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Radiographic and Microbiologic Predictors of Treatment Outcomes in Patients Treated with a Shortened All-Oral Regimen for Multidrug- or Rifampicin-Resistant Tuberculosis (MDR/RR-TB) in Lesotho

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Abstract

Background Shortened, all-oral regimens endorsed by the WHO have improved tolerability and outcomes for MDR/RR-TB, treatment but predictors of poor outcomes under these regimens remain incompletely characterized. We evaluated baseline microbiologic and radiographic predictors of unfavorable outcomes among patients receiving a 9-month all-oral regimen in Lesotho. Methods We conducted a prospective study of adults with bacteriologically-confirmed, fluoroquinolone-susceptible pulmonary MDR/RR-TB treated with a 9-month regimen of levofloxacin, bedaquiline, delamanid, linezolid, and clofazimine. Baseline radiographic features (cavitation, fibrosis, bilateral involvement) and sputum smear grade were assessed. Associations with time to culture conversion, end-of-treatment outcomes, and final post-treatment outcomes were evaluated using Cox and logistic regression. Results Among 238 participants (median age 41 [IQR 31–56], 29% female, 62% living with HIV), 90.8% and 88.7% achieved favorable end-of-treatment and final post-treatment outcomes, respectively. Fibrosis, cavitation, bilateral disease, and high smear grade were associated with delayed culture conversion and lower odds of treatment success. Bilateral disease was more strongly associated with unfavorable outcomes in those without HIV, whereas fibrosis and high smear grade showed stronger associations among those with HIV. Phenotypes of cavitation plus high smear grade (OR 0.36, 95% CI 0.13–0.99), and severe fibrocavitary disease (multi-lobar fibrosis and any cavities, or cavities ≥5 cm and any fibrosis) (OR 0.20, 95% CI 0.06–0.65) were associated with reduced odds of favorable final outcomes. Conclusion Baseline radiographic and microbiologic features, particularly in combination, identify patients at higher risk of unfavorable outcomes with shortened all-oral MDR/RR-TB regimens and may inform risk-adapted strategies in high-burden settings.

40-Word Summary

Baseline chest radiographic and smear features, particularly in combination, predict poor outcomes among patients receiving a shortened all-oral regimen for pulmonary MDR/RR-TB in Lesotho. Early radiographic and sputum findings may contribute to patient risk-stratification.

INTRODUCTION

Multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) continues to represent a substantial global public health concern, accounting for a significant proportion of the overall tuberculosis (TB) disease burden [1]. Treatment of MDR/RR-TB has historically been limited by reliance on prolonged 18 to 24-month, injectable containing regimens associated with considerable toxicity, contributing to poor adherence, high rates of adverse events, and suboptimal therapeutic efficacy [2].

Recent advancements in pharmacotherapy, including the development and evaluation of shorter, all-oral regimens, have marked a turning point in MDR/RR-TB management. A growing body of randomized clinical trials has demonstrated that shortened all-oral regimens of 6 to 12 months can achieve treatment outcomes comparable, if not superior, to those of conventional longer regimens, with improved tolerability and simplified implementation [3-5]. This has led the World Health Organization (WHO) to issue updated

recommendations supporting the use of several standardized, shortened all-oral regimens for treating MDR/RR-TB. Subsequent prospective cohorts implemented under operational research settings have supported the effectiveness and safety of these regimens in real-world settings [6-9].

To-date, patient-level factors associated with unfavorable outcomes for those who are treated with shortened all-oral regimens remain incompletely characterized, with existing evidence limited by heterogeneous regimens and endpoints, and limited evaluation of detailed radiographic features and key subgroups. Small cohorts of patients with pulmonary MDR/RR-TB treated with prolonged, injectable-containing regimens have reported prolonged time to culture conversion in those with baseline cavitary disease [10, 11]. One meta-analysis of individual patient data from three phase 3 trials also suggested that microbiologic and radiographic clinical phenotypes, namely concomitant presence of both cavitary disease and a high smear grade, may hold predictive value in identifying patients with difficult-to-treat disease [12]. This study was conducted for drug-susceptible pulmonary TB; similar findings regarding the combined phenotype were subsequently reported in a large prospective cohort of patients with MDR/RR-TB treated with bedaquiline- or delamanid-containing prolonged regimens, and an individual participant meta-analysis of 5,596 patients with MDR/RR-TB treated with longer regimens [13, 14]. Prolonged time to culture conversion associated with this phenotype was also observed in a small prospective cohort of patients treated with a shortened all-oral regimen [9].

Whether additional radiographic features, such as baseline presence of fibrosis, bilateral pulmonary involvement, or the relative size and number of cavitary/fibrotic lesions, may improve prediction of poor outcomes among patients with pulmonary MDR/RR-TB is largely unknown. The prognostic utility of these features among patients with HIV co-infection—which has been associated with atypical radiographic presentation—also requires further investigation [15, 16].

Identifying microbiological and radiographic characteristics that distinguish individuals at high risk for unfavorable outcomes may permit further optimization of therapeutic strategies. This is particularly pertinent in high-burden, resource-limited settings of sub-Saharan Africa, where timely identification of patients at risk for poor outcomes may help to improve treatment success and enhance resource allocation. Lesotho, which has one of the highest TB incidence rates globally, high rates of HIV co-infection, and a high prevalence of MDR/RR-TB, represents a priority setting for such analyses [17]. In this context, we aim to characterize radiographic and microbiologic predictors—individually and in combination—of unfavorable treatment outcomes among individuals who received a standardized 9-month all-oral regimen for MDR/RR-TB, implemented under operational research conditions in Lesotho. Given the high rates of HIV co-infection prevalence within the study population, we also aim to assess how these predictors perform when applied to those living with and without HIV.

METHODS

Study Design and Population

We conducted a prospective observational study within the Lesotho National Tuberculosis and Leprosy Program. We enrolled adults (aged ≥18 years) with confirmed pulmonary MDR/RR-TB from clinics at national public sector referral hospitals between September 2020 and October 2023. A full list of exclusion criteria can be found in the Supplementary Material (Appendix A). For this analysis, we excluded participants if they were withdrawn from the study (e.g., late exclusion due to baseline drug resistance, or severe extra-pulmonary disease) (n=11), lost to follow-up (n=2), or transferred to a non-study site (e.g., South Africa) (n=4). Final post-treatment follow-up for those treated with the standardized regimen continued through April 2025.

Standardized All-Oral Treatment Regimen

Eligible participants who provided consent received the five-drug all-oral study regimen for pulmonary MDR/RR-TB consisted of bedaquiline, linezolid, levofloxacin, clofazimine, and delamanid. The planned treatment course was 39 weeks, but treatment could be extended to 12 months based on response at four months or clinical discretion.

Study Procedures

National guidelines and the endTB clinical treatment guide for all-oral shortened treatment regimens informed patient monitoring. These details have been reported [18]. and included a thorough medical history, clinical exam, HIV testing and counselling, sputum collection and chest X-ray.

Laboratory evaluation of the collected sputum sample included sputum smear microscopy, culture, Xpert MTB/RIF (or other molecular resistance testing, as available), and culture-based first and second-line drug susceptibility testing (DST). Smear results were graded semi-quantitatively from scanty to 3+ based on national and WHO/Global Laboratory Initiative guidelines [19]. Baseline chest radiography was evaluated for specific disease features, including cavitation (with measurement of lesions for diameter <5cm versus ≥5cm), fibrosis (single versus multiple lobes), and bilateral involvement. Follow-up sputum smear and culture were conducted monthly throughout treatment. After treatment completion, patients were asked to return monthly for 12 of post-treatment follow-up; sputum was collected for smear and culture at each follow-up appointment.

Clinical Phenotypes of Interest

In addition to the aforementioned individual radiographic and smear features, we evaluated two candidate phenotypes. The first was concomitant baseline presence of high smear grade and cavitary disease, previously identified as a ‘difficult-to-treat' phenotype[12]. The second was severe fibrocavitary disease, defined here as baseline radiographic evidence of both cavitary disease and fibrosis, with at least one of the following: (a) cavitary lesion ≥5cm in diameter, or (b) multi-lobar involvement of fibrotic lesions.

Outcomes Reporting

We considered three primary outcomes: time to culture conversion, end-of-treatment outcome, and final post-treatment outcome. Culture conversion was defined as two consecutive negative sputum cultures obtained at least 7 days apart, with the specimen collection date of the first negative result used as the date of conversion [20].

Study clinicians determined end-of-treatment outcomes, based on definitions provided by the 2013 WHO reporting framework for tuberculosis [21]. Participants were considered 'cured' if treatment was completed without evidence of failure, with three or more negative consecutive cultures taken at least 30 days apart at the end of treatment. The outcome of 'completed' was assigned if treatment was completed without evidence of failure, but there was no record of obtaining three or more consecutive negative cultures at least 30 days apart by the end of treatment. Treatment failure was defined as a permanent regimen change of at least two initial agents due to lack of conversion, bacteriological reversion, evidence of acquired resistance, or adverse drug reactions. End-of-treatment outcome was deemed overall 'favorable' if a participant was assigned the status of 'cured' or 'completed' and deemed 'unfavorable' if treatment failed (based on outcomes reporting definitions described above) or if the participant died during treatment [21].

Post-treatment outcomes were assessed among individuals with a favorable end-of-treatment outcome. TB recurrence was defined as either (a) two consecutive positive cultures, or (b) one positive culture with clinical signs and symptoms and radiographic deterioration after completion of treatment. For any documented post-treatment deaths, chart review, clinical history, and collateral information provided by the participant's contacts were used to assess whether the event may have been TB-related.

Final post-treatment outcome was classified as 'favorable' if a participant had an initially favorable end-of-treatment outcome, and subsequently did not have any documented evidence of TB recurrence or TB-related mortality during the follow-up window. Final post-treatment outcome was 'unfavorable' for all participants who died or failed during therapy, and those found to have TB recurrence or a TB-related death during the follow-up window.

Statistical Analysis

We conducted univariable and multivariable regressions of baseline chest radiographic and sputum smear features on the three outcomes. Baseline radiographic variables of interest included the presence of cavitary disease, fibrotic disease, and bilateral pulmonary involvement. Baseline sputum smears and cultures were defined as those collected in the window from 90 days before to 7 days after treatment initiation. Although extending the baseline window beyond treatment initiation can introduce selection bias in culture conversion analyses [22], this risk was negligible in our cohort, given that only one death occurred in the first 7 days of treatment. Smears were classified as 'high-grade' if assessed to be at least 2+ on initial microscopy.

We conducted Cox proportional hazards regression analyses to estimate associations with time to culture conversion from treatment start and logistic regression analyses for end-of-treatment and post-treatment

outcomes. For time-to-culture-conversion, participants were right-censored if they died or experienced treatment failure prior to confirmed conversion. For each of the three outcomes, we evaluated the four baseline predictors using univariable models and in a single multivariable model including all four predictors. We then evaluated combined phenotypes of these clinical characteristics in separate models.

Due to the high prevalence of HIV/TB co-infection in Lesotho, we also stratified analyses by HIV status to examine whether individual factors predicted outcomes similarly among those with and without HIV. We used Firth penalized logistic regression in stratified analyses with complete separation/perfect prediction [23]. Stratified analyses were not conducted for the combined clinical phenotypes due to small numbers.

We report hazard ratios (HRs) for Cox regressions, odds ratios (ORs) for logistic regressions, and their respective 95% Wald confidence intervals and two-sided Wald p-values.

The missing indicator method was applied to account for the small amount of missing data. We assessed collinearity between individual smear and radiographic predictors by calculating variance inflation factors and pairwise correlation coefficients. We conducted sensitivity analyses using complete case analyses, and sensitivity analyses with inclusion of the two participants who were lost to follow-up as having unfavorable end-of-treatment and final post-treatment outcomes. Analyses were conducted in STATA 18 (College Station, TX: StataCorp LLC).

Research Ethics

This study was approved by the Lesotho Ministry of Health National Ethics Committee and the Harvard Longwood Campus Institutional Review Board. All participants gave written informed consent.

RESULTS

Overview

In all enrolled participants, 238 (93.3%) were analyzed (Supplementary Figure 1). Of these, 148 (62.2%) were living with HIV (Table 1). At baseline, 67 (32.3%) participants had evidence of cavitary disease, 59 (28.6%) of fibrotic lesions, and 95 (46.1%) of bilateral pulmonary involvement. Thirty-one (13.0%) did not have a baseline chest X-ray available. High sputum smear grade was noted in 67 (32.5%) participants. Baseline radiographic and smear features among those living with HIV and those living without HIV were similar (Table 1). Among those with HIV, 43 had cavitary disease (34.1%), and 42 (33.4%) had a sputum smear grade ≥2.

Both cavitary disease and high smear grade was present in 33 (18.3%) participants. Severe fibrocavitary disease was present in 14 (6.4%); there was partial overlap in the distribution of these two phenotypes (Supplementary Figure 2).

Time to Culture Conversion

145 (69.7%) had a positive baseline culture. Of these, 139 (95.9%) achieved culture conversion. Six participants (4.2%) did not experience culture conversion: five died prior to conversion, and treatment failed in one individual. The median time to conversion was 55 days (IQR: 29-80) among those who converted.

In univariable analyses, bilateral disease (univariable HR: 0.52, 95% confidence interval [CI]: 0.36-0.75) or high smear grade (univariable HR: 0.61, 95%CI: 0.43-0.87) were associated with longer time-to-conversion in the overall cohort (Table 2). In multivariable analyses including all four features, bilateral disease was most strongly associated with prolonged time-to-conversion (multivariable HR: 0.57, 95%CI: 0.37-0.86).

Among those without HIV, baseline fibrosis (univariable HR: 0.42, 95%CI: 0.22-0.82; multivariable HR: 0.57, 95%CI: 0.25-1.29) and cavitary disease (univariable HR: 0.50, 95%CI: 0.26-0.96; multivariable HR 0.63, 95%CI: 0.31-1.32) were the individual factors with strongest association with prolonged time-to-conversion. Among those with HIV, baseline bilateral disease (univariable HR: 0.45, 95%CI: 0.28-0.71; multivariable HR: 0.44, 95%CI: 0.26-0.73) was the individual factor most strongly associated with culture conversion (Table 3).

Participants with both cavitary disease and a high smear grade (unadjusted HR: 0.57, 95%CI: 0.37-0.88), and those with severe fibrocavitary disease, had longer times to culture conversion (unadjusted HR: 0.49, 95%CI: 0.24-1.00) (Figure 1A, 1B).

End-of-Treatment Outcome

Of the 238 participants, 216 (90.8%) had a favorable end-of-treatment outcome (Supplementary Figure 1). Unfavorable outcomes included 19 deaths and three failures of treatment.

Presence of cavitary disease, fibrotic lesions, bilateral pulmonary involvement, or high smear grade were inversely associated with odds of favorable outcomes (Table 2). Overall, baseline fibrosis demonstrated the strongest inverse association with favorable outcome status (univariable OR: 0.31, 95%CI: 0.12-0.83; multivariable OR: 0.45, 95%CI: 0.16-1.27). Mean variance inflation factor of the individual predictors was 1.22 (range: 1.07-1.36). There were no pairwise correlation coefficients above 0.5 (maximum: 0.43, cavitary disease and bilateral disease).

Among those without HIV, bilateral disease was the individual factor with strongest inverse association with favorable outcome status (univariable OR: 0.20, 95%CI: 0.03-1.23; multivariable OR: 0.29, 95%CI: 0.04-2.04). The association was weaker for those living with HIV (univariable OR: 0.54, 95%CI: 0.16-1.80, multivariable OR: 0.76, 95%CI: 0.19-2.98). Among those with HIV, fibrosis was the individual factor with the strongest inverse association (univariable OR: 0.30, 95%CI: 0.09-1.00, multivariable OR: 0.37, 95%CI: 0.10-1.35).

Participants with both cavitary disease and a high smear grade (univariable OR: 0.33, 95%CI: 0.11-0.98), and those with severe fibrocavitary disease (univariable OR: 0.24, 95%CI:0.07-0.84), had lower odds of a favorable end-of-treatment outcome (Figure 2). Among patients who had a low smear grade (negative,

scanty, or 1+), severe fibrocavitary disease remained associated with lower odds of a favorable outcome (OR: 0.14, 95%CI: 0.02-0.86).

Final Post-Treatment Outcome

Among 216 participants with favorable end-of-treatment outcomes, 5 (2.3%) had an unfavorable post-treatment event related to TB—one individual died with clinical evaluation suggestive of post-TB lung disease, and four experienced TB recurrence (Supplementary Figure 1).

Presence of cavitary disease, fibrotic lesions, bilateral pulmonary involvement, or high smear grade were inversely associated with odds of a favorable final outcome (Table 2). Among those without HIV, bilateral disease held the strongest inverse association with favorable outcomes (univariable OR: 0.14, 95%CI: 0.02-0.85; multivariable OR: 0.19, 95%CI: 0.03-1.20) (Table 3). Among those with HIV, fibrosis (univariable OR: 0.33, 95%CI: 0.11-1.01; multivariable OR: 0.46, 95%CI: 0.14-1.49) and high smear grade (univariable OR: 0.27, 95%CI: 0.08-0.88; multivariable OR: 0.38, 95%CI: 0.10-1.36) had the strongest inverse associations.

Participants with both cavitary disease and a high smear grade (univariable OR: 0.28, 95%CI: 0.10-0.75), and those with severe fibrocavitary disease (univariable OR: 0.20, 95%CI: 0.06-0.65) had lower odds of favorable final outcomes (Figure 2). Among patients who had a low smear grade, severe fibrocavitary disease remained associated with lower odds of a favorable final outcome (OR: 0.13, 95%CI: 0.02-0.83).

Across all three outcomes, models adjusting the two clinical phenotypes for each other yielded similar estimates to univariable models, though confidence intervals were wider (Figure 2).

Treatment Outcomes Sensitivity Analyses

Sensitivity analyses using a complete-case approach and including the two participants lost to follow-up as ‘unfavorable’ outcomes yielded similar findings (Supplementary Tables 2-6).

DISCUSSION

In this prospective observational cohort of individuals treated with a standardized 5-drug, 9-month all-oral regimen for MDR/RR-TB in Lesotho, specific baseline radiographic and microbiologic features demonstrated notable associations with prolonged culture conversion and lower odds of successful therapy.

Individually, the presence of cavitary disease, fibrotic lesions, bilateral pulmonary involvement, and high sputum smear grade were associated with longer times to culture conversion and favorable end-of-treatment or post-treatment outcomes. To our knowledge, this is among the first studies to characterize these associations within the context of a shortened, all-oral regimen for pulmonary MDR/RR-TB. These results align with several prior studies of drug-susceptible or MDR-TB (treated with prolonged, injectable-containing regimens) which have identified radiographic features (cavitation, bilateral disease) as markers

of delayed sputum conversion or a more chronic, slow-to-improve disease state [10, 11, 13, 24, 25]. Multivariable analyses including all four features generally resulted in wider confidence intervals, likely the result of several factors including the small number of unfavorable outcomes and some limited degree of collinearity between predictors (though variance inflation factor and pairwise correlations were reassuringly low).

Of note, when comparing across the three outcome measures, we find that fibrosis demonstrated strong inverse associations with favorable end-of-treatment and post-treatment outcomes, but limited signal for time to culture conversion. This stands in contrast to bilateral disease, for which magnitudes of overall point estimates across outcomes remained relatively similar. These observations suggest that baseline fibrotic lesions may hold prognostic utility particularly for final treatment outcomes. Fibrotic lesions may be reflective of a more extensive prior history of TB disease and/or treatment [26]. As mining is also common in Lesotho and South Africa; it is possible that the higher frequencies of fibrosis observed in this population are reflective of pulmonary risks associated with this occupational exposure.

Given the associations we observed for individual radiographic and microbiologic features, it is not surprising that their co-occurrence as part of combined clinical phenotypes was also associated with greater risk. Participants presenting with both cavitary disease and high smear grade had markedly prolonged time to culture conversion and were substantially less likely to experience treatment success, reaffirming prior reports of a “difficult-to-treat” clinical phenotype [9, 12-14]. We also identify a second phenotype consisting of severe fibrocavitary disease which was associated with poor end-of-treatment and post-treatment outcomes, including in the subset of participants with low sputum smear grades. These alternative criteria may be relevant for patient subgroups which are more likely to present with low-grade smear results, such as those with HIV, those who are older, and those with no tobacco use—further evaluation in larger cohorts is needed to validate these results.

Stratification by HIV status also revealed several differences among individual predictors. For example, bilateral pulmonary involvement, which demonstrated an association with unfavorable end-of-treatment and final post-treatment outcomes in those without HIV, had an attenuated point estimate among those living with HIV. In those living with HIV, baseline fibrosis and high smear grade had stronger individual estimates. These differential patterns may reflect variations in the pathophysiology and immune response of TB disease among those living with HIV. Furthermore, it raises the possibility that additional criteria may be needed to identify high-risk patients depending on HIV status and degree of immunosuppression, particularly given that fibrotic and cavitary disease may manifest at different rates or be more difficult to interpret radiographically in immunocompromised individuals [16, 27]. Given the size of our study cohort, it is also possible that some of the observed differences by HIV status are due to sampling variability. Further evaluation in larger cohorts is needed to validate these findings and to assess potential differences between those with high and low CD4 counts.

Of note, the majority of unfavorable outcomes in our cohort were attributable to early mortality rather than bacteriologic failure or post-treatment relapse. This suggests that the prognostic value of baseline radiographic and smear features may be relevant for early risk stratification and raises additional

questions about how best to tailor therapeutic strategies in the era of shortened all-oral regimens. Rather than primarily focusing on which patients with MDR/RR-TB should receive longer regimens, an alternative approach may be to identify those who are at the highest risk for early clinical deterioration, and would thus benefit most from intensive upfront intervention (e.g. hospitalization at start of treatment, adjunctive medical therapy, closer clinical monitoring, nutritional support). The use of baseline chest radiographic and smear findings to define such high-risk subgroups could facilitate the development of risk-adapted treatment pathways to improve survival and reduce early attrition.

One limitation of this analysis is that the fortunately small number of unfavorable outcomes reduced the precision of estimates, particularly in analyses stratified by HIV status. Additionally, while all radiographs were interpreted using standardized definitions, inter-reader variability and limitations in radiographic quality, which influence the classification of certain features, cannot be ruled out. Reassuringly, radiographs were read prospectively, and any bias is thus likely to be nondifferential with respect to outcomes. Finally, we used the missing indicator approach to account for the small amount of missing data, rather than multiple imputation, because the relatively small number of missing baseline observations and unfavorable outcomes constrained parameters for developing a stable imputation model. A disadvantage of the missing indicator approach is that there may be a small degree of residual confounding by covariates with missing data.

Our findings suggest that readily identifiable radiographic and smear-based phenotypes may hold prognostic value in identifying patients at elevated risk for poor outcomes, even within the context of a highly efficacious shortened regimen. However, heterogeneity exists depending on participant HIV status, and on the select outcome measure. Future studies are needed to validate these candidate high-risk phenotypes in other cohorts receiving shortened MDR/RR-TB regimens, particularly in settings with differing burdens of HIV or prior TB treatment. Additional work may also seek to further elaborate the pathogenesis of fibrotic pulmonary TB disease, including social and clinical factors that predispose patients to development of fibrotic versus cavitary lesions and differences in risk conferred by these sequelae. Further research on how radiographic predictors differ by HIV status may also enable refinement of prognostic algorithms tailored to high-risk patient subpopulations.

CONCLUSION

Specific baseline radiographic and microbiologic features—including cavitary disease, fibrosis, bilateral involvement, and high smear grade—are associated with prolonged time to culture conversion and lower odds of treatment success, in the context of an effective shortened oral regimen for MDR/RR-TB. Two clinical phenotypes, one previously-described and one newly proposed, may offer utility for identifying individuals at high risk of poor outcomes. These findings contribute to the emerging literature regarding the potential value of baseline chest imaging and sputum microscopy in guiding risk-adapted management strategies for MDR/RR-TB.

Declarations

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Author Contributions

Study design: K. J. S., M. L. R., M. F. F., C. D. M., K.M.K., L.M.

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Data interpretation: all authors.

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Approved final version of the manuscript: all authors.

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DISCLAIMER

The funders had no role in the conceptualization, analysis, or presentation of findings of this study.

DATA AVAILABILITY

To researchers with a methodologically sound proposal, pseudo-anonymized individual participant data that underlie the results reported in the text and tables of this article and a data dictionary may be made available upon request to the corresponding author, and execution of a data sharing agreement or alternate means that allows assurance that principles of Lesotho regulations will be met.

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Tables

Table 1. Baseline Characteristics of Participants, STEM-TB Lesotho Cohort (N = 238)

Characteristics	Overall (n = 238)	No HIV (n = 90)	HIV (n = 148)
Demographics and Clinical Comorbidities			
Age (median, IQR)	41 (31-56)	49.5 (28-65)	40 (34-50)
Female	70 (29.4)	24 (26.7)	46 (31.1)
Unemployed	99 (41.6)	35 (38.9)	64 (43.2)
Alcohol Consumption (n = 237)	123 (52.1)	41 (45.6)	83 (56.5)
Actively Smoking (n = 237)	86 (36.3)	30 (33.3)	56 (38.1)
HIV Infection	148 (62.2)	--	--
CD4 count (median, IQR) (n = 147)[+]	--	--	239 (84-530)
Diabetes (n = 234)	18 (7.7)	11 (12.4)	7 (4.8)
Low BMI (<18.5) (n = 237)	88 (37.1)	32 (35.6)	56 (38.0)
Hospitalized During Initial Treatment	60 (25.2)	16 (17.8)	44 (29.7)
Previous Use of First-Line Anti-TB Agents	107 (45.0)	35 (38.9)	72 (48.6)
Baseline Chest Radiographic Findings			
Bilateral Disease (n = 207)	96 (46.4)	40 (49.4)	56 (44.4)
Cavitary Disease (n = 207)	67 (32.3)	24 (29.6)	43 (34.1)
Cavitation(s) less than 5cm in diameter	34 (16.4)	9 (11.1)	25 (19.8)
Cavitation(s) of 5cm or greater in diameter	33 (15.9)	15 (18.5)	18 (14.3)
Fibrosis (n = 206)	59 (28.6)	27 (33.3)	32 (25.6)
One lobe or less	25 (12.1)	10 (12.3)	15 (12.0)
More than one lobe	34 (16.5)	17 (21.0)	17 (13.6)
Missing Baseline CXR	31 (13.0)	9 (10.0)	22 (14.9)
Baseline Microbiologic Results			
Sputum Smear (n = 206)			
Negative	111 (53.9)	45 (56.3)	66 (52.4)
Scanty	10 (4.9)	6 (7.5)	4 (3.2)
1+	18 (8.7)	4 (5.0)	14 (11.1)
2+	13 (6.3)	6 (7.5)	7 (5.6)

3+	54 (26.2)	19 (23.8)	35 (27.8)
Sputum Culture Positivity (n = 223)	145 (69.7)	51 (63.8)	94 (73.4)
Clinical Phenotypes			
Cavitary Disease and High Smear Grade (n = 180)	33 (18.3)	11 (15.5)	22 (20.2)
Severe Fibrocavitary Disease (n = 206) [++]	14 (6.8)	9 (11.1)	5 (4.0)

[+] One participant with HIV did not have a baseline CD4 cell count. Among those with a baseline CD4 cell count, 71 (48.6%) had CD4 < 200 cells / mm^3

[++] Defined by baseline radiographic evidence of both cavitary and fibrotic lesions, with at least one of the following: (a) cavitary lesion ≥5cm in diameter, or (b) multi-lobar involvement of fibrotic lesions

Table 2. Analyses of Baseline Chest X-Ray Findings and Sputum Smear Grade on Primary Outcomes, STEM-TB Lesotho Cohort (N = 238)

	Time to Culture Conversion (N = 145)		Favorable End-of-Treatment Outcome (N = 238)		Favorable Final Post-Treatment Outcome (N = 238)	
	Hazard Ratio (95% Confidence Interval)		Odds Ratio (95% Confidence Interval)		Odds Ratio (95% Confidence Interval)	
Baseline Variable	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**
Cavitary Disease	0.75	0.95	0.39	0.68	0.35	0.61
	(0.52 - 1.08)	(0.63 - 1.44)	(0.15 - 1.02)	(0.23 - 2.00)	(0.15 – 0.84)	(0.23 – 1.62)
P-value	*0.13*	*0.81*	*0.05*	*0.49*	*0.02*	*0.33*
Fibrosis	0.79	1.06	0.32	0.45	0.35	0.52
	(0.53 - 1.18)	(0.69 - 1.65)	(0.12 - 0.83)	(0.16 - 1.27)	(0.15 - 0.82)	(0.20 – 1.33)
P-value	*0.25*	*0.78*	*0.02*	*0.13*	*0.02*	*0.17*
Bilateral Disease	0.52	0.57	0.37	0.54	0.31	0.45
	(0.36 - 0.75)	(0.37 - 0.86)	(0.13 – 1.00)	(0.18 - 1.67)	(0.12 - 0.79)	(0.16 - 1.26)
P-value	*<0.01*	*0.01*	*0.05*	*0.29*	*0.01*	*0.13*
High Smear Grade	0.61	0.75	0.39	0.59	0.40	0.63
	(0.43 - 0.87)	(0.50 - 1.11)	(0.15 – 1.07)	(0.20 - 1.73)	(0.16 - 0.98)	(0.23 - 1.68)
P-value	*0.01*	*0.15*	*0.07*	*0.33*	*0.05*	*0.36*

Multivariable models include all four baseline variables.

Missing indicator method applied to all univariable and multivariable analyses. For baseline cavitary disease, fibrosis, and bilateral disease, a ‘missing CXR’ indicator was used. For baseline high smear grade, a ‘missing baseline smear’ indicator was used.

Table 3. Analyses of Baseline Chest X-Ray Findings and Sputum Smear Grade on Primary Outcomes, by HIV Status, STEM-TB Lesotho Cohort

No HIV

	Time to Conversion (N = 51)		Favorable End of Treatment Outcome (N = 90)†		Favorable Final Post-Treatment Outcome (N = 90)†	
	Hazard Ratio (95% Confidence Interval)		Odds Ratio (95% Confidence Interval)		Odds Ratio (95% Confidence Interval)	
Baseline Variable	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**	**Univariable**	**Multivariable**
Cavitary Disease	0.50	0.63	0.29	0.57	0.30	0.52
	(0.26 - 0.96)	(0.31 - 1.32)	(0.07 - 1.29)	(0.11 – 3.07)	(0.08 - 1.15)	(0.11 – 2.44)
P-value	*0.04*	*0.22*	*0.11*	*0.51*	*0.08*	*0.41*
Fibrosis	0.42	0.57	0.36	0.75	0.37	0.77
	(0.22 - 0.82)	(0.25 - 1.29)	(0.08 - 1.56)	(0.14 – 4.00)	(0.10 - 1.39)	(0.17 – 3.53)
P-value	*0.01*	*0.18*	*0.17*	*0.74*	*0.14*	*0.74*
Bilateral Disease	0.61	0.99	0.20	0.29	0.14	0.19
	(0.32 - 1.15)	(0.47 - 2.06)	(0.03 - 1.23)	(0.04 – 2.04)	(0.02 - 0.85)	(0.03 - 1.20)
P-value	*0.12*	*0.97*	*0.08*	*0.22*	*0.03*	*0.08*
High Smear Grade	0.52	0.79	0.43	0.78	0.70	1.42
	(0.29 - 0.95)	(0.39 - 1.56)	(0.09 - 2.04)	(0.15 – 4.13)	(0.17 - 2.92)	(0.29 – 6.92)
P-value	*0.03*	*0.49*	*0.29*	*0.77*	*0.63*	*0.66*

Living with HIV

	Time to Conversion (N = 94)		Favorable End of Treatment Outcome (N = 148)		Favorable Final Post-Treatment Outcome (N = 148)	
Cavitary Disease	0.90	1.23	0.48	0.78	0.40	0.68
	(0.57 - 1.41)	(0.73 - 2.07)	(0.15 - 1.59)	(0.21 - 2.98)	(0.14 - 1.20)	(0.20 - 2.31)
P-value	*0.65*	*0.43*	*0.23*	*0.72*	*0.10*	*0.54*

Fibrosis	1.20	1.57	0.30	0.37	0.33	0.46
	(0.73 - 1.99)	(0.90 - 2.75)	(0.09 - 1.00)	(0.10 - 1.35)	(0.11 – 1.01)	(0.14 - 1.49)
P-value	*0.48*	*0.11*	*0.05*	*0.13*	*0.05*	*0.19*
Bilateral Disease	0.45	0.44	0.54	0.76	0.49	0.72
	(0.28 - 0.71)	(0.26 - 0.73)	(0.16 - 1.80)	(0.19 - 2.98)	(0.16 - 1.47)	(0.21 - 2.54)
P-value	*<0.01*	*<0.01*	*0.31*	*0.70*	*0.20*	*0.61*
High Smear Grade	0.66	0.73	0.38	0.51	0.27	0.38
	(0.43 - 1.01)	(0.44 - 1.21)	(0.11 - 1.33)	(0.13 - 2.02)	(0.08 – 0.88)	(0.10 - 1.36)
P-value	*0.06*	*0.22*	*0.13*	*0.34*	*0.03*	*0.14*

† Firth logistic regression (OR_{firth}) was used in place of traditional logistic regression.

Multivariable models include all four baseline variables.

Figures

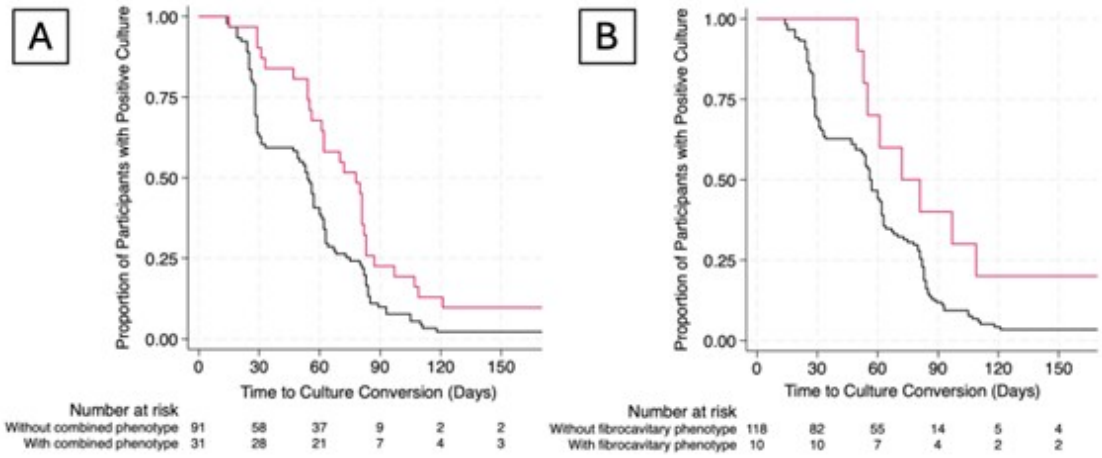


Figure 1

Kaplan-Meier Curves of Time to Culture Conversion, by High-Risk Clinical Phenotype, STEM-TB Lesotho Cohort (N = 145)

(A) Red line represents participants with high smear grade and cavitary disease. Black line represents participants without this specific phenotype. Log-rank p-value of 0.008. Schoenfeld residual proportional

hazards p-value of 0.16. Kaplan Meier derived median time-to-conversion among those with the phenotype was 78 days (IQR:54-87); median time among those without the phenotype was 54 days (IQR:28-75).

(B) Red line represents participants with severe fibrocavitary disease. Black line represents participants without this specific phenotype. Log-rank p-value of 0.04. Schoenfeld residual proportional hazards p-value of 0.44. Kaplan Meier derived median time-to-conversion among those with the phenotype was 76.5 days (IQR:55-109); median time among those without the phenotype was 56.5 days (IQR:25-82).

Results are unadjusted.

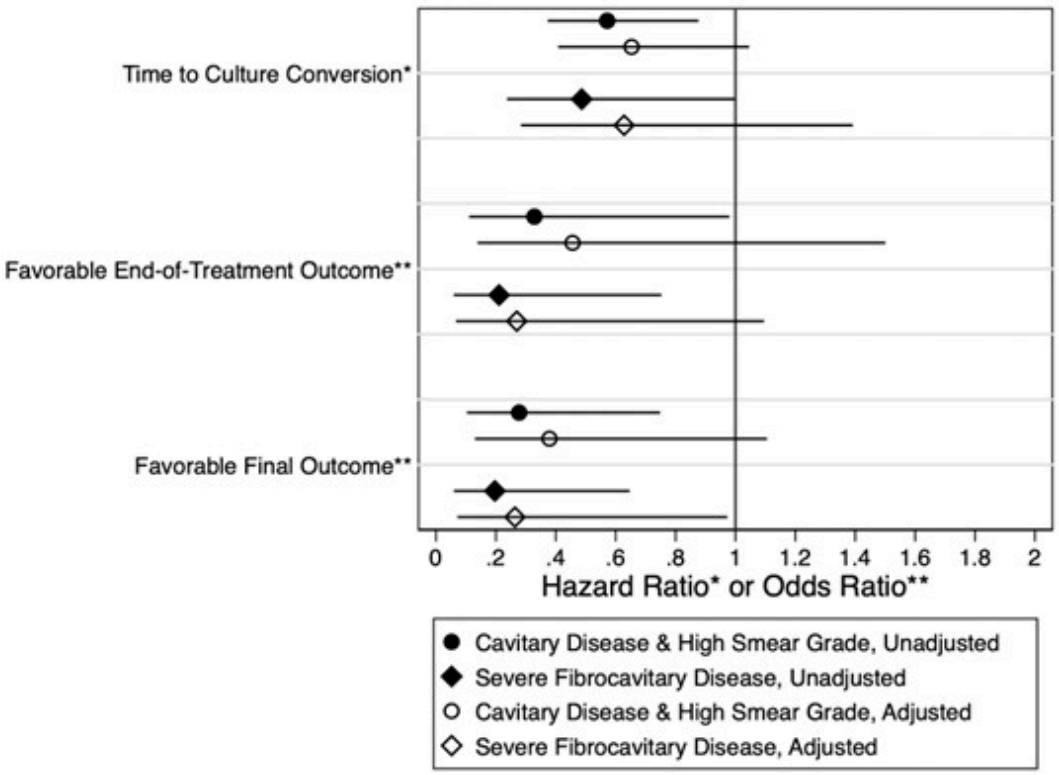


Figure 2

Forest Plot of High-Risk Clinical Chest X-Ray and Sputum Smear Grade Phenotypes on Primary Outcomes, STEM-TB Lesotho Cohort

Severe fibrocavitary disease defined by baseline radiographic evidence of both cavitary and fibrotic lesions, with at least one of the following: (a) cavitary lesion ≥5cm in diameter, or (b) multi-lobar involvement of fibrotic lesions

Lines represent 95% confidence intervals. Multivariable models included both phenotypes, adjusted for each other

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- STEMTBLesothoPredictorsSupplement.docx
- STEMTBLesothoPredictors.txt