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# Changes in weight-for-age z-score predict effectiveness of childhood tuberculosis therapy

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Running title: Early weight change predicts TB outcome

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Summary: In a cohort of children treated for tuberculosis disease, the degree of weight change early in therapy predicted final treatment outcome. This finding can lead to improved management and clinical trial design in childhood tuberculosis therapy.

ABSTRACT

Background: International guidelines recommend monitoring weight as an indicator of therapeutic response in childhood tuberculosis (TB) disease. This recommendation is based on observations in adults. In this study, we evaluated the association between weight change and treatment outcome, the accuracy of using weight change to predict regimen efficacy, and whether successfully treated children achieve catch-up weight gain.

Methods: We enrolled children treated for drug-susceptible TB disease (Group 1) and multidrug-resistant TB disease (Group 2) in Peru. We calculated the change in weight-for-age z-score (ΔWAZ) between baseline and the end of treatment months 2-5 for Group 1, and between baseline and months 2-8 for Group 2. We used logistic regression and generalized estimating equation (GEE) models to evaluate the relationship between ΔWAZ and outcome. We plotted receiver operating characteristic curves to determine the accuracy of ΔWAZ for predicting treatment failure/death.

Results: Groups 1 and 2 included 100 and 94 children, respectively. In logistic regression, lower ΔWAZ in months 3-5 and month 7 was associated with treatment failure/death in Groups 1 and 2, respectively. In GEE models, children in both group who experienced treatment failure or death had lower ΔWAZ than successfully treated children. ΔWAZ predicted treatment failure/death with 60-90% sensitivity and 60-86% specificity in months 2-5 for Group 1 and months 7-8 for Group 2. All successfully treated children—except Group 2 subjects with unknown microbiologic confirmation status—achieved catch-up weight gain.

Conclusions: Weight change early in therapy can predict outcome of childhood TB treatment.

## INTRODUCTION

Each year, ~~an estimated~~approximately one million children ~~become sick with~~develop tuberculosis (TB) disease [1, 2]. Failure to thrive—~~which refers to~~i.e., weight loss or lack of expected weight gain—is a ~~well-recognized~~ complication of TB disease [3]. International guidelines recommend using weight gain as an indicator of good therapeutic response in childhood TB [3-5].~~;~~ ~~however, t~~This recommendation is based on expert opinion. While studies ~~in adults~~ have shown associations between weight gain and good therapeutic response in adults with TB [6-13],~~ and~~ few studies have described weight trends in children on TB treatment [14, 15].

From a clinical perspective, the early identification of children who are failing therapy allows for timely intervention, such as adherence support or regimen modification. From a research perspective, a well-validated surrogate endpoint would facilitate clinical trials. For adults with TB disease, sputum smear and/or culture conversion are used to evaluate regimen efficacy [16]. However, <30% of children have microbiologically confirmed disease [17]. Resolution of radiographic abnormalities and clinical symptoms are suboptimal markers of treatment response: radiographic abnormalities lag behind clinical response, and symptom reporting ~~of symptoms~~ is subjective. Therefore, there is a need to evaluate other ~~objective~~ markers—like weight change—of treatment response in children.

Another ~~important~~ knowledge gap is whether children who are successfully treated for TB disease achieve catch-up weight gain. Characterizing weight reconstitution among TB-affected

children could identify needs for nutritional supplementation and help clinicians provide anticipatory guidance to families.

We addressed these knowledge gaps using data from children treated for TB disease in Lima, Peru. Our cohort included children treated for drug-susceptible TB and children treated for multidrug-resistant (MDR)-TB, caused by strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin. ~~We had three objectives~~We aimed to~~:~~ (1) ~~to~~ evaluate the association between weight change early in therapy and treatment outcome; (2) ~~to~~ determine the accuracy of weight change as a predictor of regimen efficacy; and (3) ~~to~~ assess whether successfully treated children achieve catch-up weight gain.

## METHODS

### *Setting and study population*

This study took place in Lima, Peru's capital and home to 30% of its population of 32 million [18]. Lima accounts for 54% of the 31,000 TB cases notified annually in the country [19]. Peru has a human immunodeficiency virus (HIV) prevalence of 0.3% among 15-49 year-olds [20].

Peru's National TB Program (NTP) provides free TB treatment ~~to TB patients~~ at public health centers, where clinical charts for these patients are kept. Additionally, the NTP maintains medical records of all patients treated for MDR-TB in Peru.

We enrolled children treated for TB that was microbiologically confirmed or clinically diagnosed ~~according to~~per NTP guidelines [21, 22]. We enrolled all children ≤17 years of age who began treatment for drug-susceptible TB between 2012 and 2014 at eight health centers with high volumes of TB patients and longstanding collaborations with our research group. We also enrolled all children ≤15 years of age who initiated MDR-TB therapy anywhere in the Lima metropolitan area between 2005 and 2009. We did not include 16- and 17-year-olds who initiated MDR-TB therapy because their clinical data were not available to us. We divided ~~the~~ participants into two groups. Group 1 consisted of children initially treated for drug-susceptible TB, which included subjects who failed treatment for drug-susceptible TB disease and were subsequently diagnosed with MDR-TB. Group 2 consisted of participants with confirmed MDR-TB (i.e. they had their own *M. tuberculosis* isolate with ~~drug susceptibility test (DST)~~

confirmeding resistance to at least isoniazid and rifampin) or probable MDR-TB (i.e. they lacked their own DST isolate but had a presumed source case with confirmed MDR-TB) [23]. Some children with MDR-TB had extensively drug-resistant (XDR)-TB, caused by MDR strains of *M. tuberculosis* with additional resistance to a fluoroquinolone and a second-line injectable agent. During the study period, DSTs were performed with the proportional method, microscopic observation drug susceptibility [24], and/or the nitrate reduction assay [25].

*Weight-for-age Z-scores*

Weight-for-age z-score (WAZ) is a measurecompares of how a child's weight relates to children of the same age and sex from a healthy reference population. A Ddistributions of weight-for-age measures is are created for each sex over the spectrum of ages, with; the z-score being is the number of standard deviations (SDs) from the mean of that distributionfrom . WAZ of 0 represents the age- and sex-appropriate mean. The change in WAZ between two time points, or ΔWAZ, can be used to evaluatedenotes weight change in comparison to the reference population. ΔWAZ of 0 represents age- and sex-appropriate weight gain. ΔWAZ>0 indicates cCatch-up weight gain, or weight attainment above normal limits following a period of slowed development, is represented by ΔWAZ>0. Since the World Health Organization (WHO) does not publish WAZ standards for children >10 -years of age, we used the reference from the U.S. Centers for Disease Control and Prevention (CDC) to calculate WAZ scores [26].

*Definitions*

We defined microbiologic~~al~~ confirmation as the visualization of bacilli on acid-fast smear or the isolation of *M. tuberculosis* from culture. Following Wiseman *et al*., we classified participants into those with severe and non-severe disease [27].

At the end of therapy, participants were ~~classified into~~assigned treatment outcomes by a clinician according to NTP guidelines: cure~~,~~, treatment completion~~,~~, loss to follow-up~~,~~, transfer~~,~~, treatment failure~~,~~ or death [21, 22]. For this analysis, we grouped cure and treatment completion together under treatment success. ~~In addition, w~~We classified participants as having an unknown outcome if no treatment outcome was recorded in the medical record~~;~~ t~~T~~his category ~~is distinct~~differs from loss to follow-up, which is an outcome recorded in the patient's chart.

Health center staff measured each ~~TB patient~~participant's weight at the end of every treatment month, defined as 25 days of supervised doses. We defined baseline weights as those taken ≤ ~~*within* 30~~ days of the initiation of the first-line regimen for Group 1 and a second-line regimen for Group 2; end-of-therapy weights as those taken in the final treatment month of successful therapy (month 6 for most Group 1 subjects, month 12 or later for Group 2 subjects); and interim weights as all other weights taken during therapy. ~~A child's baseline WAZ (~~$WAZ_{baseline}$~~)~~ and $WAZ_{final}$ refer~~s~~ to ~~the~~ z-score~~s~~ calculated from ~~the~~ baseline and end-of-therapy weight~~s~~, respectively. ~~$WAZ_{final}$ refers to the z-score calculated from the end-of-therapy weight.~~

*Clinical care*

Group 1 received first-line regimens—isoniazid, rifampin, ethambutol, and pyrazinamide daily for the first two months, followed by isoniazid and rifampin thrice weekly for ≥4 ~~at least four~~ more months. Group 2 received second-line regimens that were tailored to the DST result of the participant or his/her presumed source case, contained ≥4 ~~at least four~~ drugs to which the *M. tuberculosis* strain was susceptible, and lasted ≥~~at least~~ 12 months. Health workers administered directly observed therapy (DOT) at the health center six days a week. No supervised or self-administered doses were given on Sundays. Subjects did not receive nutritional supplements as part of TB therapy.

*Data collection*

At the eight health centers, we collected data on children who received only first-line regimens. At NTP headquarters, we collected data on children who received any second-line regimen; this group included children who experienced treatment failure on the first-line regimen prior to being diagnosed with MDR-TB. From each subject's chart, we abstracted date of birth; sex; HIV status; anatomic site of TB disease; smear, culture, DST, and radiograph results; antibiotics received; treatment outcome; and all weights.

*Exclusion criteria*

We excluded children who lacked baseline and/or interim weights, were lost to follow-up, or had an unknown outcome~~, or whose $WAZ_{baseline}$ was more than three SDs from the mean~~. Suspecting errors in data entry, we excluded children whose WAZ scores were >6 SDs from the mean. Some

participants in Group 1 were classified as having failed treatment if their DST or a source case's DST demonstrated resistance to isoniazid and rifampin. We included these children in Group 1 only if they had documentation of smear or culture positivity and/or radiological worsening after ≥2 ~~at least two~~ months of treatment, despite documented good adherence [3]. ~~If they lacked this documentation, we excluded them.~~ Participants who had received first-line therapy in the six months preceding their second-line regimen were excluded from Group 2.

*Analysis*

We used SAS version 9.4 (SAS Institute, Cary, NC) to perform analyses. To check for selection and loss-to-follow-up biases, we used ~~the chi-square or~~ Fisher's exact test to compare characteristics between included and excluded subjects.

To examine the relationship between weight change and treatment outcome, we used ΔWAZ ~~as the measurement~~ because it accounts for age- and sex-specific differences in normal childhood growth. We examined ΔWAZ through treatment month 5 for Group 1 since the standard first-line regimen lasts six months, and through month 8 for Group 2 since eight months typically is the maximum duration of the intensive phase of MDR-TB therapy. We calculated ΔWAZ using the following formula: $\Delta WAZ_x = WAZ_x - WAZ_{baseline}$, where x represents the month of interest.

We performed two separate analyses to address the first aim of this study. First, using logistic regression, we evaluated the associations of the following independent variables and treatment outcome (success vs. failure/death) for Groups 1 and 2 separately: $WAZ_{baseline}$, $\Delta WAZ_2$, $\Delta WAZ_3$,

$\Delta WAZ_4$, $\Delta WAZ_5$, age (0-4 vs. 5-9 vs. ≥10), sex, microbiologic confirmation, and disease severity. For Group 2, we assessed additional independent variables: $\Delta WAZ_6$, $\Delta WAZ_7$, $\Delta WAZ_8$, and resistance pattern (MDR vs. XDR).

Second, we used generalized estimating equation (GEE) models using the first-order autoregressive correlation structure to detect differences in ΔWAZs between successfully treated children vs. those with failed treatment/died. To determine which covariates (age, sex, microbiologic confirmation, disease severity, resistance pattern) to include in the GEE models, we performed stepwise selection and maintained covariates with $p$-value <0.05.

To address the second aim of this study, we plotted receiver operating characteristic (ROC) curves and calculated area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) to determine the accuracy of ΔWAZ at our time points of interest for predicting treatment failure/death.

Finally, we assessed catch-up weight gain for successfully treated subjects by comparing ΔWAZ between $WAZ_{baseline}$ and $WAZ_{final}$. We used the Student's t-test and analysis of variance with Bonferroni post-hoc tests to compare ΔWAZ between subgroups stratified by age, sex, microbiologic confirmation, and disease severity.

*Ethics*

The Institutional Review Boards (IRBs) of Peru's National Institute of Health, Harvard Medical School, and Baylor College of Medicine approved this study and waived informed consent.

RESULTS

We excluded 71 of 171 subjects from Group 1 and 138 of 232 subjects from Group 2 (Figure 1). Table 1 compares included and excluded ~~subjects~~participants. Median ages for Groups 1 and 2 were 14.4 (interquartile range [IQR] 12.3-16.65) years and 9.5 (IQR 3.49-13.73) years, respectively. In Group 1, ~~the 74 successfully treated subjects had a~~ median treatment durations ~~of~~ were 6.~~2~~ 4 (~~SD: 1.8~~IQR 6.0-6.9) months in the 74 successfully treated subjects ~~; the 26 who died or failed therapy had a mean treatment duration of~~ and 4.~~82~~ (~~SD: 1.5~~IQR 3.6-5.7) months in the 26 subjects in whom therapy failed. No participants in Group 1 died. In Group 2, median treatment durations were ~~the 83 successfully treated subjects had a mean treatment duration of~~ 20.~~05~~ (~~SD: 9.0~~IQR 18.0-23.8) months for the 83 successfully treated subjects and ~~; the 11 who died or failed therapy had a mean treatment duration of 12.7~~14.1 (~~SD: 8.3~~IQR 5.9-21.9) months for the 10 subjects in whom therapy failed. The one subject in Group 2 who died received treatment for 7.8 months.

*Association between ΔWAZ and treatment outcome*

In logistic regression, female sex and lower $\Delta WAZ_3$, $\Delta WAZ_4$, and $\Delta WAZ_5$ were associated with treatment failure~~/death~~ in Group 1. Lower $\Delta WAZ_7$ was associated with treatment failure/death in Group 2 (Table 2).

In the GEE model for Group 1, after adjusting for $WAZ_{baseline}$ and age group, children in whom treatment failed ~~or who died~~ had significantly lower $\Delta WAZ_2$, $\Delta WAZ_3$, $\Delta WAZ_4$, and $\Delta WAZ_5$

~~values~~ than successfully treated children. For Group 2, the GEE model was not adjusted because no covariates were significant in stepwise selection; children in whom treatment failed or who died had lower $\Delta WAZ_6$, $\Delta WAZ_7$, and $\Delta WAZ_8$ ~~values~~ compared to successfully treated children (Figure 2a). When we repeated the GEE model for participants with microbiologically confirmed TB, the findings for Group 1 did not change. In Group 2, children in whom treatment failed or who died had lower $\Delta WAZ_7$ and $\Delta WAZ_8$ values compared to successfully treated children (Figure 2b).

*Accuracy of ΔWAZ as a predictor of treatment outcome*

The AUC of ΔWAZ as a predictor of treatment failure~~/death~~ increased as therapy progressed for Group 1. The selected cut-off values had sensitivities of 60-90% and specificities of 60-85% at the end of months 2-5. For Group 2, the AUC of ΔWAZ as a predictor of treatment failure/death was highest at the end of months 7-8. Before month 7, the selected ΔWAZ cut-off values had <43% sensitivity for predicting treatment failure/death (Figure 3, Table 3).

*Catch-up weight gain among successfully treated children*

In Groups 1 and 2, children with severe TB started therapy with lower $WAZ_{baseline}$ compared to children with non-severe TB: -0.97 for severe disease vs. -0.37 for non-severe disease (p=0.02) in Group 1, and -0.82 for severe disease vs. -0.31 for non-severe disease (p=0.04) in Group 2 (Supplementary Table 1). At the end of successful therapy, there were no significant differences in $WAZ_{final}$ for children with severe vs. non-severe TB in Group 1 or 2 (Supplementary Table 2).

There were no significant differences in $WAZ_{baseline}$ or $WAZ_{final}$ between subjects stratified by sex, age group, microbiologic confirmation, or resistance pattern in Group 1 or 2.

All successfully treated children achieved catch-up weight gain, except for Group 2 subjects with unknown microbiologic confirmation ~~status~~. In Group 1, children with microbiologically confirmed or severe TB experienced more weight gain than those with unconfirmed or non-severe TB, respectively (Figure 4).

## DISCUSSION

In this study, we found ~~an association between weight gain during childhood TB therapy and treatment success.~~ that c~~C~~hildren who ultimately ~~have~~ had treatment success~~ful~~ ~~outcomes~~ had different weight trajectories compared to those who experienced treatment failure or death. ~~We further found that~~Furthermore, ΔWAZ early in therapy may serve as a moderately sensitive predictor of treatment failure/death for children on first-line TB regimens. ΔWAZ lacks sensitivity for predicting unsuccessful MDR-TB treatment, but its high specificity means that clinicians should strongly consider regimen modification for children with ΔWAZ values below the cut-off value.

For children ≤10 years, clinicians can calculate WAZ using WHO Anthro~~, which is available for free download onto computers and mobile devices~~ (www.who.int/childgrowth/software/en/). PediTools (https://peditools.org) and the Children's Hospital of Philadelphia (https://zscore.research.chop.edu) provide links to CDC's WAZ calculator for children ages 2-20. Manual calculation of ΔWAZ is likely to be inaccurate, since growth charts do not capture sufficiently small units of age and weight. Therefore, clinicians in ~~the~~ resource-constrained settings, where these technologies may be unavailable, may have difficulty using this tool.

The accuracy of ΔWAZ for predicting pediatric TB treatment outcome should be evaluated in other groups of children. In clinical trials and prospective cohorts of children with TB, it would be useful to collect weights, heights, and mid-upper arm circumference (MUAC) of children and evaluate ΔWAZ and other nutritional measures as predictors of treatment outcome. If validated,

ΔWAZ could serve as a red flag to prompt further evaluation of children on TB therapy who may need regimen modification. From a research perspective, ΔWAZ could serve as a surrogate endpoint for clinical trials, reducing cost and duration and facilitating the use of novel trial designs, such as the multi-stage, multi-arm trial.

In this cohort, we found that all groups of children with successfully treated TB disease achieved catch-up weight gain. In Group 1, children with microbiologically confirmed or severe disease had more weight gain than children with non-microbiologically confirmed or non-severe disease~~, respectively~~. This finding suggests that successful treatment of TB disease leads to weight recovery; this improvement is most pronounced for the sickest children, who likely begin treatment with a greater weight deficit.

Previous work has shown that children gain weight on TB therapy [14, 15], but our study is the first to demonstrate different weight trends in children who are successfully treated and those who experienced treatment failure or death. This finding is consistent with reported associations between weight gain and treatment outcome in adults on TB treatment [6, 8, 9]. Studies of HIV-infected children on antiretroviral therapy also have shown associations between good treatment response and catch-up growth [28, 29]. Our study is the first to quantify the degree of weight gain in early TB therapy that predicts ultimate outcome.

This analysis had several limitations. The data, which were obtained under programmatic conditions, had missing values. Twenty-seven percent of children in Group 1 and 16% of children in Group 2 were excluded from the analysis due to missing weights; the exclusion of

these subjects may have led to a selection bias. In Group 2, there were higher proportions of microbiologically confirmed and severe disease among excluded subjects compared to included subjects. This exclusion may have minimized the difference in WAZ trajectories between successfully treated children and those who experienced treatment failure or death, considering our finding that children in Group 1 with microbiologically confirmed or severe TB gained more weight than those with non-confirmed or non-severe TB. Second, because few subjects had documented heights and no subjects had MUACs, we could not undertake a more complete evaluation of nutritional recovery, including weight adjusted for height and linear growth. This limitation may be problematic for adolescents, who undergo pubertal growth spurts at different times. Adolescents with earlier-than-average puberty will have relatively higher WAZ, while body mass index-for-age z-scores may track more consistently. Despite the fact that our sample consisted mostly of adolescents, we were still able to demonstrate a clear difference in the weight trajectories of successfully treated subjects vs. those who experienced treatment failure or death.

An important limitation specific to Group 2 was the heterogeneity of second-line regimens, which were individualized to DST profiles~~. Additionally, some regimens were~~ and adjusted ~~modified~~ during therapy because of new DST results, adverse drug events, or stock-outs. Regimen heterogeneity may have impacted our results since different medications have distinct effects on appetite; moreover, ethionamide, a second-line drug used in Peru, may affect thyroid function. Nonetheless, we can still conclude from this analysis that children successfully treated for MDR-TB achieve catch-up weight gain and achieved more early weight gain compared to those who experienced treatment failure or death.

This analysis also had strengths. The enrollment of consecutive children treated for TB disease reduces the potential for selection bias. These data were collected as part of routine care delivered at public health centers; as a result, the data reflect clinical practice and treatment response in a "real-world" setting. Our study also evaluates weight change in children being treated for drug-susceptible and MDR-TB; this analysis has not been undertaken previously in adults or children.

In conclusion, our study establishes the potential for using weight change early in therapy to predict childhood TB treatment outcome and provides reassurance that successfully treated children achieve catch-up weight gain. If validated in other cohorts, the use of weight change to predict treatment outcome can lead to better outcomes for children with TB disease and more efficient clinical trial design in childhood TB therapy.

## AUTHOR CONTRIBUTIONS

SSC, JFF, JAS, and MCB conceptualized the study. SSC, EW, HDC, and LL collected and managed the data. SP performed the analyses. SSC, SP, JFF, ATC, JAS, and MCB interpreted the results of the analyses. SSC, SP, and EW drafted the manuscript, tables, and figures. All authors revised and approved the final version of this work for publication.

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**Table 1: Comparison between included and excluded subjects**

| | Group 1 (n=171) | | | Group 2 (n=232) | | |
|---|---|---|---|---|---|---|
| | Included (n=100) | Excluded (n=71) | p-value | Included (n=94) | Excluded (n=138) | p-value |
| **Age** | | | 0.55 | | | 0.025 |
| • 0-4 | 6 (6.0%) | 9 (12.7%) | | 35 (37.2%) | 29 (21.0%) | |
| • 5-9 | 6 (6.0%) | 5 (7.0%) | | 12 (12.8%) | 23 (16.7%) | |
| • ≥10 | 88 (88.0%) | 57 (80.3%) | | 47 (50.0%) | 86 (62.3%) | |
| **Sex** | | | 0.32 | | | 0.41 |
| • Female | 43 (43.0%) | 36 (50.7%) | | 48 (51.1%) | 78 (56.5%) | |
| • Male | 57 (57.0%) | 35 (49.3%) | | 46 (48.9%) | 60 (43.5%) | |
| **Microbiologic confirmation** | | | 0.78 | | | 0.011 |
| • Confirmed | 59 (59.0%) | 45 (63.4%) | | 54 (57.4%) | 99 (71.7%) | |
| • Unconfirmed | 13 (13.0%) | 7 (9.9%) | | 28 (29.8%) | 19 (13.8%) | |
| • Unknown | 28 (28.0%) | 19 (26.8%) | | 12 (12.8%) | 20 (14.5%) | |
| **Disease severity** | | | 0.07 | | | 0.021 |
| • Severe | 24 (24.0%) | 26 (36.6%) | | 25 (26.6%) | 57 (41.3%) | |
| • Non-severe | 76 (76.0%) | 45 (63.4%) | | 69 (73.4%) | 81 (58.7%) | |
| **Resistance pattern** | | | --- | | | 0.06 |
| • MDR | --- | --- | | 88 (93.6%) | 136 (98.6%) | |
| • XDR | --- | --- | | 6 (6.4%) | 2 (1.4%) | |

Data are presented as n (% of total).

Abbreviations: MDR, multi-drug resistant; WAZ, weight-for-age z-score; XDR, extensively-drug resistant.

**Table 2: Associations between study subject characteristics and treatment outcome**

| | Group 1 (n=100) | | | Group 2 (n=94) | | |
|---|---|---|---|---|---|---|
| | Treatment success | Treatment failure/death | OR (95% CI) | Treatment success | Treatment failure/death | OR (95% CI) |
| **Mean $WAZ_{baseline}$** | -0.44 (SD: 1.18) | -0.72 (SD: 0.83) | 0.79 (0.52-1.19) | -0.44 (SD: 0.98) | -0.56 (SD: 1.76) | 0.90 (0.50-1.60) |
| **Mean $\Delta WAZ_2$** | 0.22 (SD: 0.47) | 0.01 (SD: 0.37) | 0.35 (0.11-1.12) | 0.18 (SD: 0.49) | -0.08 (SD: 0.26) | 0.19 (0.01-2.83) |
| **Mean $\Delta WAZ_3$** | 0.41 (SD: 0.88) | -0.08 (SD: 0.47) | 0.25 (0.08-0.78)* | 0.18 (SD: 0.52) | 0.00 (SD: 0.27) | 0.46 (0.10-2.18) |
| **Mean $\Delta WAZ_4$** | 0.32 (SD: 0.58) | -0.07 (SD: 0.41) | 0.33 (0.11-1.00)* | 0.25 (SD: 0.60) | 0.10 (SD: 0.34) | 0.62 (0.18-2.17) |
| **Mean $\Delta WAZ_5$** | 0.40 (SD: 0.41) | -0.20 (SD: 0.53) | 0.02 (0.00-0.29)** | 0.282 (SD: 0.5576) | -0.21 (SD: 0.79) | 0.58 23 (0.2706-1.240.90)* |
| **Mean $\Delta WAZ_6$** | --- | --- | --- | 0.20 (SD: 0.65) | -0.12 (SD: 0.45) | 0.45 (0.13-1.54) |
| **Mean $\Delta WAZ_7$** | --- | --- | --- | 0.25 (SD: 0.59) | -0.25 (SD: 0.48) | 0.22 (0.05-0.92)* |
| **Mean $\Delta WAZ_8$** | --- | --- | --- | 0.30 (SD: 0.63) | -0.27 (SD: 0.55) | 0.20 (0.04-1.05) |
| **Age** | | | | | | |
| • 0-4 years | 6 (100%) | 0 (0%) | Reference | 28 (96.6%) | 1 (3.5%) | Reference |
| • 5-9 years | 6 (100%) | 0 (0%) | --- | 16 (94.1 %) | 1 (5.9%) | 1.75 (0.10-29.92) |
| • ≥10 years | 62 (70.5%) | 26 (29.5%) | --- | 39 (81.3%) | 9 (18.8%) | 6.46 (0.77-53.95) |
| **Sex** | | | | | | |
| • Male | 47 (82.5%) | 10 (17.5%) | Reference | 41 (89.1%) | 5 (10.9%) | Reference |
| • Female | 27 (62.8%) | 16 (37.2%) | 2.79 (1.11-7.00)* | 42 (87.5%) | 6 (12.5%) | 1.17 (0.33-4.14) |
| **Microbiologic confirmation** | | | | | | |
| • Unconfirmed | 13 (100%) | 0 (0%) | Reference | 28 (100%) | 0 (0%) | Reference |
| • Confirmed | 35 (59.3%) | 24 (40.7%) | --- | 44 (81.5%) | 10 (18.5%) | --- |
| • Unknown | 26 (92.9%) | 2 (7.1%) | --- | 11 (91.7%) | 1 (8.3%) | --- |
| **Disease severity** | | | | | | |
| • Non-severe | 55 (72.4%) | 21 (27.6%) | Reference | 61 (89.7%) | 7 (10.3%) | Reference |
| • Severe | 19 (79.2%) | 5 (20.8%) | 0.69 (0.23-2.08) | 22 (84.6%) | 4 (15.4%) | 1.58 (0.42-5.94) |
| **Resistance pattern** | | | | | | |
| • MDR | --- | --- | --- | 77 (87.5%) | 11 (12.5%) | Reference |
| • XDR | --- | --- | --- | 6 (100%) | 0 (0%) | --- |

Unless otherwise stated, data are presented as n (% of total number of each variable).
*p<0.05, **p<0.01
Abbreviations: MDR, multidrug-resistant; N/A, not applicable; SD, standard deviation; WAZ, weight-for-age z-score; XDR, extensively-drug resistant.

**Table 3: Receiver operating characteristic curves characteristics for using change in weight-for-age z-score to predict treatment failure/death**

| | AUC | ΔWAZ cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| **Group 1** | | | | | | |
| • $\Delta WAZ_2$ | 0.68 | 0.142 | 60.0 | 73.1 | 85.7 | 40.4 |
| • $\Delta WAZ_3$ | 0.73 | 0.029 | 81.5 | 60.0 | 86.9 | 50.0 |
| • $\Delta WAZ_4$ | 0.78 | 0.153 | 72.3 | 84.6 | 95.9 | 37.9 |
| • $\Delta WAZ_5$ | 0.83 | -0.024 | 89.8 | 80.0 | 96.4 | 57.1 |
| **Group 2** | | | | | | |
| • $\Delta WAZ_2$ | 0.64 | 0.151 | 42.2 | 100 | 100 | 11.9 |
| • $\Delta WAZ_3$ | 0.61 | 0.342 | 28.6 | 100 | 100 | 15.3 |
| • $\Delta WAZ_4$ | 0.57 | 0.303 | 42.9 | 88.9 | 96.8 | 16.7 |
| • $\Delta WAZ_5$ | 0.~~6~~869 | 0.425 | 40.~~0~~6 | 100 | 100 | 16.~~0~~3 |
| • $\Delta WAZ_6$ | 0.67 | 0.320 | 40.3 | 100 | 100 | 14.9 |
| • $\Delta WAZ_7$ | 0.75 | 0.145 | 62.3 | 85.7 | 97.7 | 18.8 |
| • $\Delta WAZ_8$ | 0.76 | 0.129 | 64.6 | 80.0 | 97.7 | 14.8 |

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; WAZ, weight-for-age z-score; $\Delta WAZ_x$, change in WAZ between baseline and the end of treatment month x.

1

**Supplementary Table 1: $WAZ_{baseline}$ of Study Subjects**

| | Group 1 | | | Group 2 | | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) | p-value | n | Mean (SD) | p-value |
| **All participants** | 100 | -0.51 (1.10) | --- | 94 | -0.45 (1.09) | --- |
| **Age** | | | | | | |
| • 0-4 years | 6 | -0.69 (0.70) | 0.74 | 29 | -0.44 (0.80) | 0.09 |
| • 5-9 years | 6 | -0.21 (1.05) | | 17 | 0.04 (1.45) | |
| • ≥10 years | 88 | -0.52 (1.13) | | 48 | -0.64 (1.06) | |
| **Sex** | | | | | | |
| • Male | 57 | -0.49 (1.21) | 0.76 | 46 | -0.38 (1.11) | 0.51 |
| • Female | 43 | -0.55 (0.95) | | 48 | -0.53 (1.07) | |
| **Microbiologic confirmation** | | | | | | |
| • Unconfirmed | 13 | -0.19 (1.47) | 0.14 | 28 | -0.35 (0.91) | 0.12 |
| • Confirmed | 59 | -0.69 (1.07) | | 54 | -0.62 (1.08) | |
| • Unknown | 28 | -0.29 (0.93) | | 12 | 0.05 (1.39) | |
| **Disease severity** | | | | | | |
| • Non-severe | 76 | -0.37 (1.02) | 0.019 | 68 | -0.31 (1.13) | 0.044 |
| • Severe | 24 | -0.97 (1.25) | | 26 | -0.82 (0.89) | |
| **Resistance pattern** | | | | | | |
| • MDR | --- | --- | --- | 88 | -0.45 (1.07) | 0.83 |
| • XDR | --- | --- | | 6 | -0.54 (1.46) | |
| **Treatment outcome** | | | | | | |
| • Treatment success | 74 | -0.44 (1.18) | 0.19 | 83 | -0.44 (0.98) | 0.82 |
| • Treatment failure or death | 26 | -0.72 (0.83) | | 11 | -0.56 (1.76) | |

Abbreviations: IQR, interquartile range; MDR, multi-drug resistant; WAZ, weight-for-age z-score; XDR, extensively-drug resistant.

1

**Supplementary Table 2: $WAZ_{final}$ of Study Subjects**

| | Group 1 | | | Group 2 | | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) | p-value | n | Mean (SD) | p-value |
| **All participants** | 100 | -0.08 (1.05) | --- | 94 | -0.04 (1.01) | --- |
| **Age** | | | | | | |
| • 0-4 years | 6 | -0.26 (0.87) | 0.78 | 29 | 0.34 (0.76) | 0.10 |
| • 5-9 years | 6 | 0.18 (0.94) | | 17 | 0.06 (1.35) | |
| • ≥10 years | 88 | -0.10 (1.08) | | 48 | -0.28 (0.95) | |
| **Sex** | | | | | | |
| • Male | 57 | -0.05 (1.13) | 0.72 | 46 | 0.06 (1.09) | 0.41 |
| • Female | 43 | -0.15 (0.88) | | 48 | -0.15 (0.93) | |
| **Microbiologic confirmation** | | | | | | |
| • Unconfirmed | 13 | -0.03 (1.12) | 0.63 | 28 | 0.19 (0.74) | 0.31 |
| • Confirmed | 59 | 0.02 (1.13) | | 54 | -0.21 (1.03) | |
| • Unknown | 28 | -0.26 (0.88) | | 12 | 0.13 (1.55) | |
| **Disease severity** | | | | | | |
| • Non-severe | 76 | 0.05 (1.03) | 0.10 | 68 | 0.10 (1.00) | 0.08 |
| • Severe | 24 | -0.45 (1.05) | | 26 | -0.39 (0.98) | |
| **Resistance pattern** | | | | | | |
| • MDR | --- | --- | --- | 88 | -0.05 (1.03) | 0.71 |
| • XDR | --- | --- | | 6 | 0.17 (0.78) | |

Abbreviations: IQR, interquartile range; MDR, multi-drug resistant; WAZ, weight-for-age z-score; XDR, extensively-drug resistant.

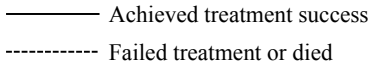
2

# FIGURE LEGENDS

**Figure 1**

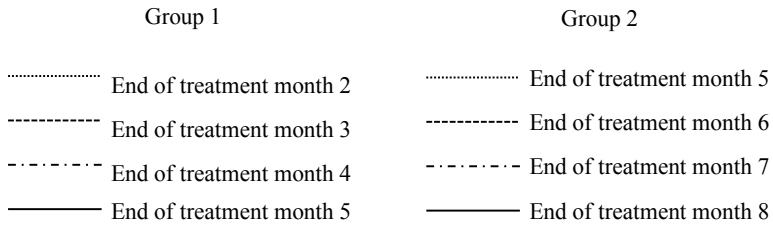
Abbreviations: MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis; WAZbaseline, weight-for-age z-score within 30 days of the start of tuberculosis therapy. The start of tuberculosis therapy refers to the start of a first-line regimen for Group 1 and a second-line regimen for Group 2.

**Figure 2**




Abbreviations: ΔWAZ, delta (change in) weight-for-age z-score.
*p-value <0.05.
**p-value <0.01.
***p-value <0.001.
Values represent least square mean +/- 95% confidence interval for each time point using generalized estimating equation models. After stepwise selection, we adjusted for $WAZ_{baseline}$ and microbiologic confirmation in Group 1, but did not adjust for any covariates in Group 2.
The numbers of participants in Group 1 contributing to the overall analysis were as follows: 96 for month 2, 85 for month 3, 78 for month 4, and 69 for month 5. In Group 2, the numbers were 69 for month 2, 79 for month 3, 79 for month 4, 78 for month 5, 74 for month 6, 76 for month 7, and 70 for month 8. The numbers of participants in Group 1 contributing to the sensitivity analysis were as follows: 58 for month 2, 52 for month 3, 46 for month 4, and 39 for month 5. In Group 2, the numbers were 39 for month 2, 46 for month 3, 43 for month 4, 43 for month 5, 41 for month 6, 43 for month 7, and 38 for month 8.

**Figure 3**

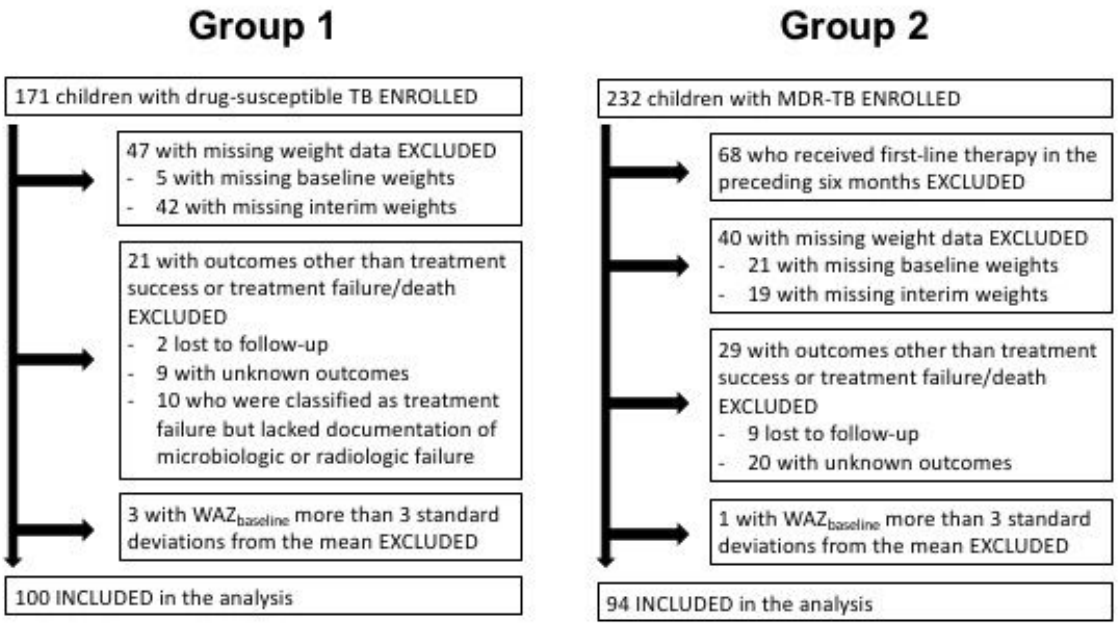



See Table 3 for area under the curve (AUC) values.

**Figure 4**

Abbreviations: ΔWAZ, delta (change in) weight-for-age z-score.
This analysis excludes study subjects without documented end-of-therapy weights. Number of subjects in each subgroup appears in parentheses below subgroup name. The only significant differences among subgroups are indicated in the figure.

**Figure 1: Included and excluded subjects**



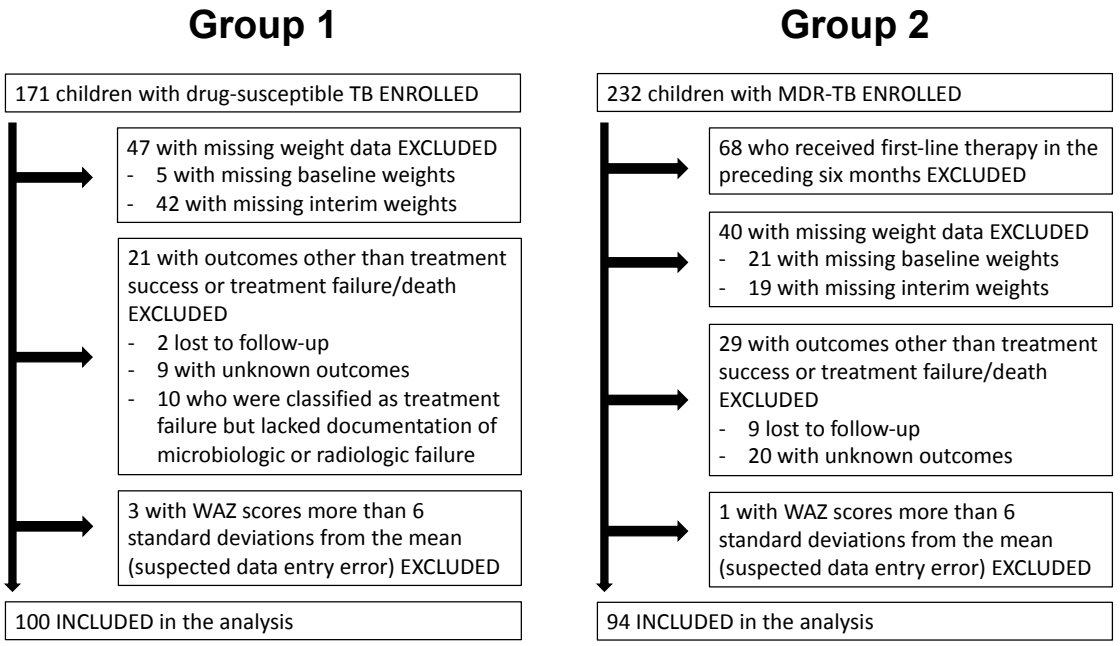



**Figure 2a: Adjusted ΔWAZ for children who were successfully treated vs. children who failed treatment/died (microbiologically confirmed and clinically diagnosed cases)**

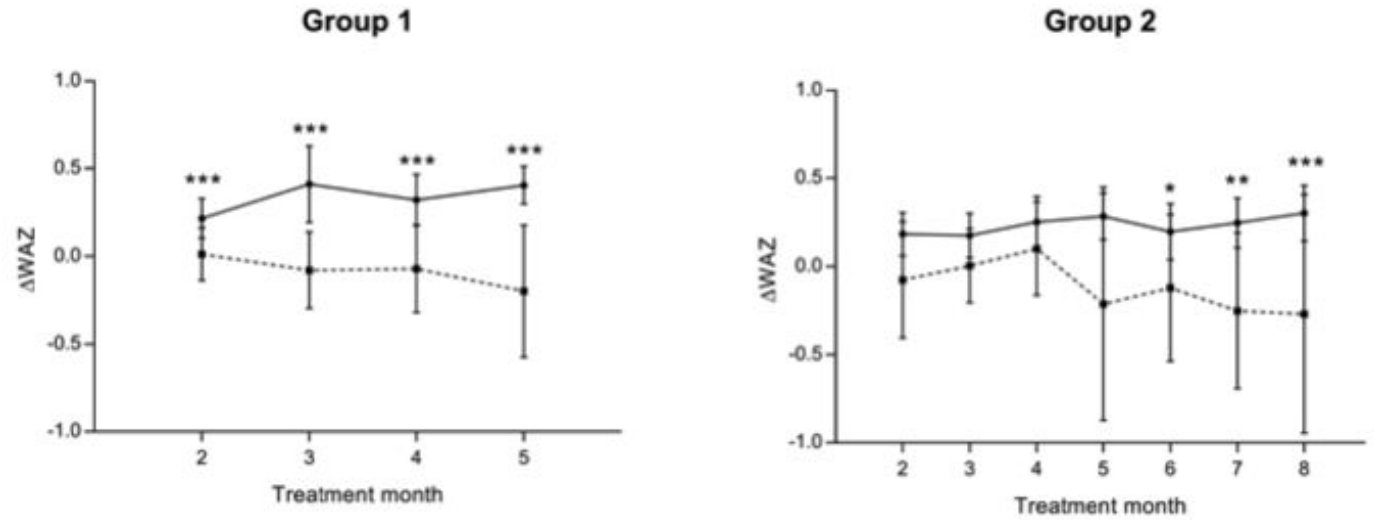
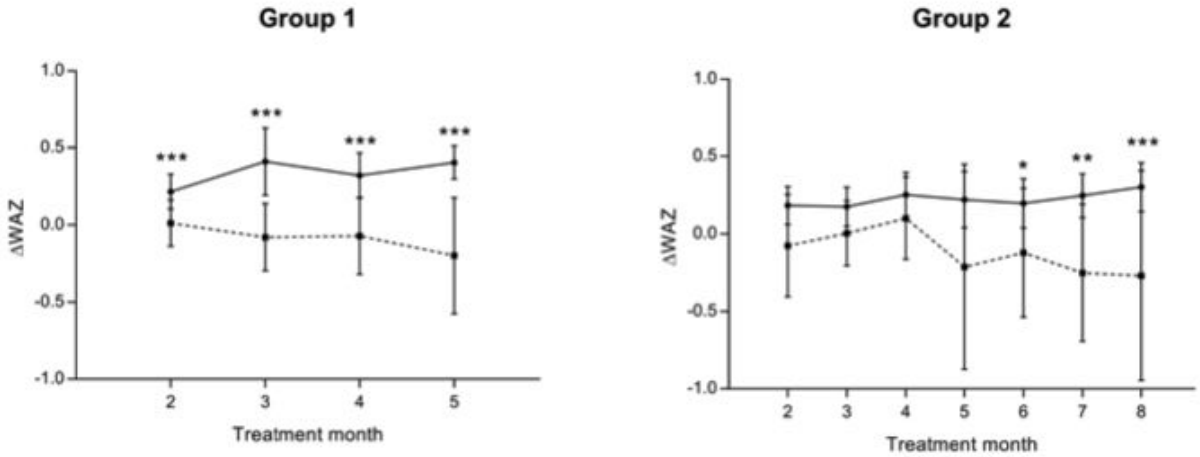



**Figure 2b: Adjusted ΔWAZ for children who were successfully treated vs. children who failed treatment/died (microbiologically confirmed cases only)**



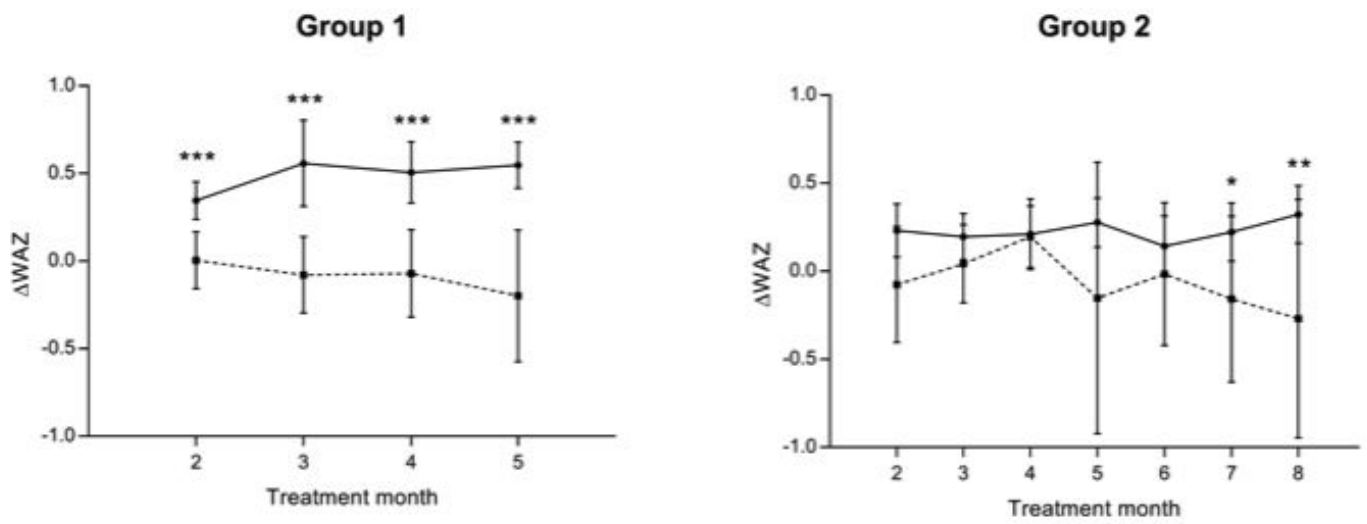


**Figure 3: Receiver operating characteristic curves for using change in weight-for-age z-score to predict treatment failure/death**

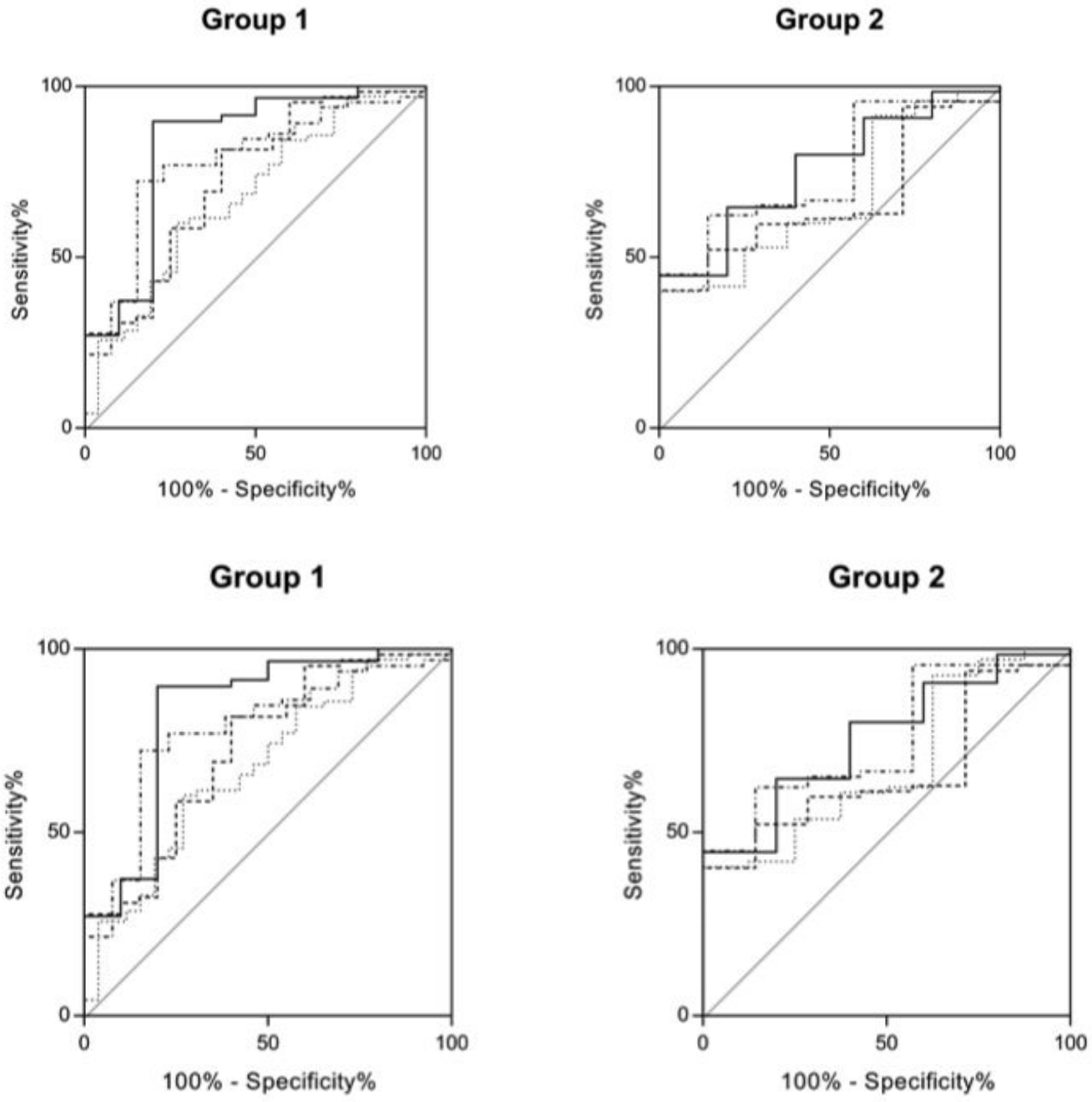
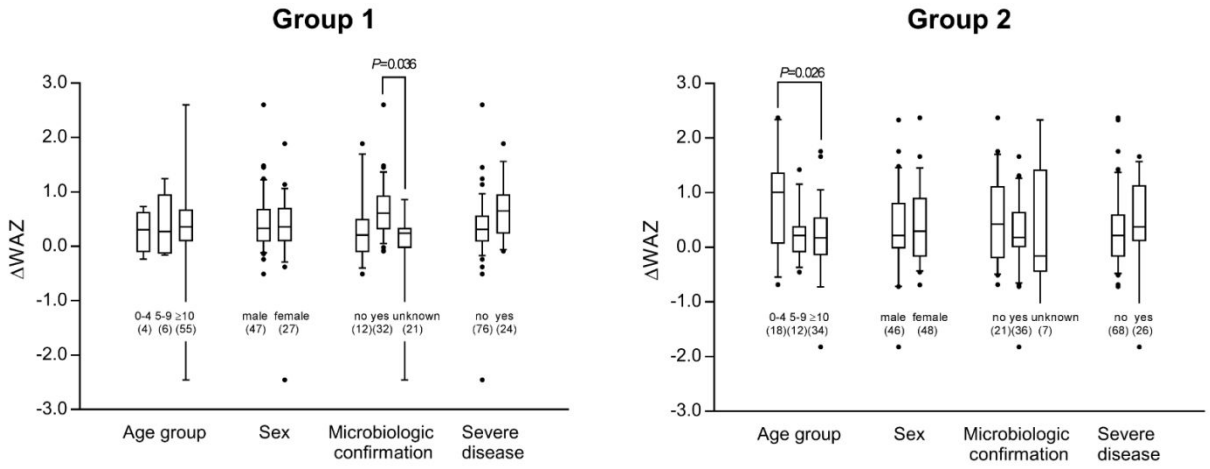


**Figure 4: Change in weight-for-age z-score between baseline and end-of-therapy among successfully treated children**



# Changes in weight-for-age z-score predict effectiveness of childhood tuberculosis therapy

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Key words: multidrug-resistant tuberculosis, treatment outcome, nutritional status, growth and development, Peru

Running title: Early weight change predicts TB outcome

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Summary: In a cohort of children treated for tuberculosis disease, the degree of weight change early in therapy predicted final treatment outcome. This finding can lead to improved management and clinical trial design in childhood tuberculosis therapy.

ABSTRACT

Background: International guidelines recommend monitoring weight as an indicator of therapeutic response in childhood tuberculosis (TB) disease. This recommendation is based on observations in adults. In this study, we evaluated the association between weight change and treatment outcome, the accuracy of using weight change to predict regimen efficacy, and whether successfully treated children achieve catch-up weight gain.

Methods: We enrolled children treated for drug-susceptible TB disease (Group 1) and multidrug-resistant TB disease (Group 2) in Peru. We calculated the change in weight-for-age z-score (ΔWAZ) between baseline and the end of treatment months 2-5 for Group 1, and between baseline and months 2-8 for Group 2. We used logistic regression and generalized estimating equation (GEE) models to evaluate the relationship between ΔWAZ and outcome. We plotted receiver operating characteristic curves to determine the accuracy of ΔWAZ for predicting treatment failure/death.

Results: Groups 1 and 2 included 100 and 94 children, respectively. In logistic regression, lower ΔWAZ in months 3-5 and month 7 was associated with treatment failure/death in Groups 1 and 2, respectively. In GEE models, children in both group who experienced treatment failure or death had lower ΔWAZ than successfully treated children. ΔWAZ predicted treatment failure/death with 60-90% sensitivity and 60-86% specificity in months 2-5 for Group 1 and months 7-8 for Group 2. All successfully treated children—except Group 2 subjects with unknown microbiologic confirmation status—achieved catch-up weight gain.

Conclusions: Weight change early in therapy can predict outcome of childhood TB treatment.

## INTRODUCTION

Each year, approximately one million children develop tuberculosis (TB) disease [1, 2]. Failure to thrive—i.e., weight loss or lack of expected weight gain—is a complication of TB disease [3]. International guidelines recommend using weight gain as an indicator of good therapeutic response in childhood TB [3-5]. This recommendation is based on expert opinion. While studies have shown associations between weight gain and good therapeutic response in adults with TB [6-13], few studies have described weight trends in children on TB treatment [14, 15].

From a clinical perspective, the early identification of children who are failing therapy allows for timely intervention, such as adherence support or regimen modification. From a research perspective, a well-validated surrogate endpoint would facilitate clinical trials. For adults with TB disease, sputum smear and/or culture conversion are used to evaluate regimen efficacy [16]. However, <30% of children have microbiologically confirmed disease [17]. Resolution of radiographic abnormalities and clinical symptoms are suboptimal markers of treatment response: radiographic abnormalities lag behind clinical response, and symptom reporting is subjective. Therefore, there is a need to evaluate other markers—like weight change—of treatment response in children.

Another knowledge gap is whether children who are successfully treated for TB disease achieve catch-up weight gain. Characterizing weight reconstitution among TB-affected children could identify needs for nutritional supplementation and help clinicians provide anticipatory guidance to families.

We addressed these knowledge gaps using data from children treated for TB disease in Lima, Peru. Our cohort included children treated for drug-susceptible TB and children treated for multidrug-resistant (MDR)-TB, caused by strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin. We aimed to (1) evaluate the association between weight change early in therapy and treatment outcome; (2) determine the accuracy of weight change as a predictor of regimen efficacy; and (3) assess whether successfully treated children achieve catch-up weight gain.

## METHODS

### *Setting and study population*

This study took place in Lima, Peru's capital and home to 30% of its population of 32 million [18]. Lima accounts for 54% of the 31,000 TB cases notified annually in the country [19]. Peru has a human immunodeficiency virus (HIV) prevalence of 0.3% among 15-49 year-olds [20].

Peru's National TB Program (NTP) provides free TB treatment at public health centers, where clinical charts for these patients are kept. Additionally, the NTP maintains medical records of all patients treated for MDR-TB in Peru.

We enrolled children treated for TB that was microbiologically confirmed or clinically diagnosed per NTP guidelines [21, 22]. We enrolled all children ≤17 years of age who began treatment for drug-susceptible TB between 2012 and 2014 at eight health centers with high volumes of TB patients and longstanding collaborations with our research group. We also enrolled all children ≤15 years of age who initiated MDR-TB therapy anywhere in the Lima metropolitan area between 2005 and 2009. We did not include 16- and 17-year-olds who initiated MDR-TB therapy because their clinical data were not available to us. We divided participants into two groups. Group 1 consisted of children initially treated for drug-susceptible TB, which included subjects who failed treatment for drug-susceptible TB disease and were subsequently diagnosed with MDR-TB. Group 2 consisted of participants with confirmed MDR-TB (i.e. they had their own *M. tuberculosis* isolate with confirmed resistance to at least isoniazid and rifampin) or

probable MDR-TB (i.e. they lacked their own isolate but had a presumed source case with confirmed MDR-TB) [23]. Some children with MDR-TB had extensively drug-resistant (XDR)-TB, caused by MDR strains of *M. tuberculosis* with additional resistance to a fluoroquinolone and a second-line injectable agent. During the study period, DSTs were performed with the proportional method, microscopic observation drug susceptibility [24], and/or the nitrate reduction assay [25].

*Weight-for-age Z-scores*

Weight-for-age z-score (WAZ) compares a child's weight to children of the same age and sex from a healthy reference population. Distributions of weight-for-age measures are created for each sex over the spectrum of ages; the z-score is the number of standard deviations (SDs) from the age- and sex-appropriate mean. The change in WAZ between two time points, or ΔWAZ, denotes weight change in comparison to the reference population. ΔWAZ of 0 represents age- and sex-appropriate weight gain. ΔWAZ>0 indicates catch-up weight gain, or weight attainment above normal limits following a period of slowed development. Since the World Health Organization (WHO) does not publish WAZ standards for children >10 years, we used the reference from the U.S. Centers for Disease Control and Prevention (CDC) to calculate WAZ scores [26].

*Definitions*

We defined microbiologic confirmation as the visualization of bacilli on acid-fast smear or the isolation of *M. tuberculosis* from culture. Following Wiseman *et al*., we classified participants into those with severe and non-severe disease [27].

At the end of therapy, participants were assigned treatment outcomes by a clinician according to NTP guidelines: cure, treatment completion, loss to follow-up, transfer, treatment failure, or death [21, 22]. For this analysis, we grouped cure and treatment completion together under treatment success. We classified participants as having an unknown outcome if no treatment outcome was recorded in the medical record; this category differs from loss to follow-up, which is an outcome recorded in the patient's chart.

Health center staff measured each participant's weight at the end of every treatment month, defined as 25 days of supervised doses. We defined baseline weights as those taken ≤30 days of the initiation of the first-line regimen for Group 1 and a second-line regimen for Group 2; end-of-therapy weights as those taken in the final treatment month of successful therapy (month 6 for most Group 1 subjects, month 12 or later for Group 2 subjects); and interim weights as all other weights taken during therapy. $WAZ_{baseline}$ and $WAZ_{final}$ refer to z-scores calculated from baseline and end-of-therapy weights, respectively.

*Clinical care*

Group 1 received first-line regimens—isoniazid, rifampin, ethambutol, and pyrazinamide daily for the first two months, followed by isoniazid and rifampin thrice weekly for ≥4 more months.

Group 2 received second-line regimens that were tailored to the DST result of the participant or his/her presumed source case, contained ≥4 drugs to which the *M. tuberculosis* strain was susceptible, and lasted ≥12 months. Health workers administered directly observed therapy (DOT) at the health center six days a week. No supervised or self-administered doses were given on Sundays. Subjects did not receive nutritional supplements as part of TB therapy.

*Data collection*

At the eight health centers, we collected data on children who received only first-line regimens. At NTP headquarters, we collected data on children who received any second-line regimen; this group included children who experienced treatment failure on the first-line regimen prior to being diagnosed with MDR-TB. From each subject's chart, we abstracted date of birth; sex; HIV status; anatomic site of TB disease; smear, culture, DST, and radiograph results; antibiotics received; treatment outcome; and all weights.

*Exclusion criteria*

We excluded children who lacked baseline and/or interim weights, were lost to follow-up, or had an unknown outcome. Suspecting errors in data entry, we excluded children whose WAZ scores were >6 SDs from the mean. Some participants in Group 1 were classified as having failed treatment if their DST or a source case's DST demonstrated resistance to isoniazid and rifampin. We included these children in Group 1 only if they had documentation of smear or culture positivity and/or radiological worsening after ≥2 months of treatment, despite documented good

adherence [3]. Participants who had received first-line therapy in the six months preceding their second-line regimen were excluded from Group 2.

*Analysis*

We used SAS version 9.4 (SAS Institute, Cary, NC) to perform analyses. To check for selection and loss-to-follow-up biases, we used Fisher's exact test to compare characteristics between included and excluded subjects.

To examine the relationship between weight change and treatment outcome, we used ΔWAZ because it accounts for age- and sex-specific differences in normal childhood growth. We examined ΔWAZ through treatment month 5 for Group 1 since the standard first-line regimen lasts six months, and through month 8 for Group 2 since eight months typically is the maximum duration of the intensive phase of MDR-TB therapy. We calculated ΔWAZ using the following formula: $\Delta WAZ_x = WAZ_x - WAZ_{baseline}$, where x represents the month of interest.

We performed two separate analyses to address the first aim of this study. First, using logistic regression, we evaluated the associations of the following independent variables and treatment outcome (success vs. failure/death) for Groups 1 and 2 separately: $WAZ_{baseline}$, $\Delta WAZ_2$, $\Delta WAZ_3$, $\Delta WAZ_4$, $\Delta WAZ_5$, age (0-4 vs. 5-9 vs. ≥10), sex, microbiologic confirmation, and disease severity. For Group 2, we assessed additional independent variables: $\Delta WAZ_6$, $\Delta WAZ_7$, $\Delta WAZ_8$, and resistance pattern (MDR vs. XDR).

Second, we used generalized estimating equation (GEE) models using the first-order autoregressive correlation structure to detect differences in ΔWAZs between successfully treated children vs. those with failed treatment/died. To determine which covariates (age, sex, microbiologic confirmation, disease severity, resistance pattern) to include in the GEE models, we performed stepwise selection and maintained covariates with $p$-value <0.05.

To address the second aim of this study, we plotted receiver operating characteristic (ROC) curves and calculated area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive values (NPV) to determine the accuracy of ΔWAZ at our time points of interest for predicting treatment failure/death.

Finally, we assessed catch-up weight gain for successfully treated subjects by comparing ΔWAZ between $WAZ_{baseline}$ and $WAZ_{final}$. We used the Student's t-test and analysis of variance with Bonferroni post-hoc tests to compare ΔWAZ between subgroups stratified by age, sex, microbiologic confirmation, and disease severity.

*Ethics*

The Institutional Review Boards (IRBs) of Peru's National Institute of Health, Harvard Medical School, and Baylor College of Medicine approved this study and waived informed consent.

RESULTS

We excluded 71 of 171 subjects from Group 1 and 138 of 232 subjects from Group 2 (Figure 1). Table 1 compares included and excluded participants. Median ages for Groups 1 and 2 were 14.4 (interquartile range [IQR] 12.3-16.65) years and 9.5 (IQR 3.49-13.73) years, respectively. In Group 1, median treatment durations were 6.4 (IQR 6.0-6.9) months in the 74 successfully treated subjects and 4.8 (IQR 3.6-5.7) months in the 26 subjects in whom therapy failed. No participants in Group 1 died. In Group 2, median treatment durations were 20.0 (IQR 18.0-23.8) months for the 83 successfully treated subjects and 14.1 (IQR 5.9-21.9) months for the 10 subjects in whom therapy failed. The one subject in Group 2 who died received treatment for 7.8 months.

*Association between ΔWAZ and treatment outcome*

In logistic regression, female sex and lower $\Delta WAZ_3$, $\Delta WAZ_4$, and $\Delta WAZ_5$ were associated with treatment failure in Group 1. Lower $\Delta WAZ_7$ was associated with treatment failure/death in Group 2 (Table 2).

In the GEE model for Group 1, after adjusting for $WAZ_{baseline}$ and age group, children in whom treatment failed had significantly lower $\Delta WAZ_2$, $\Delta WAZ_3$, $\Delta WAZ_4$, and $\Delta WAZ_5$ than successfully treated children. For Group 2, the GEE model was not adjusted because no covariates were significant in stepwise selection; children in whom treatment failed or who died had lower $\Delta WAZ_6$, $\Delta WAZ_7$, and $\Delta WAZ_8$ compared to successfully treated children (Figure 2a).

When we repeated the GEE model for participants with microbiologically confirmed TB, the findings for Group 1 did not change. In Group 2, children in whom treatment failed or who died had lower $\Delta WAZ_7$ and $\Delta WAZ_8$ values compared to successfully treated children (Figure 2b).

*Accuracy of ΔWAZ as a predictor of treatment outcome*

The AUC of ΔWAZ as a predictor of treatment failure increased as therapy progressed for Group 1. The selected cut-off values had sensitivities of 60-90% and specificities of 60-85% at the end of months 2-5. For Group 2, the AUC of ΔWAZ as a predictor of treatment failure/death was highest at the end of months 7-8. Before month 7, the selected ΔWAZ cut-off values had <43% sensitivity for predicting treatment failure/death (Figure 3, Table 3).

*Catch-up weight gain among successfully treated children*

In Groups 1 and 2, children with severe TB started therapy with lower $WAZ_{baseline}$ compared to children with non-severe TB: -0.97 for severe disease vs. -0.37 for non-severe disease (p=0.02) in Group 1, and -0.82 for severe disease vs. -0.31 for non-severe disease (p=0.04) in Group 2 (Supplementary Table 1). At the end of successful therapy, there were no significant differences in $WAZ_{final}$ for children with severe vs. non-severe TB in Group 1 or 2 (Supplementary Table 2). There were no significant differences in $WAZ_{baseline}$ or $WAZ_{final}$ between subjects stratified by sex, age group, microbiologic confirmation, or resistance pattern in Group 1 or 2.

All successfully treated children achieved catch-up weight gain, except for Group 2 subjects with unknown microbiologic confirmation. In Group 1, children with microbiologically confirmed or severe TB experienced more weight gain than those with unconfirmed or non-severe TB, respectively (Figure 4).

## DISCUSSION

In this study, we found that children who ultimately had treatment success had different weight trajectories compared to those who experienced treatment failure or death. Furthermore, ΔWAZ early in therapy may serve as a moderately sensitive predictor of treatment failure/death for children on first-line TB regimens. ΔWAZ lacks sensitivity for predicting unsuccessful MDR-TB treatment, but its high specificity means that clinicians should strongly consider regimen modification for children with ΔWAZ values below the cut-off value.

For children ≤10 years, clinicians can calculate WAZ using WHO Anthro (www.who.int/childgrowth/software/en/). PediTools (https://peditools.org) and the Children's Hospital of Philadelphia (https://zscore.research.chop.edu) provide links to CDC's WAZ calculator for children ages 2-20. Manual calculation of ΔWAZ is likely to be inaccurate, since growth charts do not capture sufficiently small units of age and weight. Therefore, clinicians in resource-constrained settings, where these technologies may be unavailable, may have difficulty using this tool.

The accuracy of ΔWAZ for predicting pediatric TB treatment outcome should be evaluated in other groups of children. In clinical trials and prospective cohorts of children with TB, it would be useful to collect weights, heights, and mid-upper arm circumference (MUAC) of children and evaluate ΔWAZ and other nutritional measures as predictors of treatment outcome. If validated, ΔWAZ could serve as a red flag to prompt further evaluation of children on TB therapy who may need regimen modification. From a research perspective, ΔWAZ could serve as a surrogate

endpoint for clinical trials, reducing cost and duration and facilitating the use of novel trial designs, such as the multi-stage, multi-arm trial.

In this cohort, we found that all groups of children with successfully treated TB disease achieved catch-up weight gain. In Group 1, children with microbiologically confirmed or severe disease had more weight gain than children with non-microbiologically confirmed or non-severe disease. This finding suggests that successful treatment of TB disease leads to weight recovery; this improvement is most pronounced for the sickest children, who likely begin treatment with a greater weight deficit.

Previous work has shown that children gain weight on TB therapy [14, 15], but our study is the first to demonstrate different weight trends in children who are successfully treated and those who experienced treatment failure or death. This finding is consistent with reported associations between weight gain and treatment outcome in adults on TB treatment [6, 8, 9]. Studies of HIV-infected children on antiretroviral therapy also have shown associations between good treatment response and catch-up growth [28, 29]. Our study is the first to quantify the degree of weight gain in early TB therapy that predicts ultimate outcome.

This analysis had several limitations. The data, which were obtained under programmatic conditions, had missing values. Twenty-seven percent of children in Group 1 and 16% of children in Group 2 were excluded from the analysis due to missing weights; the exclusion of these subjects may have led to a selection bias. In Group 2, there were higher proportions of microbiologically confirmed and severe disease among excluded subjects compared to included

subjects. This exclusion may have minimized the difference in WAZ trajectories between successfully treated children and those who experienced treatment failure or death, considering our finding that children in Group 1 with microbiologically confirmed or severe TB gained more weight than those with non-confirmed or non-severe TB. Second, because few subjects had documented heights and no subjects had MUACs, we could not undertake a more complete evaluation of nutritional recovery, including weight adjusted for height and linear growth. This limitation may be problematic for adolescents, who undergo pubertal growth spurts at different times. Adolescents with earlier-than-average puberty will have relatively higher WAZ, while body mass index-for-age z-scores may track more consistently. Despite the fact that our sample consisted mostly of adolescents, we were still able to demonstrate a clear difference in the weight trajectories of successfully treated subjects vs. those who experienced treatment failure or death.

An important limitation specific to Group 2 was the heterogeneity of second-line regimens, which were individualized to DST profiles and adjusted during therapy because of new DST results, adverse drug events, or stock-outs. Regimen heterogeneity may have impacted our results since different medications have distinct effects on appetite; moreover, ethionamide, a second-line drug used in Peru, may affect thyroid function. Nonetheless, we can still conclude from this analysis that children successfully treated for MDR-TB achieve catch-up weight gain and achieved more early weight gain compared to those who experienced treatment failure or death.

This analysis also had strengths. The enrollment of consecutive children treated for TB disease reduces the potential for selection bias. These data were collected as part of routine care

delivered at public health centers; as a result, the data reflect clinical practice and treatment response in a "real-world" setting. Our study also evaluates weight change in children being treated for drug-susceptible and MDR-TB; this analysis has not been undertaken previously in adults or children.

In conclusion, our study establishes the potential for using weight change early in therapy to predict childhood TB treatment outcome and provides reassurance that successfully treated children achieve catch-up weight gain. If validated in other cohorts, the use of weight change to predict treatment outcome can lead to better outcomes for children with TB disease and more efficient clinical trial design in childhood TB therapy.

## AUTHOR CONTRIBUTIONS

SSC, JFF, JAS, and MCB conceptualized the study. SSC, EW, HDC, and LL collected and managed the data. SP performed the analyses. SSC, SP, JFF, ATC, JAS, and MCB interpreted the results of the analyses. SSC, SP, and EW drafted the manuscript, tables, and figures. All authors revised and approved the final version of this work for publication.

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**Table 1: Comparison between included and excluded subjects**

| | Group 1 (n=171) | | | Group 2 (n=232) | | |
|---|---|---|---|---|---|---|
| | Included (n=100) | Excluded (n=71) | p-value | Included (n=94) | Excluded (n=138) | p-value |
| **Age** | | | 0.55 | | | 0.025 |
| • 0-4 | 6 (6.0%) | 9 (12.7%) | | 35 (37.2%) | 29 (21.0%) | |
| • 5-9 | 6 (6.0%) | 5 (7.0%) | | 12 (12.8%) | 23 (16.7%) | |
| • ≥10 | 88 (88.0%) | 57 (80.3%) | | 47 (50.0%) | 86 (62.3%) | |
| **Sex** | | | 0.32 | | | 0.41 |
| • Female | 43 (43.0%) | 36 (50.7%) | | 48 (51.1%) | 78 (56.5%) | |
| • Male | 57 (57.0%) | 35 (49.3%) | | 46 (48.9%) | 60 (43.5%) | |
| **Microbiologic confirmation** | | | 0.78 | | | 0.011 |
| • Confirmed | 59 (59.0%) | 45 (63.4%) | | 54 (57.4%) | 99 (71.7%) | |
| • Unconfirmed | 13 (13.0%) | 7 (9.9%) | | 28 (29.8%) | 19 (13.8%) | |
| • Unknown | 28 (28.0%) | 19 (26.8%) | | 12 (12.8%) | 20 (14.5%) | |
| **Disease severity** | | | 0.07 | | | 0.021 |
| • Severe | 24 (24.0%) | 26 (36.6%) | | 25 (26.6%) | 57 (41.3%) | |
| • Non-severe | 76 (76.0%) | 45 (63.4%) | | 69 (73.4%) | 81 (58.7%) | |
| **Resistance pattern** | | | --- | | | 0.06 |
| • MDR | --- | --- | | 88 (93.6%) | 136 (98.6%) | |
| • XDR | --- | --- | | 6 (6.4%) | 2 (1.4%) | |

Data are presented as n (% of total).

Abbreviations: MDR, multi-drug resistant; WAZ, weight-for-age z-score; XDR, extensively-drug resistant.

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**Table 2: Associations between study subject characteristics and treatment outcome**

| | Group 1 (n=100) | | | Group 2 (n=94) | | |
|---|---|---|---|---|---|---|
| | Treatment success | Treatment failure/death | OR (95% CI) | Treatment success | Treatment failure/death | OR (95% CI) |
| **Mean $WAZ_{baseline}$** | -0.44 (SD: 1.18) | -0.72 (SD: 0.83) | 0.79 (0.52-1.19) | -0.44 (SD: 0.98) | -0.56 (SD: 1.76) | 0.90 (0.50-1.60) |
| **Mean $\Delta WAZ_2$** | 0.22 (SD: 0.47) | 0.01 (SD: 0.37) | 0.35 (0.11-1.12) | 0.18 (SD: 0.49) | -0.08 (SD: 0.26) | 0.19 (0.01-2.83) |
| **Mean $\Delta WAZ_3$** | 0.41 (SD: 0.88) | -0.08 (SD: 0.47) | 0.25 (0.08-0.78)* | 0.18 (SD: 0.52) | 0.00 (SD: 0.27) | 0.46 (0.10-2.18) |
| **Mean $\Delta WAZ_4$** | 0.32 (SD: 0.58) | -0.07 (SD: 0.41) | 0.33 (0.11-1.00)* | 0.25 (SD: 0.60) | 0.10 (SD: 0.34) | 0.62 (0.18-2.17) |
| **Mean $\Delta WAZ_5$** | 0.40 (SD: 0.41) | -0.20 (SD: 0.53) | 0.02 (0.00-0.29)** | 0.28 (SD: 0.55) | -0.21 (SD: 0.79) | 0.23 (0.06-0.90)* |
| **Mean $\Delta WAZ_6$** | --- | --- | --- | 0.20 (SD: 0.65) | -0.12 (SD: 0.45) | 0.45 (0.13-1.54) |
| **Mean $\Delta WAZ_7$** | --- | --- | --- | 0.25 (SD: 0.59) | -0.25 (SD: 0.48) | 0.22 (0.05-0.92)* |
| **Mean $\Delta WAZ_8$** | --- | --- | --- | 0.30 (SD: 0.63) | -0.27 (SD: 0.55) | 0.20 (0.04-1.05) |
| **Age** | | | | | | |
| • 0-4 years | 6 (100%) | 0 (0%) | Reference | 28 (96.6%) | 1 (3.5%) | Reference |
| • 5-9 years | 6 (100%) | 0 (0%) | --- | 16 (94.1 %) | 1 (5.9%) | 1.75 (0.10-29.92) |
| • ≥10 years | 62 (70.5%) | 26 (29.5%) | --- | 39 (81.3%) | 9 (18.8%) | 6.46 (0.77-53.95) |
| **Sex** | | | | | | |
| • Male | 47 (82.5%) | 10 (17.5%) | Reference | 41 (89.1%) | 5 (10.9%) | Reference |
| • Female | 27 (62.8%) | 16 (37.2%) | 2.79 (1.11-7.00)* | 42 (87.5%) | 6 (12.5%) | 1.17 (0.33-4.14) |
| **Microbiologic confirmation** | | | | | | |
| • Unconfirmed | 13 (100%) | 0 (0%) | Reference | 28 (100%) | 0 (0%) | Reference |
| • Confirmed | 35 (59.3%) | 24 (40.7%) | --- | 44 (81.5%) | 10 (18.5%) | --- |
| • Unknown | 26 (92.9%) | 2 (7.1%) | --- | 11 (91.7%) | 1 (8.3%) | --- |
| **Disease severity** | | | | | | |
| • Non-severe | 55 (72.4%) | 21 (27.6%) | Reference | 61 (89.7%) | 7 (10.3%) | Reference |
| • Severe | 19 (79.2%) | 5 (20.8%) | 0.69 (0.23-2.08) | 22 (84.6%) | 4 (15.4%) | 1.58 (0.42-5.94) |
| **Resistance pattern** | | | | | | |
| • MDR | --- | --- | --- | 77 (87.5%) | 11 (12.5%) | Reference |
| • XDR | --- | --- | --- | 6 (100%) | 0 (0%) | --- |

Unless otherwise stated, data are presented as n (% of total number of each variable).

*p<0.05, **p<0.01

Abbreviations: MDR, multidrug-resistant; N/A, not applicable; SD, standard deviation; WAZ, weight-for-age z-score; XDR, extensively-drug resistant.

**Table 3: Receiver operating characteristic curves characteristics for using change in weight-for-age z-score to predict treatment failure/death**

| | AUC | ΔWAZ cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| **Group 1** | | | | | | |
| • $\Delta WAZ_2$ | 0.68 | 0.142 | 60.0 | 73.1 | 85.7 | 40.4 |
| • $\Delta WAZ_3$ | 0.73 | 0.029 | 81.5 | 60.0 | 86.9 | 50.0 |
| • $\Delta WAZ_4$ | 0.78 | 0.153 | 72.3 | 84.6 | 95.9 | 37.9 |
| • $\Delta WAZ_5$ | 0.83 | -0.024 | 89.8 | 80.0 | 96.4 | 57.1 |
| **Group 2** | | | | | | |
| • $\Delta WAZ_2$ | 0.64 | 0.151 | 42.2 | 100 | 100 | 11.9 |
| • $\Delta WAZ_3$ | 0.61 | 0.342 | 28.6 | 100 | 100 | 15.3 |
| • $\Delta WAZ_4$ | 0.57 | 0.303 | 42.9 | 88.9 | 96.8 | 16.7 |
| • $\Delta WAZ_5$ | 0.69 | 0.425 | 40.6 | 100 | 100 | 16.3 |
| • $\Delta WAZ_6$ | 0.67 | 0.320 | 40.3 | 100 | 100 | 14.9 |
| • $\Delta WAZ_7$ | 0.75 | 0.145 | 62.3 | 85.7 | 97.7 | 18.8 |
| • $\Delta WAZ_8$ | 0.76 | 0.129 | 64.6 | 80.0 | 97.7 | 14.8 |

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; WAZ, weight-for-age z-score; $\Delta WAZ_x$, change in WAZ between baseline and the end of treatment month x.

**Supplementary Table 1: $WAZ_{baseline}$ of Study Subjects**

| | Group 1 | | | Group 2 | | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) | p-value | n | Mean (SD) | p-value |
| **All participants** | 100 | -0.51 (1.10) | --- | 94 | -0.45 (1.09) | --- |
| **Age** | | | | | | |
| • 0-4 years | 6 | -0.69 (0.70) | 0.74 | 29 | -0.44 (0.80) | 0.09 |
| • 5-9 years | 6 | -0.21 (1.05) | | 17 | 0.04 (1.45) | |
| • ≥10 years | 88 | -0.52 (1.13) | | 48 | -0.64 (1.06) | |
| **Sex** | | | | | | |
| • Male | 57 | -0.49 (1.21) | 0.76 | 46 | -0.38 (1.11) | 0.51 |
| • Female | 43 | -0.55 (0.95) | | 48 | -0.53 (1.07) | |
| **Microbiologic confirmation** | | | | | | |
| • Unconfirmed | 13 | -0.19 (1.47) | 0.14 | 28 | -0.35 (0.91) | 0.12 |
| • Confirmed | 59 | -0.69 (1.07) | | 54 | -0.62 (1.08) | |
| • Unknown | 28 | -0.29 (0.93) | | 12 | 0.05 (1.39) | |
| **Disease severity** | | | | | | |
| • Non-severe | 76 | -0.37 (1.02) | 0.019 | 68 | -0.31 (1.13) | 0.044 |
| • Severe | 24 | -0.97 (1.25) | | 26 | -0.82 (0.89) | |
| **Resistance pattern** | | | | | | |
| • MDR | --- | --- | --- | 88 | -0.45 (1.07) | 0.83 |
| • XDR | --- | --- | | 6 | -0.54 (1.46) | |
| **Treatment outcome** | | | | | | |
| • Treatment success | 74 | -0.44 (1.18) | 0.19 | 83 | -0.44 (0.98) | 0.82 |
| • Treatment failure or death | 26 | -0.72 (0.83) | | 11 | -0.56 (1.76) | |

Abbreviations: IQR, interquartile range; MDR, multi-drug resistant; WAZ, weight-for-age z-score; XDR, extensively-drug resistant.

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**Supplementary Table 2: $WAZ_{final}$ of Study Subjects**

| | Group 1 | | | Group 2 | | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) | p-value | n | Mean (SD) | p-value |
| **All participants** | 100 | -0.08 (1.05) | --- | 94 | -0.04 (1.01) | --- |
| **Age** | | | | | | |
| • 0-4 years | 6 | -0.26 (0.87) | 0.78 | 29 | 0.34 (0.76) | 0.10 |
| • 5-9 years | 6 | 0.18 (0.94) | | 17 | 0.06 (1.35) | |
| • ≥10 years | 88 | -0.10 (1.08) | | 48 | -0.28 (0.95) | |
| **Sex** | | | | | | |
| • Male | 57 | -0.05 (1.13) | 0.72 | 46 | 0.06 (1.09) | 0.41 |
| • Female | 43 | -0.15 (0.88) | | 48 | -0.15 (0.93) | |
| **Microbiologic confirmation** | | | | | | |
| • Unconfirmed | 13 | -0.03 (1.12) | 0.63 | 28 | 0.19 (0.74) | 0.31 |
| • Confirmed | 59 | 0.02 (1.13) | | 54 | -0.21 (1.03) | |
| • Unknown | 28 | -0.26 (0.88) | | 12 | 0.13 (1.55) | |
| **Disease severity** | | | | | | |
| • Non-severe | 76 | 0.05 (1.03) | 0.10 | 68 | 0.10 (1.00) | 0.08 |
| • Severe | 24 | -0.45 (1.05) | | 26 | -0.39 (0.98) | |
| **Resistance pattern** | | | | | | |
| • MDR | --- | --- | --- | 88 | -0.05 (1.03) | 0.71 |
| • XDR | --- | --- | | 6 | 0.17 (0.78) | |

Abbreviations: IQR, interquartile range; MDR, multi-drug resistant; WAZ, weight-for-age z-score; XDR, extensively-drug resistant.

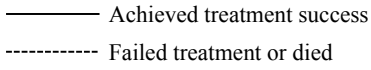
2

# FIGURE LEGENDS

**Figure 1**

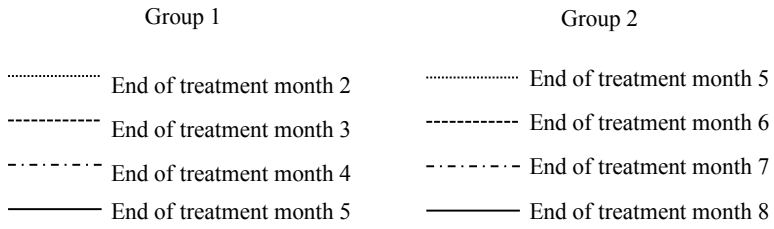
Abbreviations: MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis; WAZbaseline, weight-for-age z-score within 30 days of the start of tuberculosis therapy. The start of tuberculosis therapy refers to the start of a first-line regimen for Group 1 and a second-line regimen for Group 2.

**Figure 2**




Abbreviations: ΔWAZ, delta (change in) weight-for-age z-score.
*p-value <0.05.
**p-value <0.01.
***p-value <0.001.
Values represent least square mean +/- 95% confidence interval for each time point using generalized estimating equation models. After stepwise selection, we adjusted for $WAZ_{baseline}$ and microbiologic confirmation in Group 1, but did not adjust for any covariates in Group 2.
The numbers of participants in Group 1 contributing to the overall analysis were as follows: 96 for month 2, 85 for month 3, 78 for month 4, and 69 for month 5. In Group 2, the numbers were 69 for month 2, 79 for month 3, 79 for month 4, 78 for month 5, 74 for month 6, 76 for month 7, and 70 for month 8. The numbers of participants in Group 1 contributing to the sensitivity analysis were as follows: 58 for month 2, 52 for month 3, 46 for month 4, and 39 for month 5. In Group 2, the numbers were 39 for month 2, 46 for month 3, 43 for month 4, 43 for month 5, 41 for month 6, 43 for month 7, and 38 for month 8.

**Figure 3**




See Table 3 for area under the curve (AUC) values.

**Figure 4**

Abbreviations: ΔWAZ, delta (change in) weight-for-age z-score.
This analysis excludes study subjects without documented end-of-therapy weights. Number of subjects in each subgroup appears in parentheses below subgroup name. The only significant differences among subgroups are indicated in the figure.

**Figure 1: Included and excluded subjects**

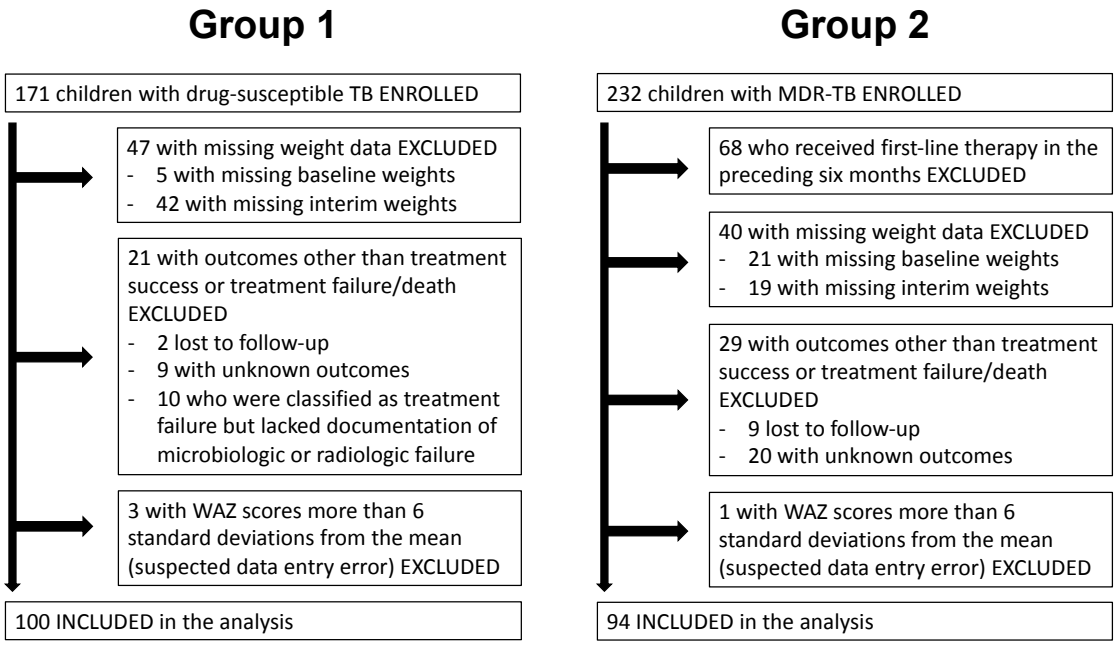


**Figure 2a: Adjusted ΔWAZ for children who were successfully treated vs. children who failed treatment/died (microbiologically confirmed and clinically diagnosed cases)**

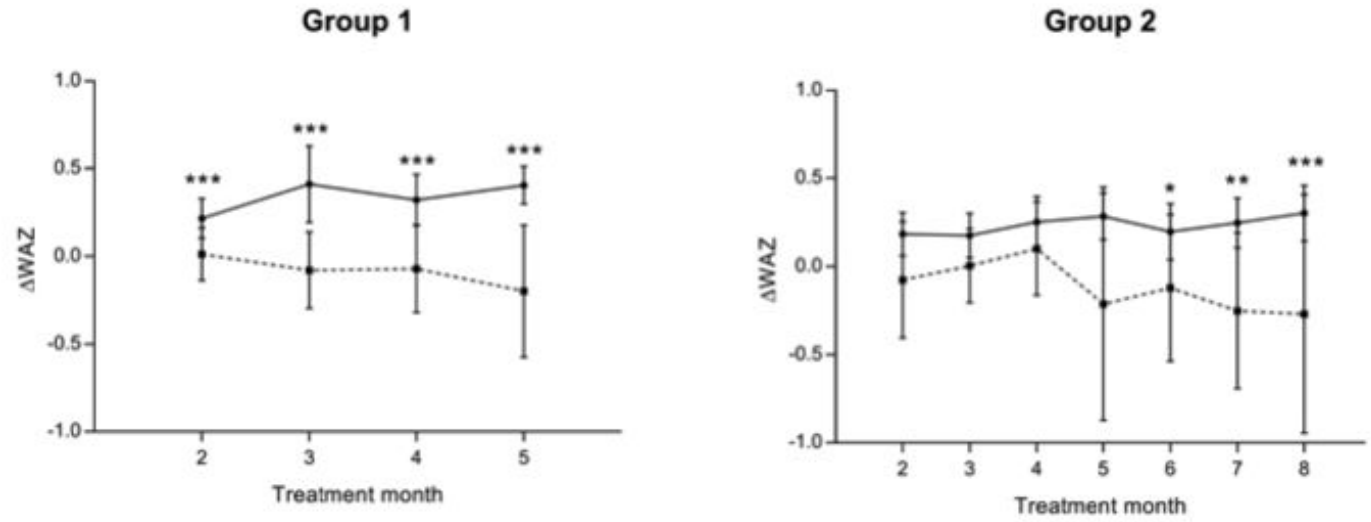



**Figure 2b: Adjusted ΔWAZ for children who were successfully treated vs. children who failed treatment/died (microbiologically confirmed cases only)**

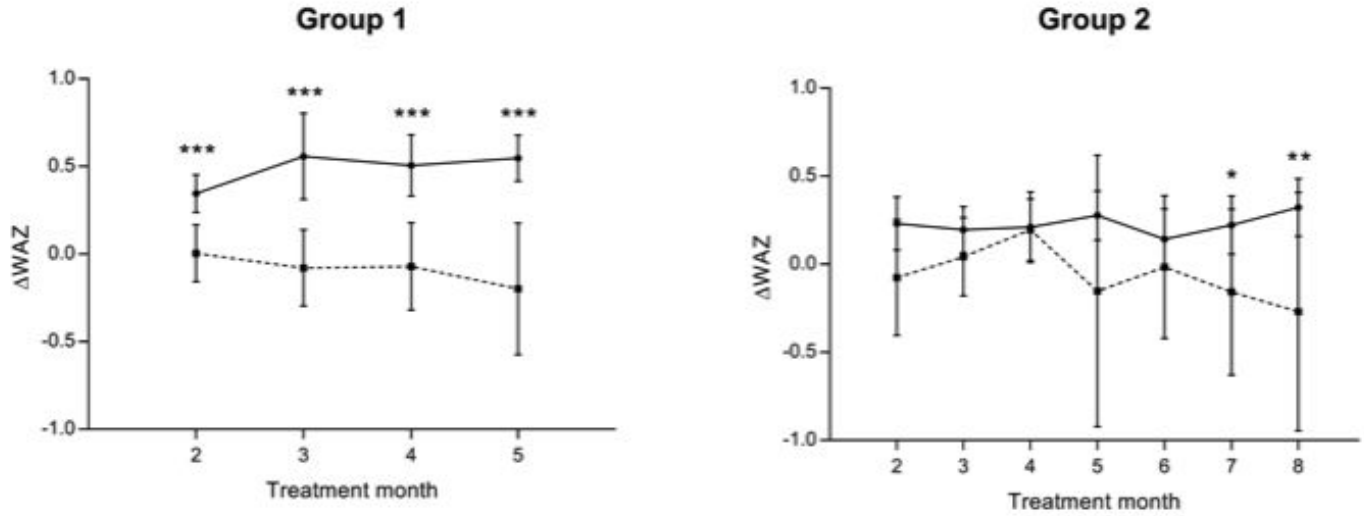


**Figure 3: Receiver operating characteristic curves for using change in weight-for-age z-score to predict treatment failure/death**

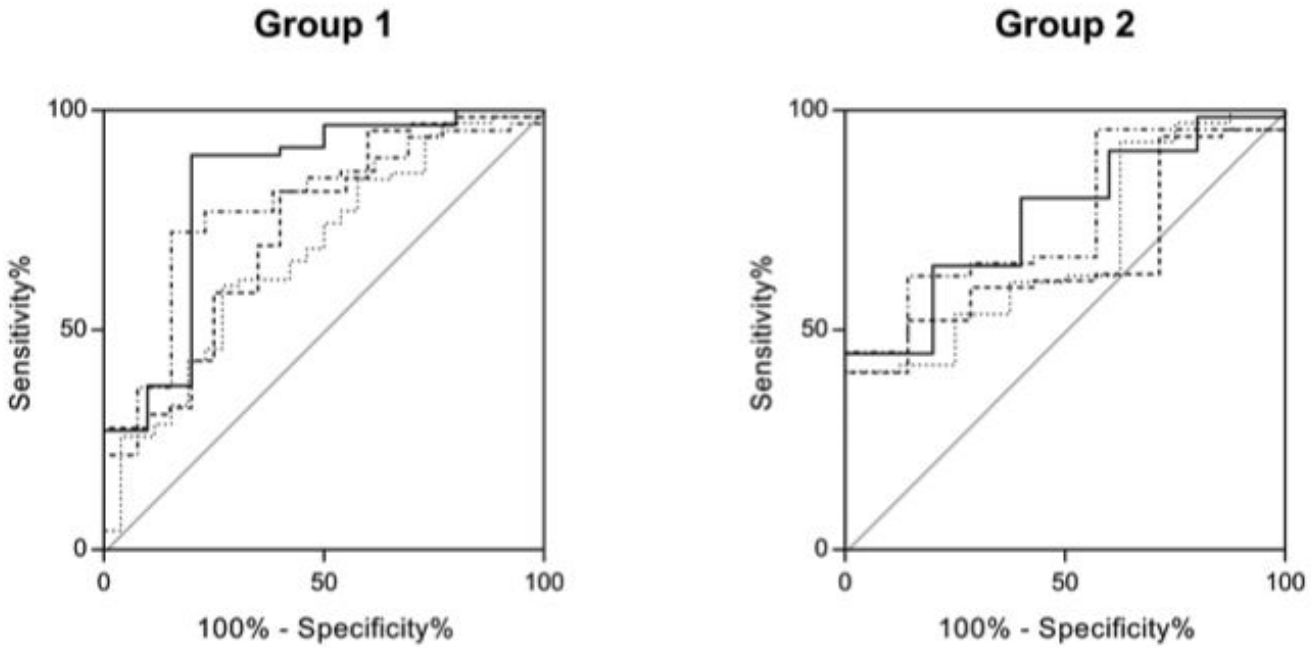


**Figure 4: Change in weight-for-age z-score between baseline and end-of-therapy among successfully treated children**