR) and 95 % confidence intervals (CI). For each outcome, univariate associations with p-value < 0.20 were entered into a primary multivariable logistic regression. For each outcome, a secondary multivariable logistic regression model was created using structured backward elimination discarding variables with p-values > 0.05. For unfavorable treatment outcome, a separate model was constructed with full-time TB nurse at the TB clinic replacing the health facility variable.

The extent and pattern of missing data were also analyzed to detect indicators of bias, and cases were excluded from multivariable analysis only if they lacked data on variables included in each respective model. P-value < 0.05 was considered statistically significant. Statistical analysis was performed in R statistics software, version 3.5.1 [17].

2.3. Ethical considerations

Ethical approval was obtained from the Ethical Review Committees at AHRI and the Oromia Regional Health Bureau (ORHB), both in Addis Ababa, Ethiopia.

3. Results

3.1. Participant characteristics

During the study period, 3545 persons initiating treatment for active TB were identified from TB registers. Of those, 186 had registered transfer of care to other districts and were excluded from analysis. The hospitals and health centres had a total of 889 cases (median 226, range 46–390) and 2470 cases (median 213, range 34–470), respectively (Table 1). Two hospital facilities had full-time TB nurses.

Participant characteristics are shown in Table 2. The median age was 28 years (quartiles 22–40 years), 241/3506 (6.9 %) were aged < 15

Table 1
Description of the health facilities included in the study.

Health facility	Type	Full-time TB Nurse	ART clinic Available	Cases included in the analysis	Successful Treatment Outcome (%)
Hospital facility A	Hospital	yes	yes	390	367 (94.1)
Hospital facility B	Hospital	yes	yes	357	344 (96.4)
Hospital facility C	Hospital	no	yes	96	88 (91.7)
Hospital facility D	Hospital	no	yes	46	40 (87.0)
Health centre A	Outpatient clinic	no	yes	470	371 (78.9)
Health centre B	Outpatient clinic	no	yes	354	330 (93.2)
Health centre C	Outpatient clinic	no	yes	306	300 (98.0)
Health centre D	Outpatient clinic	no	yes	244	238 (97.5)
Health centre E	Outpatient clinic	no	yes	221	198 (89.6)
Health centre F	Outpatient clinic	no	no	213	189 (88.7)
Health centre G	Outpatient clinic	no	no	193	172 (89.1)
Health centre H	Outpatient clinic	no	yes	181	166 (91.7)
Health centre I	Outpatient clinic	no	yes	153	143 (93.5)
Health centre J	Outpatient clinic	no	no	101	86 (85.1)
Health centre K	Outpatient clinic	no	no	34	31 (91.8)

ART; Antiretroviral therapy. MC; Medical College. HC; Health Centre.

Table 2
Descriptive comparison of successful and unsuccessful treatment outcome; death, loss to follow up.

Characteristics	Successful N (%)	Unsuccessful N (%)	Dead N (%)	Loss to Follow up N (%)
Sample size	3063 (91.2)	296 (8.8)	102 (3.0)	178 (5.3)
Gender				
Male	1580 (89.9)	177 (10.1)	54 (3.1)	110 (6.3)
Female	1446 (92.6)	115 (7.4)	46 (3.0)	66 (4.3)
Unreported	37 (90.2)	4 (9.8)	2 (4.9)	2 (4.9)
Age group (years)				
0–4	56 (87.5)	8 (12.5)	1 (1.6)	7 (11.0)
5–14	162 (94.2)	10 (5.8)	4 (2.3)	5 (2.9)
15–24	841 (92.0)	73 (8.042)	8 (0.8)	58 (6.2)
25–44	1423 (92.1)	122 (7.9)	44 (2.9)	72 (4.6)
45–64	424 (87.8)	59 (12.2)	34 (7.0)	23 (4.8)
≥65	127 (86.4)	20 (13.6)	10 (6.8)	10 (5.0)
Unreported	30 (88.2)	4 (91.8)	1 (2.9)	3 (7.1)
HIV status				
Negative	2457 (92.8)	191 (7.2)	50 (1.9)	130 (4.9)
Positive	574 (86.5)	90 (13.5)	46 (6.9)	39 (6.0)
Unknown	32 (68.1)	15 (31.9)	6 (12.8)	9 (19.2)
TB type				
PTB+	1078 (90.9)	108 (9.1)	32 (2.7)	63 (5.3)
PTB-	768 (90.0)	85 (10.0)	39 (4.6)	45 (5.3)
EPTB	1210 (92.4)	99 (7.6)	31 (2.4)	66 (5.0)
Unreported	7 (63.6)	4 (36.4)	0	4 (36.4)
Treatment category				
New	2711 (91.8)	241 (8.2)	83 (2.8)	148 (5.0)
Relapse	163 (84.0)	31 (16.0)	9 (4.6)	16 (8.3)
Unreported	189 (88.7)	24 (11.3)	10 (4.7)	14 (6.6)
Study site		p < 0.0001	P < 0.0001	p < 0.0001
Hospital facility A	367 (94.1)	23 (5.9)	11 (2.8)	9 (2.4)
Hospital facility B	344 (96.4)	13 (3.6)	10 (2.8)	2 (0.6)
Hospital facility C	88 (91.7)	8 (8.3)	7 (7.3)	1 (1.0)
Hospital facility D	40 (87.0)	6 (13.0)	5 (10.9)	1 (2.2)
Health centre A	371 (78.9)	99 (21.1)	8 (1.7)	90 (19.2)
Health centre B	330 (93.2)	24 (6.8)	11 (3.1)	10 (2.8)
Health centre C	300 (98.0)	6 (2.0)	3 (1.0)	2 (0.7)
Health centre D	238 (97.5)	6 (2.5)	0 (0)	5 (2.1)
Health centre E	198 (89.6)	23 (10.4)	15 (6.8)	5 (2.3)
Health centre F	189 (88.7)	24 (11.3)	5 (2.0)	19 (8.8)
Health centre G	172 (89.1)	21 (10.9)	10 (5.2)	11 (5.8)
Health centre H	166 (91.7)	15 (8.3)	6 (3.3)	8 (4.5)
Health centre I	143 (93.5)	10 (6.5)	5 (3.3)	4 (2.6)
Health centre J	86 (85.2)	15 (14.8)	4 (4.0)	10 (9.9)
Health centre K	31 (91.2)	3 (8.8)	2 (5.9)	1 (2.9)

PTB+; Smear-positive pulmonary TB. PTB-; Smear-negative pulmonary TB. EPTB; Extrapulmonary tuberculosis. MC; Medical College. HC; Health Centre. P-values compare the distribution of unsuccessful outcome, LTFU and death pairwise against successful outcome using Chi-square tests.

years, 1871/3501 (53.4 %) were males. Two-hundred-three (5.7 %) cases were relapses, 683/3492 (19.6 %) were HIV-positive.

3.2. Factors associated with unfavorable treatment outcome

In total, 296 patients (8.8 %) had unfavorable treatment outcome: overall, 102 (3.0 %) died before completing treatment, 16 (0.4 %) were classified as treatment failure, and 178 (5.3 %) were LTFU. The median proportion of unfavorable treatment outcome was 8.3 % (range 2.0 % to 21.1 %) between health facilities, with statistically significant variability across facilities ($p < 0.0001$). For the 4 hospitals, the median proportion of unfavorable outcomes was 7.1 % (range 3.6 %-13 %), and for the 11 health centers the corresponding figures were median 8.8 % (range 2.0 %-21.1 %, Table 2) (Table 3).

In multivariable analysis, three health centres had significantly higher odds of unfavorable treatment outcome (Health Centre F: adjusted odds ratios [AOR] 2.29, 95 % confidence intervals [CI] 1.18–4.40; Health Centre J: AOR 3.40, 95 % CI 1.61–6.97; Health Centre A: AOR 4.93, 95 % CI 3.06–8.28, Table 4), whereas one facility had significantly lower odds of unfavorable outcome (AOR 0.34, 95 % CI 0.11–0.85). The two health facilities with a full-time TB nurse had significantly higher success rate compared to facilities without full-time TB nurses (95.2 % vs 90.1 %, AOR 2.27, 95 % CI 1.58–3.35, $p < 0.0001$, Supplementary Table 1).

Moreover, age categories 45–64 years (AOR 1.96, 95 % CI 1.36–2.79) and > 65 years (AOR 2.40, 95 % CI 1.31–4.22) compared to ages 25–44 years had higher risk of unfavorable outcome. Previous TB treatment (AOR 1.83, 95 % CI 1.15–2.84) and HIV co-infection (AOR 2.29, 95 % CI 1.67–3.11) were also significantly associated with unfavorable treatment outcome.

3.3. Factors associated with death

Overall, 102 deaths were reported, with a median proportion of 3.3 % between facilities (range 0–10.9 %). Significant variability across facilities was observed ($p < 0.0001$). In multivariable analysis, two health facilities had significantly higher proportions of reported deaths (Hospital facility D: AOR 3.95 95 % CI 1.02–12.77; Hospital facility C: AOR 2.75, 95 % CI 0.96–7.42). Furthermore, HIV co-infection (AOR 3.70, 95 % CI 2.36–5.80), age categories 45–64 years (AOR 2.93 95 % CI 1.79–4.76) and ≥ 65 years (AOR 2.94, 95 % CI 1.21–6.39) compared to 25–44 years (Table 5) were significantly associated with death, whereas age category 15–24 years had lower rates of death (AOR 0.41, 95 % CI 0.17–0.89), Table 5). Of note, patients with HIV co-infection accounted for 46/96 (47.9 %) of deaths.

3.4. Factors associated with LTFU

Proportions of LTFU ranged between 0.6 % and 19.2 % between health facilities (median 2.6 %, $p < 0.0001$). In multivariable analysis, proportions of LTFU were significantly greater at three health facilities (Health Centre A: AOR 10.12, CI 5.26–21.99; Health Centre J: AOR 5.07, 95 % CI 1.97–13.22 and Health Centre F: AOR 3.68, 95 % CI 1.59–8.99). Furthermore, age category 15–24 years (AOR 1.65, 95 % CI 1.11–2.45) compared to 25–44 years of age, and HIV co-infection (AOR 1.79, 95 % CI 1.18–2.68, Table 5) were associated with LTFU.

4. Discussion

In this study, we found considerable differences in TB treatment outcomes between fifteen different public health facilities in an uptake area in Central Ethiopia. These differences remained significant after controlling for HIV serostatus and age, factors known to influence treatment outcomes.

Overall, 91.2 % of patients treated at these facilities had successful treatment outcomes, in line with a recent mapping of TB treatment outcomes in Ethiopia [18], thus meeting the 90 % target set by the WHO's End TB Strategy (1). However, we observed substantial variability in rates of unfavorable treatment outcomes, ranging from 2.0 % to 21.1 %. Importantly, the two facilities with full-time TB nurses (both hospitals) had significantly higher success rates (96.4 % and 94.1 %), compared to a median of 90.1 % among facilities where the nurses responsible for TB care were also involved in other clinical activities. This observation should not necessarily lead to the conclusion that every primary care facility must have dedicated, full-time nurses. However, it suggests that the intensity and specificity of the service provided contributes to the achievement of favorable treatment outcomes, and should prompt the assessment if sufficient qualified staff capable of providing

Table 3
Logistic regression model with successful and unsuccessful treatment outcomes, reporting adjusted OR and corresponding p-values. Crude OR of univariate analysis are also reported.

	Univariate analysis	Multivariable analysis, model 1		Multivariable analysis, model 2	
Characteristics	**Crude OR (95 % CI)**	**AOR (95 % CI)**	**P-value**	**AOR (95 % CI)**	**P-value**
Age group (years)					
<5	1.67 (0.72–3.38)	2.46 (0.89–5.75)	0.054	2.39 (0.87–5.53)	0.061
5–14	0.72 (0.35–1.33)	0.93 (0.42–1.82)	0.84	0.90 (0.41–1.76)	0.78
15–24	1.01 (0.75–1.37)	1.23 (0.87–1.75)	0.24	1.22 (0.86–1.72)	0.26
25–44	Ref	Ref		Ref	
45–64	1.62 (1.16–2.25)	1.95 (1.35–2.79)	0.00028	**1.96** (1.36–2.79)	**0.00025**
≥65	1.84 (1.08–2.99)	2.41 (1.30–4.24)	0.0034	**2.40** (1.31–4.22)	**0.0032**
Gender					
Male	Ref	Ref			
Female	0.71 (0.55–0.91)	0.82 (0.63–1.08)	0.16		
Clinical form					
PTB+	Ref	Ref			
PTB-	1.10 (0.82–1.49)	0.95 (0.67–1.33)	0.76		
EPTB	0.82 (0.61–1.09)	0.93 (0.67–1.29)	0.67		
Treatment category					
New cases	Ref	Ref		Ref	
Retreatment	2.14 (1.40–3.17)	1.75 (1.09–2.73)	0.018	**1.83** (1.15–2.84)	**0.0085**
HIV status					
Negative	Ref	Ref		Ref	
Positive	2.02 (1.54–2.63)	2.31 (1.69–3.14)	<0.0001	**2.29** (1.67–3.11)	**<0.0001**
Study sites					
Hospital facility A	Ref	Ref		Ref	
Hospital facility B	0.60 (0.29–1.19)	0.61 (0.29–1.25)	0.19	0.63 (0.30–1.28)	0.21
Hospital facility C	1.45 (0.59–3.23)	1.50 (0.60–3.40)	0.36	1.54 (0.62–3.51)	0.32
Hospital facility D	2.39 (0.84–5.90)	2.27 (0.72–6.03)	0.12	2.34 (0.74–6.19)	0.11
Health centre A	4.26 (2.69–7.00)	4.81 (2.98–8.09)	<0.0001	**4.93** (3.06–8.28)	**<0.0001**
Health centre B	1.16 (0.64–2.11)	1.19 (0.64–2.23)	0.58	1.23 (0.66–2.28)	0.52
Health centre C	0.32 (0.12–0.75)	0.39 (0.14–0.92)	0.045	**0.40** (0.14–0.94)	0.051
Health centre D	0.40 (0.15–0.94)	0.32 (0.11–0.81)	0.026	**0.34** (0.11–0.85)	**0.034**
Health centre E	1.85 (1.01–3.40)	1.61 (0.85–3.06)	0.14	1.63 (0.86–3.08)	0.13
Health centre F	2.03 (1.11–3.70)	2.26 (1.16–4.34)	0.015	**2.29** (1.18–4.40)	**0.013**
Health centre G	1.95 (1.04–3.62)	2.66 (0.56–9.35)	0.16	2.64 (0.56–9.28)	0.16
Health centre H	1.44 (0.72–2.81)	1.70 (0.84–3.38)	0.13	1.75 (0.86–3.46)	0.12
Health centre I	1.12 (0.50–2.34)	1.35 (0.59–2.88)	0.45	1.33 (0.59–2.84)	0.47
Health centre J	2.78 (1.37–5.51)	3.32 (1.57–6.82)	0.0012	**3.40** (1.61–6.97)	**0.00097**
Health centre K	1.54 (0.35–4.76)	1.37 (0.21–5.04)	0.69	1.41 (0.22–5.19)	0.65

PTB+; Smear-positive pulmonary TB. PTB-; Smear-negative pulmonary TB. EPTB; Extrapulmonary tuberculosis. MC; Medical College. HC; Health Centre.

proper care is equally distributed in all facilities to respond effectively to the burden of a given disease.

Two hospital facilities had significantly higher proportions of reported deaths among TB patients, although their rates of unfavorable outcome were similar to the reference category. This might reflect a selection bias, in which more severe TB cases were more likely to be retained for treatment as in-patients, instead of being transferred to other facilities as occurs in cases of less advanced TB disease. One health center (located in the same town as one of the two hospitals) had no recorded deaths and overall lower rates of unfavorable treatment outcome, thus strengthening the hypothesis that patients managed at hospital clinics were more likely to have more severe TB disease. Of note, these two hospitals had relatively low numbers of TB patients during the study period (96 and 46, respectively), and neither of them had a full-time TB nurse.

In accordance with most previous data, higher age was associated with mortality [19,20]. Furthermore, HIV co-infection was significantly associated with unfavorable treatment outcome, both for reported deaths and LTFU. This finding is in agreement with evidence from a recent review showing a 1.98 fold increase in unfavorable TB treatment outcome among people with HIV in Ethiopia [19]. Indeed, nearly half of recorded deaths occurred in people living with HIV, despite widespread access to antiretroviral therapy in this uptake area.

LTFU was observed in 5.3 % of cases, and this phenomenon was independently associated with specific health facilities after adjustment for HIV co-infection and age category. The occurrence of LTFU showed great variations across facilities, ranging from 0.6 % to 19.2 %. Our data sources did not allow control for other conditions that could influence LTFU, for example socio-economic conditions. The fact that three facilities in the uptake area had significantly higher rates of LTFU suggests that aspects of the provided TB care could underly these differences.

Irregular and/or interrupted treatment is often due to inadequate adherence to therapy. However, in turn, TB care provision characteristics can influence patient adherence. Factors related to the structure of care, such as workload and training of healthcare staff responsible for TB care, routines for patient education and availability of medical support for management of complications during treatment have been shown to impact long-term adherence [5]. In addition, other factors such as patient counselling and education, as well as regular follow-up visits have been linked to improved adherence [21].

Previous studies performed in Ethiopia have found associations between poor adherence and several other factors related to TB care provision, including lack of patient counseling, long outpatient waiting times, longer distance to TB clinics, untrained health personnel and poor management of treatment complications and comorbidities [22–26]. In a recent review inadequate adherence, defined as >10 % missed doses of TB drugs, was observed in 21 % of Ethiopian TB patients, with poor education, long clinic waiting times and greater distance from health facility as contributing factors [26].

To our knowledge, four previous studies have compared treatment outcomes between Ethiopian health facilities to identify structural barriers for successful TB care, apart from geographical and population differences [8,10–12]. However, only two of these studies adjusted for other factors known to influence treatment outcome (HIV co-infection, age, sex and residence), and three studies were restricted to patients treated up to 2013. Our study is one of the largest recent studies of TB

Table 4
Univariate p-value and logistic regression model comparing 102 cases of death with successful treatment outcomes, through adjusted odds ratios and corresponding p-values.

	Univariate	Multivariable analysis, model 1		Multivariable analysis, model 2	
Characteristics	**Crude OR**	**AOR (95 % CI)**	**P-value**	**AOR (95 % CI)**	**P-value**
Age group (years)					
<5	0.58 (0.03–2.72)	1.06 (0.06–5.35)	0.95	0.92 (0.05–4.52)	0.94
5–14	0.80 (0.24–2.00)	0.77 (0.18–2.23)	0.67	0.97 (0.29–2.51)	0.96
15–24	0.31 (0.13–0.62)	0.34 (0.11–0.81)	0.026	**0.41** (0.17–0.89)	**0.036**
25–44	Ref	Ref		Ref	
45–64	2.59 (1.63–4.10)	3.28 (1.97–5.46)	<0.0001	**2.93** (1.79–4.76)	**<0.0001**
≥65	2.55 (1.19–4.98)	3.29 (1.33–7.32)	0.0057	**2.94** (1.21–6.39)	**0.0099**
Gender					
Male	Ref	Ref			
Female	0.93 (0.62–1.39)	0.43	0.43		
Clinical form					
PTB+	Ref	Ref			
PTB-	1.71 (1.06–2.77)	1.38 (0.79–2.45)	0.26		
EPTB	0.86 (0.52–1.43)	1.11 (0.62–1.90)	0.73		
Treatment category					
New cases	Ref	Ref			
Retreatment	1.80 (0.83–3.47)	1.25 (0.53–2.61)	0.58		
HIV status					
Negative	Ref	Ref		Ref	
Positive	3.94 (2.61–5.94)	3.44 (2.14–5.55)	<0.0001	**3.70** (2.36–5.80)	**<0.0001**
Study sites					
Hospital facility A	Ref	Ref		Ref	
Hospital facility B	0.97 (0.40–2.33)	0.92 (0.36–2.31)	0.86	0.92 (0.36–2.28)	0.85
Hospital facility C	2.65 (0.95–6.94)	2.78 (0.96–7.61)	0.049	2.75 (0.96–7.42)	**0.049**
Hospital facility D	4.17 (1.26–12.10)	3.77 (0.96–12.47)	0.038	**3.95** (1.02–12.77)	**0.029**
Health centre A	0.72 (0.28–1.80)	0.81 (0.30–2.07)	0.66	0.81 (0.31–2.07)	0.67
Health centre B	1.11 (0.47–2.63)	1.29 (0.53–3.13)	0.57	1.24 (0.52–2.98)	0.63
Health centre C	0.33 (0.07–1.08)	0.42 (0.09–1.39)	0.19	0.42 (0.09–1.39)	0.19
Health centre D	0 (0–0.51)	NA		NA	
Health centre E	2.53 (1.15–5.75)	1.83 (0.77–4.42)	0.17	1.98 (0.85–4.68)	0.11
Health centre F	0.88 (0.27–2.46)	1.48 (0.45–4.31)	0.50	1.42 (0.43–4.08)	0.53
Health centre G	1.94 (0.79–4.69)	1.99 (0.10–13.31)	0.55	2.16 (0.84–5.47)	0.10
Health centre H	1.21 (0.41–3.23)	1.69 (0.56–4.67)	0.33	1.63 (0.54–4.48)	0.36
Health centre I	1.17 (0.36–3.27)	1.44 (0.44–4.18)	0.52	1.46 (0.44–4.20)	0.50
Health centre J	1.55 (0.42–4.66)	1.59 (0.34–5.47)	0.50	1.45 (0.32–4.94)	0.58
Health centre K	2.15 (0.32–8.49)	2.15 (0.11–12.41)	0.48	1.93 (0.10–10.91)	0.54

PTB+; Smear-positive pulmonary TB. PTB-; Smear-negative pulmonary TB. EPTB; Extrapulmonary tuberculosis. Medical College. HC; Health Centre.

treatment outcomes in Ethiopia and included nearly all public health facilities providing TB care in the uptake area. Although it was conducted in a mainly urban uptake area in central Ethiopia, we think that the finding of variations in TB treatment outcomes between facilities is a finding with relevance to other parts of this country, as well as to other settings in sub-Saharan Africa. While the comparison of outcomes across health facilities may reveal differences, the underlying mechanisms cannot be determined. Because the full-time TB nurses were found in the two hospitals with large patient volumes, it may be possible that other factors related to these facilities may have led to a more successful treatment outcome. Consequently, more studies directly addressing provision of TB care may identify targets for further improvement of TB care in Ethiopia.

Our study has some limitations. First, data collection was based on clinic registers, and both the quality and completeness of data may vary between facilities. Second, residual confounding cannot be excluded; for example, differences in socio-economic condition between patients treated at different facilities might explain some of the variations in outcomes observed. Moreover, despite the availability of Gene Xpert MTB/RIF testing in Ethiopia, several registered TB cases were not tested for drug resistance; therefore, it is plausible that unrecognized drug resistance could explain a proportion of unfavorable outcomes. Finally, we chose to consider patients without reported treatment outcome as being LTFU. It is possible that some of these persons had successful treatment outcome which was not recorded.

5. Conclusion

In this study, we found an overall high treatment success rate of 91.2 % among 15 facilities (4 hospitals and 11 health clinics) in central Ethiopia. However, considerable variations in proportions of unfavorable outcomes were observed, ranging from 2.0 % to 21 %, with specific facilities having significantly higher proportions of deaths and LTFU. Furthermore, the likelihood of successful treatment outcome was 2.27 times higher in facilities with full-time TB nurses compared to facilities where nurses had multiple assignments. The variability in treatment outcomes between different facilities in the same catchment area might reflect quality and intensity of TB care provision.

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CRediT authorship contribution statement

Giuseppe Zenatti: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Software, Visualization, Writing – original draft, Writing – review & editing. **Mario Raviglione:** Conceptualization, Supervision, Writing – review & editing. **Fregenet Tesfaye:** Project administration, Writing – review & editing. **Kidist**

Table 5
Univariate p-value and logistic regression model comparing 178 cases of LTFU with successful treatment outcomes using adjusted odds ratios and corresponding p-values.

	Univariate	Multivariable analysis, model 1		Multivariable analysis, model 2	
Characteristics	**Crude OR**	**AOR (95 % CI)**	**P-value**	**AOR (95 % CI)**	**P-value**
Age group (years)					
<5	2.47 (1.00–5.28)	3.55 (1.12–9.31)	0.017	2.70 (0.87–6.89)	0.055
5–14	0.61 (0.21–1.39)	0.87 (0.29–2.09)	0.78	0.79 (0.27–1.87)	0.62
15–24	1.36 (0.95–1.94)	1.60 (1.05–2.42)	0.027	**1.65** (1.11–2.45)	**0.013**
25–44	Ref	Ref		Ref	
45–64	1.07 (0.65–1.71)	1.26 (0.73–2.08)	0.39	1.12 (0.66–1.83)	0.67
≥65	1.56 (0.74–2.96)	2.06 (0.89–4.35)	0.073	1.87 (0.82–3.88)	0.11
Gender					
Male	Ref	Ref		Ref	
Female	0.66 (0.48–0.89)	0.72 (0.51–1.02)	0.070	**0.65** (0.46–0.91)	**0.013**
Clinical form					
PTB+	Ref				
PTB-	1.00 (0.67–1.48)				
EPTB	0.93 (0.65–1.33)				
Treatment category					
New cases	Ref	Ref			
Retreatment	1.80 (1.01–3.00)	1.62 (0.85–2.94)	0.12		
Negative	Ref	Ref		Ref	
Positive	1.28 (0.88–1.84)	1.67 (1.07–2.55)	0.020	**1.79** (1.18–2.68)	**0.0056**
Study sites					
Hospital facility A	Ref	Ref		Ref	
Hospital facility B	0.24 (0.04–0.93)	0.28 (0.04–1.13)	0.11	0.25 (0.04–0.96)	0.074
Hospital facility C	0.46 (0.02–2.51)	0.51 (0.03–2.87)	0.53	0.46 (0.02–2.51)	0.47
Hospital facility D	1.02 (0.05–5.63)	1.13 (0.06–6.48)	0.91	1.00 (0.05–5.60)	0.98
Health centre A	9.89 (5.18–21.38)	11.48 (5.79–26.17)	<0.0001	**10.12** (5.26–21.99)	**<0.0001**
Health centre B	1.24 (0.49–3.15)	1.15 (0.42–3.17)	0.78	0.99 (0.37–2.62)	0.98
Health centre C	0.27 (0.04–1.06)	0.33 (0.05–1.32)	0.16	0.28 (0.04–1.10)	0.11
Health centre D	0.86 (0.26–2.51)	0.73 (0.19–2.37)	0.62	0.68 (0.18–2.13)	0.53
Health centre E	1.03 (0.31–3.02)	1.10 (0.33–3.35)	0.87	1.00 (0.30–2.94)	1.00
Health centre F	4.10 (1.87–9.68)	3.98 (1.66–10.22)	0.0025	**3.68** (1.59–8.99)	**0.0028**
Health centre G	2.61 (1.06–6.58)	5.22 (0.73–23.79)	0.05	2.43 (0.96–6.26)	0.059
Health centre H	1.97 (0.73–5.23)	2.22 (0.80–6.16)	0.12	1.97 (0.72–5.27)	0.17
Health centre I	1.14 (0.31–3.56)	1.39 (0.36–4.49)	0.60	1.23 (0.33–3.87)	0.73
Health centre J	4.74 (1.86–12.28)	6.12 (2.32–16.64)	0.00025	**5.07** (1.97–13.22)	**0.00070**
Health centre K	1.32 (0.07–7.34)	1.53 (0.08–8.89)	0.69	1.33 (0.07–7.51)	0.79

PTB+; Smear-positive pulmonary TB. PTB-; Smear-negative pulmonary TB. EPTB; Extrapulmonary tuberculosis. MC; Medical College. HC; Health Centre.

Bobosha: Project administration, Writing – review & editing. **Per Björkman:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. **John Walles:** Conceptualization, Methodology, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] World Health Organization. Global tuberculosis report 2022. Geneva: World Health Organization; 2022.
[2] Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. Lancet 2015;385(9979):1799–801.
[3] Mesfin MM, Newell JN, Walley JD, Gessessew A, Tesfaye T, Lemma F, et al. Quality of tuberculosis care and its association with patient adherence to treatment in eight Ethiopian districts. Health Policy Plan 2009;24(6):457–66.
[4] Peetluk LS, Ridolfi FM, Rebeiro PF, Liu D, Rolla VC, Sterling TR. Systematic review of prediction models for pulmonary tuberculosis treatment outcomes in adults. BMJ Open 2021;11(3):e044687.
[5] Sabaté E, World Health Organization, editors. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003. 198 p.
[6] Gebrezgabiher G, Romha G, Ejeta E, Asebe G, Zemene E, Ameni G, et al. Treatment outcome of tuberculosis patients under directly observed treatment short course and factors Affecting Outcome in Southern Ethiopia: a five-year retrospective study. PLoS One 2016;11(2):e0150560.
[7] Tessema B, Muche A, Bekele A, Reissig D, Emmrich F, Sack U. Treatment outcome of tuberculosis patients at Gondar University Teaching Hospital, Northwest Ethiopia. A five - year retrospective study. BMC Public Health 2009;9(1). https://doi.org/10.1186/1471-2458-9-371.
[8] Getahun B, Ameni G, Medhin G, Biadgilign S. Treatment outcome of tuberculosis patients under directly observed treatment in Addis Ababa, Ethiopia. Braz J Infect Dis 2013;17(5):521–8. https://doi.org/10.1016/j.bjid.2012.12.010.
[9] Berhe G, Enquselassie F, Aseffa A. Treatment outcome of smear-positive pulmonary tuberculosis patients in Tigray Region, Northern Ethiopia. BMC Public Health 2012;12(1). https://doi.org/10.1186/1471-2458-12-537.
[10] Muñoz-Sellart M, Cuevas LE, Tumato M, Merid Y, Yassin MA. Factors associated with poor tuberculosis treatment outcome in the Southern Region of Ethiopia. 2010;7.
[11] Hamusse SD, Demissie M, Teshome D, Lindtjørn B. Fifteen-year trend in treatment outcomes among patients with pulmonary smear-positive tuberculosis and its determinants in Arsi Zone. Central Ethiopia Glob Health Action 2014;7:25382. https://doi.org/10.3402/gha.v7.25382.
[12] Muluye AB, Kebamo S, Teklie T, Alemkere G, Hasnain SE. Poor treatment outcomes and its determinants among tuberculosis patients in selected health facilities in East Wollega, Western Ethiopia. PLoS One 2018;13(10):e0206227.
[13] HIV Prevention in Ethiopia National Road Map. Federal HIV/AIDS Prevention and Control Office. 2018.
[14] National Guidelines for TB, DR-TB and Leprosy in Ethiopia, Sixth Edition. Federal Democratic Republic of Ethiopia Ministry of Health. 2018.
[15] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208.
[16] World Health Organization. Definitions and reporting framework for tuberculosis - 2013 revision (updated December 2014). 2014.

[17] R Core Team. R: A language and environment for statistical computing. [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2020. Available from: https://www.R-project.org/.
[18] Alene KA, Viney K, Gray DJ, McBryde ES, Wagnew M, Clements ACA. Mapping tuberculosis treatment outcomes in Ethiopia. BMC Infect Dis 2019 Dec;19(1):474. https://doi.org/10.1186/s12879-019-4099-8.
[19] Eshetie S, Gizachew M, Alebel A, van Soolingen D, Subbian S. Tuberculosis treatment outcomes in Ethiopia from 2003 to 2016, and impact of HIV co-infection and prior drug exposure: A systematic review and meta-analysis. PLoS One 2018; 13(3):e0194675.
[20] Cruz-Hervert LP, Garcia-Garcia L, Ferreyra-Reyes L, Bobadilla-del-Valle M, Cano-Arellano B, Canizales-Quintero S, et al. Tuberculosis in ageing: high rates, complex diagnosis and poor clinical outcomes. Age Ageing 2012;41(4):488–95.
[21] Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Infectious Diseases Group, editor. Cochrane Database of Systematic Reviews. 2015 May 29. https://doi.org/10.1002/14651858.CD003343.pub4.
[22] Nezenega ZS, Perimal-Lewis L, Maeder AJ. Factors influencing patient adherence to tuberculosis treatment in Ethiopia: a literature review. IJERPH 2020;17(15): 5626. https://doi.org/10.3390/ijerph17155626.
[23] Woimo TT, Yimer WK, Bati T, Gesesew HA. The prevalence and factors associated for anti-tuberculosis treatment non-adherence among pulmonary tuberculosis patients in public health care facilities in South Ethiopia: a cross-sectional study. BMC Public Health 2017 Dec;17(1). https://doi.org/10.1186/s12889-017-4188-9.
[24] Alipanah N, Jarlsberg L, Miller C, Linh NN, Falzon D, Jaramillo E, et al. Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. PLoS Med 2018;15(7):e1002595.
[25] Pradipta IS, Houtsma D, van Boven JFM, Alffenaar J-W, Hak E. Interventions to improve medication adherence in tuberculosis patients: a systematic review of randomized controlled studies. npj Prim Care Respir Med 2020;30(1).
[26] Zegeye A, Dessie G, Wagnew F, Gebrie A, Islam SMS, Tesfaye B, et al. Prevalence and determinants of anti-tuberculosis treatment non-adherence in Ethiopia: A systematic review and meta-analysis. PLoS One 2019;14(1):e0210422.