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Research article

The magnitude of unfavorable tuberculosis treatment outcomes and their relation with baseline undernutrition and sustained undernutrition among children receiving tuberculosis treatment in central Ethiopia

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ABSTRACT

Background: One of the global key indicators for monitoring the implementation of the World Health Organization's End Tuberculosis (TB) Strategy is the treatment outcome rate.
Objective: This study aims to assess the magnitude of unfavorable treatment outcomes and estimate their relationship with baseline undernutrition and sustained undernutrition among children receiving TB treatment in central Ethiopia.
Methods: This retrospective cohort study included children treated for drug-susceptible TB between June 2014 and February 2022. The study comprised children aged 16 and younger who were treated in 32 randomly selected healthcare facilities. A log-binomial model was used to compute adjusted risk ratios (aRR) with 95% confidence intervals (CIs).
Results: Of 640 children, 42 (6.6%; 95% CI = 4.8–8.8%) had an unfavorable TB treatment outcomes, with 31 (73.8%; 95% CI = 58.0–86.1%) occurring during the continuation phase of TB treatment. We confirmed that baseline undernutrition (aRR = 2.68; 95% CI = 1.53–4.71), age less than 10 years (aRR = 2.69; 95% CI = 1.56–4.61), HIV infection (aRR = 2.62; 95% CI = 1.50–4.59), and relapsed TB (aRR = 3.19; 95% CI = 1.79–4.71) were independent predictors of unfavorable TB treatment outcomes. When we looked separately at children who had been on TB treatment for two months or more, we found that sustained undernutrition (aRR = 3.76; 95% CI = 1.90–7.43), age below ten years (aRR = 2.60; 95% CI = 1.31–5.15), and HIV infection (aRR = 2.26; 95% CI = 1.11–4.59) remained predictors of unfavorable outcomes, just as they had in the first two months. However, the effect of relapsed TB became insignificant (aRR = 2.81; 95% CI = 0.96–8.22) after the first two months TB treatment.
Conclusions: The magnitude of unfavorable TB treatment outcomes among children in central Ethiopia met the World Health Organization's 2025 milestone. Nearly three-quarters of unfavorable TB treatment outcomes occurred during the continuation phase of TB treatment. Baseline undernutrition, sustained undernutrition, younger age, HIV infection, and relapsed TB were found to be independent predictors of unfavorable TB treatment outcomes among children receiving TB treatment in central Ethiopia.

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1. Introduction

It was estimated that approximately 1.17 million children under the age of 15 fell ill with tuberculosis (TB) in 2021 alone, accounting for 11% of all TB patients globally. Moreover, TB killed over 216,000 children, accounting for 13.5% of all TB deaths during the same year worldwide [1].

Drug-susceptible TB is highly treatable [2]. One of the global key indicators for monitoring the implementation of the WHO's End TB Strategy [3] is the treatment success rate, which includes cure and treatment completion [4]. The global treatment success rate for children under the age of 15 was 88% in 2019 as well as in 2020, implying that the rate of unsuccessful (unfavorable) outcomes was 12% [1]. The goal is to achieve a treatment success rate, also known as a favorable treatment outcome, of more than 90% by 2025, which in other words means keeping the unfavorable outcome below 10% [3]. To that end, identifying predictors of unfavorable TB treatment outcome that constitutes of death, treatment failure, and lost-to-follow-up [5] is critical for focused intervention and thus maximizing favorable treatment outcomes [6].

A plethora of studies on this topic have been conducted, and predictors of unfavorable TB treatment outcome in children have been identified. HIV infection [6–11], age under five years [5,6,8,9,12,13], relapsed TB [6,7,14], smear positive-pulmonary TB [13–15], disseminated TB [7], TB meningitis [16,17], male sex [9,11,12], and rural residence [14,18] were among the predictors identified for unfavorable TB treatment outcome in children. Previous studies, however, have typically classified transferred out patients as having a poor or unfavorable outcomes [11,19], which may not be the case in reality, because transferred out patients may actually be cured or have their treatment completed.

Although unfavorable outcomes, such as death, are more common in the first few weeks of TB treatment, they can also occur during the continuation phase of TB treatment, which follows the first two months of an intensive phase treatment [7]. However, the effect of TB treatment phase-based predictors of unfavorable treatment outcomes in children, such as sustained undernutrition, was not independently assessed in studies. This study aims to assess the magnitude of unfavorable treatment outcomes and estimate their relationship with baseline undernutrition and sustained undernutrition among children receiving TB treatment in central Ethiopia.

2. Methods

Study design, setting and population: This retrospective cohort study was conducted in 32 randomly selected healthcare facilities located in Addis Ababa city and Adama and Bishoftu towns in central Ethiopia. In Addis Ababa, we selected three government hospitals at random using the lottery approach from a pool of six that provide TB treatment services. Similarly, we selected 23 health centers at random among 95 that provided TB treatment services. Adama and Bishoftu towns each had six governmental healthcare facilities that treat TB, and we selected three (a hospital and two health centers) at random from each. Eligible participants included children aged 16 and under who were diagnosed with drug-susceptible pulmonary or extra-pulmonary TB and treated between June 2014 and February 2022.

Study variables: Our dependent variable was TB treatment outcome, which was classified as favorable or unfavorable. Our exposure variables included the child's age, sex, baseline nutritional status (nutritional status at the time of TB treatment start), sustained nutritional status (nutritional status two months later after TB treatment start), HIV status, TB treatment history (new or relapse), and BCG vaccination status at birth or within 15 days.

We extracted patients' weight, height (length for children under two years old), and mid-upper-arm circumference (MUAC) from the TB registry. Based on their appropriateness for different age groups, the nutritional status of the children was determined using the following indices:

1. the body mass index (BMI)-for-age-z-score for those 5–18 year old children [20], with cutoff point $Z < -2$ categorized as under nutrition.
2. weight-for-height/length-(WH/L) -z-score for 0–59-month-old children [21], with cutoff point $Z < -2$ categorized as undernutrition
3. MUAC for 6- to 14-year-old children, where options 1 and 2 above could not be computed due to height or length measurements not being recorded, MUAC <125 mm, <145 mm, and <185 mm were categorized as undernutrition, respectively, for children aged 6–59 months, 5–9 years, and 10–14 years old [20].
4. Where no height/length or MUAC measurement was available, we used the CDC's weight-for-age table for children aged 2–20 years and categorized the CDC weight-for-age percentile <5th percentile as undernutrition [22].

In this study, severe acute malnutrition and moderate acute malnutrition were broadly classified as under nutrition.

Operational definitions: On the basis of the World Health Organization's definition for potential TB treatment outcomes, we broadly classified those TB patients as having favorable or unfavorable TB treatment outcomes. Patients who were cured or completed their treatment were considered to have a favorable outcome, whereas those who died, had their treatment fail, or were lost to follow-up were considered to have an unfavorable treatment outcome [4].

Drug-susceptible TB (DS-TB) was defined as a bacteriologically confirmed or clinically diagnosed case of TB without evidence of infection with strains resistant to rifampicin and isoniazid [2].

Sampling technique and data collection methods: All children who were treated for TB were included in the study; children who were transferred in to the study healthcare facilities were not eligible for our study because their baseline data could not be

obtained. Patients who were transferred outs were followed via phone call to classify them under the appropriate treatment outcome rather than categorizing them all as unfavorable treatment outcome indiscriminately. Data were collected by trained health officers and nurses.

Data analysis: We analyzed the data using Stata version-14 software. We used log-binomial regression to estimate associations between clinical characteristics and unfavorable TB outcomes. In a bivariate analysis, independent variables with a *p*-value of less than or equal to 0.2 for risk ratio (RR) were chosen for a multivariable model. Finally, independent variables with *p*-values less than 0.05 for their adjusted risk ratios (aRR) were deemed significant predictors of unfavorable TB treatment outcome in children. To avoid the effect of multi-collinearity, we ran separate multivariable models for the child's nutritional statuses at the start of TB treatment and for nutritional status two months later at the start of the continuation phase of TB treatment, and we examine their effects on TB treatment outcomes.

Ethical considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) of College of Health Sciences, Addis Ababa University (protocol number: 057/19/SPH).

Fig. 1. Finding predictors of unfavorable treatment outcome among children receiving tuberculosis treatment in central Ethiopia.

3. Results

A flow diagram for the study on predictors of unfavorable treatment outcome among children receiving tuberculosis treatment is shown below in Fig. 1.

3.1. Socio-demographic characteristics of study participants

This study involved 640 children who were treated for drug-susceptible TB. One hundred fifty-seven (24.5%) of the children were under the age of five (0–4) years, 94 (14.7%) were between the ages of five and nine, 205 (32%) were between the ages of ten and fourteen, and 184 (28.8%) were fifteen to sixteen years old. Female patients accounted for 368 (57.5%) of all the TB patients.

3.2. Magnitude of unfavorable TB treatment outcome among children

Of the 640 children treated, 42 (6.6%; 95% CI = 4.8–8.8%) had an unfavorable TB treatment outcome; 36 (5.6%) died, and 6 (0.9%) experienced treatment failure. In contrast, 598 (93.4%; 95% CI = 91.2–95.2%) had a favorable treatment outcome, with 106 (16.5%) being cured and 492 (76.9%) being treatment completed. Out of those 42 with unfavorable outcomes, 11 (26.2%; 95% CI = 13.9–42.0%) occurred during the intensive phase and 31 (73.8%; 95% C = 58.0–86.1%) occurred during the continuation phase of TB treatment. Out of 31 total deaths, 11 (30.6%; 95% CI = 16.3–48.1%) occurred during the intensive phase, while 25 (69.4%; 95% CI = 51.9%–83.7%) occurred during the continuation phase of TB treatment (Table 1).

The principal investigator (PI), along with the TB focal persons of transferring out facilities, tracked down nine patients who had been transferred out and assessed their TB treatment outcomes over the phone. As a result, we discovered one cured patient, as reported by both the receiving health facility's TB focal person and the child's parent; one died after being transferred to a tertiary hospital for better treatment, as reported by the child's parent; and seven treatments completed and sent home (1 treatment outcome confirmed by the receiving hospital's TB focal person, but six reported by the parents).

4. Overall predictors of unfavorable TB treatment outcome among children

In our unadjusted analyses, we did not detect a significant association between BCG vaccination and unfavorable TB treatment outcome (RR = 1.00; 95% CI = 0.52–1.93) in the children. In a multivariable analysis, sex was not found to be significantly associated with unfavorable treatment outcome (aRR = 0.61; 95% CI = 0.34–1.10). Overall, undernourished children at the time TB treatment began (aRR = 2.68; 95% = 1.53–4.71) as compared to normally nourished ones, children aged less than 10 years (aRR = 2.69; 95% CI = 1.56–4.61) as compared to those aged 10 or older, HIV-infected children (aRR = 2.62; 95% CI = 1.50–4.59) as compared to HIV-uninfected children, and relapsed TB patients (aRR = 3.19; 95% = 1.79–5.70) as compared to new TB patients, all had a significantly higher risk of unfavorable TB treatment outcome in the multivariable model (Table 2).

5. Predictors of TB treatment outcomes in children during the continuation phase

Of the 629 (98.3%) children who survived two months or more on TB treatment, 116 (18.4%) were undernourished, with 15 (12.9%) having an unfavorable treatment outcome and 101 (87.1%) having a favorable treatment outcome. In a separate multivariable model analysis that disregarded the child's nutritional status at the start of TB treatment, persisted under nutrition into the continuation phase of TB treatment was found to increase the risk of an unfavorable TB treatment outcome (aRR = 3.76; 95% CI = 1.90–7.43) in children. Being younger than 10 years old (aRR = 2.60; 95% CI = 1.31–5.15) and having HIV infection (aRR = 2.26; 95% CI = 1.11–4.59) were also found to significantly increase the risk of unfavorable outcome during the continuation phase. Being a relapsed TB patient (aRR = 2.81; 95% CI = 0.96–8.22), on the other hand, did not continue to increase the risk of an unfavorable outcome after the first two months of TB treatment (Table 3).

Table 1
Treatment outcomes among children with tuberculosis, central Ethiopia, 2014–2022.

Treatment outcome (n = 640)	Frequency (%)	95% CI
Unfavorable	42 (6.6)	4.8–8.8%
Died	36 (5.6)	4.0–7.7%
Treatment failed	6 (0.9)	0.3–2.0%
Favorable	598 (93.4)	91.2–95.2%
Cured	106 (16.5)	13.8–19.7%
Treatment completed	492 (76.9)	73.4–80.1%
Unfavorable outcome during intensive phase (n=42)	11 (26.2)	13.9–42.0%
Unfavorable outcome during continuation phase (n=42)	31 (73.8)	58.0–86.1%
Died during intensive phase (n=36)	11 (30.6)	16.3–48.1%
Died during continuation phase (n=36)	25 (69.4%)	51.9–83.7%

Note on transferred-out patients' TB treatment outcomes.

Table 2
A multivariable log-binomial regression model demonstrating predictors of unfavorable treatment outcome in children receiving TB treatment, central Ethiopia, 2014–2022.

Variable	TB treatment outcomes		RR (95% CI)	*p*-value	aRR (95% CI)	*p*-value
	Unfavorable	Favorable				
BCG vaccination (n = 524)						
Vaccinated	21 (6.7)	294 (93.3)	1.00			
Not vaccinated	14 (6.7)	195 (93.7)	1.00 (0.52–1.93)	0.989		
Sex (n=640)						
Male	23 (8.5)	249 (91.5)	1.00			
Female	19 (5.2)	349 (94.8)	0.61 (0.34–1.10)	0.10[a]	0.67 (0.40–1.13)	0.132
Nutritional status at treatment start (n=640)						
Normal	19 (4.3)	427 (95.7)	1.00			
Undernourished	23 (11.9)	171 (88.1)	2.78 (1.55–4.00)	0.001[a]	2.68 (1.53–4.71)	0.001[b]
Age category (n=640)						
≥10 years	16 (4.1)	373 (95.9)				
<10 years	26 (10.4)	225 (89.6)	2.52 (1.40–4.60)	0.003[a]	2.69 (1.56–4.61)	0.000[b]
HIV status (n=640)						
Negative	28 (5.0)	527 (95.0)				
Positive	14 (16.5)	71 (83.5)	3.26 (1.80–5.95)	0.000[a]	2.62 (1.50–4.59)	0.001[b]
TB category(n=640)						
New	38 (6.2)	579 (93.8)				
Relapse	4 (17.4)	19 (82.4)	2.82 (1.10–7.25)	0.031[a]	3.19 (1.79–5.70)	0.000[b]

[a] Selected for multivariable model.
[b] Significant at 5% significance level.

6. Discussion

We assessed the magnitude and identified predictors of unfavorable TB treatment outcome among children treated for presumptive drug-susceptible TB in 32 randomly selected healthcare facilities in central Ethiopia.

We found that approximately one in every fifteen (6.6%; 95% CI = 4.8–8.8%) children treated in those healthcare facilities had unfavorable TB treatment outcome. According to the complementary rule argument, the World Health Organization's recommended 2025 goal of a successful TB treatment outcome rate over 90% can be interpreted as unsuccessful or unfavorable outcome rate of less than 10% [3]. On this basis, the unfavorable outcome rate of 6.6% in our study can be considered low.

Similar percentages of unfavorable outcome were reported in recent studies conducted in Botswana (6.9%) [6], Pakistan (4.8%) [23], and Kenya (8.0%) [24], which defined unfavorable outcome as death, loss to follow-up, and treatment failure, as we did. A study in Ethiopia that involved the country's two largest regions, Oromia and Amhara, also discovered a similar amount of unfavorable outcome when transferred out was considered (4.0%; 95% CI = 3.9–4.9%) and when it was not considered (7.8%) as an unfavorable outcome category [8].

However, a higher percentage of unfavorable TB treatment outcomes were reported in studies conducted in eastern Ethiopia (11.4%; 95% CI = 10.0–12.9%) [11], Addis Ababa, Ethiopia (14.5%; 95%CI = 11.5–17.9%) [19], South Africa (14.1%; 95% CI = 13.7–14.5%) [10], and Mozambique (16.4%; 95% = 14.0–18.9%) [25]. The higher percentage could be explained by counting transferred outs as an unfavorable outcome. Despite not including transferred outs as an unfavorable outcome, the percentages of

Table 3
A multivariable log-binomial model that shows the effect of sustained under nutrition on TB treatment outcomes among children receiving TB treatment in central Ethiopia, 2014–2022.

Variable	TB treatment outcomes (n = 629)		RR (95% CI)	*P*-value	aRR (95% CI)	*p*-value
	Unfavorable	Favorable				
Sex						
Male	16 (6.0)	249 (94.0)	1.00			
Female	15 (4.1)	349 (95.9)	0.68 (0.34–1.36)	0.275		
Nutritional status after the first two months of treatment start						
Normal	16 (3.1)	497 (96.9)	1.00		1.00	
Undernourished	15 (12.9)	101 (87.1)	4.15 (2.11–8.14)	0.000*	3.76 (1.90–7.43)	0.000**
Age category						
≥10 years	14 (3.6)	373 (96.4)	1.00		1.00	
<10 years	17 (7.0)	225 (93.0)	1.94 (0.97–3.87)	0.059*	2.33 (1.18–4.60)	0.015**
HIV status						
Negative	21 (3.8)	527 (96.2)	1.00		1.00	
Positive	10 (12.3)	71 (87.7)	2.81 (1.34–5.88)	0.001*	2.26 (1.11–4.59)	0.024
TB category						
New	28 (4.6)	579 (94.4)	1.00		1.00	
Relapse	3 (13.6)	19 (86.4)	2.96 (0.97–8.99)	0.056*	2.81 (0.96–8.22)	0.059

unfavorable treatment outcome in a study conducted in Ethiopia's Tigray region (11.3%; 95% = 9.2–13.6%) and Pakistan (11.1%; 95% CI = 9.7%–12.6%) were higher than that of our study. The difference could be explained by a higher proportion of under-five-year-old children in the Tigray study (30%) [13] and the Pakistan study (66.6%) [18] as compared to lower proportion of 24.5% in our study, and younger age children are of course more prone to unfavorable treatment outcome [5,6,8,9,12,13]. Furthermore, the Balochistan province of Pakistan, where the study was conducted, shares a long porous border with war-ravaged Afghanistan and thus was home to a large number of refugees, where healthcare services are of poor quality on top of the province's high levels of poverty and malnutrition [26], and all of these disadvantages are understandably leading to a rise in magnitude of unfavorable TB treatment outcome in the setting. The higher proportions of unfavorable outcome reported by Adejumo et al. (21.3%; 95% CI = 17.9–25.0%) and Adamu et al. (47.5%; 95% CI = 41.7–53.3) in their studies conducted in Nigeria could be attributed to the fact that their study populations had a higher proportion of HIV-TB co-infection (29% and 33.3%, respectively) than ours (13.3%) [7,27].

The timing of the higher proportion of deaths in our study and a study in a large tertiary hospital in Nigeria is reversed. The majority of deaths (more than 75%) occurred during the intensive phase of treatment in the Nigeria study [7], whereas this proportion of deaths occurred later during the continuation phase in our study. Because the tertiary hospital was serving as referral centers for terminally ill patients' care, the early death rate may have been inflated, resulting in a higher proportion of unfavorable outcome during the intensive phase than during the continuation phase [7,28].

Many studies on childhood TB treatment outcomes did not consider the effect of under nutrition on TB treatment outcome [5,6,8,10,11,13,14,24,25]. However, a few studies that looked at the effect of undernutrition came to the same conclusion as ours: undernutrition is a risk factor for unfavorable treatment outcome [28,29]. Nutritional deficiencies contribute to TB disease progression and poor outcomes, whereas nutritional support improves treatment outcomes [29].

Prior research compared children on TB treatment who were under the age of five to those who were five or older and discovered that those under the age of five are at a higher risk of unfavorable outcome [5,6,9,12,30]. In our study, we compared children less than 10 years old to those 10 and older and discovered that those under 10 years old were also more likely to have an unfavorable treatment outcome.

Our finding that HIV infection is a risk factor for unfavorable TB treatment outcome is consistent with many other studies [6,7,9–11,24,28].

Relapsed TB was another risk factor identified by our study, and similar findings have been reported by other studies [5–7,14]. However, in our TB treatment phase-focused analysis, relapsed TB was not found to retain its significance to increased risk of unfavorable treatment outcome after the intensive phase of TB treatment, i.e. during the continuation phase of TB treatment, in contrast to other factors such as age less than 10 years, HIV infection, and sustained undernutrition, which demonstrated overall significance effect as well as during the continuation phases of TB treatment. There were no other studies that conducted treatment phase-focused analysis of unfavorable treatment outcome predictors that we could find.

In contrast to other studies which discovered that male sex is a risk factor for unfavorable outcome [9,11], our study did not identify sex as a risk factor. Of course, studies that found no link between demographic or clinical characteristics of childhood TB patients and treatment outcomes exist [31,32].

We did not find BCG vaccination status was associated with TB treatment outcomes as did studies in Pakistan [23] and Uganda [28].

The study's strength is that, to obtain valid statistics, we tracked down transferred out patients by phone and assigned them to a plausible treatment outcome categorization rather than classifying their treatment outcome as unsuccessful without further investigation into their true treatment outcomes.

The limitation of this study was that it did not assessed whether the deaths occurred at home or in inpatients receiving optimal care, which could have provided useful evidence for designing appropriate follow-up for the risky group during the continuation phase as well. Additionally, due to the nature of secondary data, we were unable to obtain data that separated TB types by severity, such as miliary TB, preventing us from analyzing unfavorable outcomes based on the severity of the types of TB.

7. Conclusion

The magnitude of unfavorable TB treatment outcome in children treated for TB in healthcare facilities in central Ethiopia was contained at levels as low as the 10% milestone recommended by WHO's End TB target for 2025.

Almost three-quarters of unfavorable TB treatment outcomes in children occurred during the continuation phase of TB treatment, indicating inadequate follow-up during the continuation phase of TB treatment.

Being younger than 10 years old, having relapsed TB, being undernourished at the start of TB treatment, and having HIV infection were discovered to be overall independent predictors of unfavorable TB treatment outcome in children. Being younger than 10 years old, suffering from persistent under nutrition, and being HIV positive remained independent predictors of an unfavorable TB treatment outcome even after the child entered the continuation phase, but relapsed TB did not.

As a key message, a substantial percentage of adverse TB treatment outcomes occur during the continuation phase of TB; therefore, the continuation phase of TB treatment should receive no less medical care and support than the intensive phase. Furthermore, our study is useful because it yielded information that suggests that nutritional supplementation for children getting TB therapy, even during the continuation phase, may improve TB treatment outcomes, however more evidence from interventional trials is required.

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Ethical approval statement

Ethical clearance was obtained from the Institutional Review Board (IRB) of College of Health Sciences, Addis Ababa University (protocol number: 057/19/SPH).

Data availability statement

The dataset for this study is submitted along with the manuscript as supplementary material.

CRediT authorship contribution statement

Abay Burusie: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Fikre Enquesilassie:** Conceptualization, Funding acquisition, Resources. **Nicole Salazar-Austin:** Data curation, Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Adamu Addissie:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, 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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Appendix A. Supplementary data

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