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Unfavorable treatment outcomes among patients with drug-resistant TB in Uganda

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_____ S U M M A R Y

B A C K G R O U N D : Drug-resistant TB (DR-TB) remains a significant public health burden and a threat to the progress made in TB control and prevention in sub-Saharan Africa.
O B J E C T I V E : To determine the risk-predictors of poor treatment outcomes in patients with DR-TB in Uganda.
M E T H O D S : We retrospectively reviewed medical records of adult Ugandans who had been treated for DR-TB at Mbarara Regional Referral Hospital (MRRH) in Uganda.
R E S U L T S : Of the 385 files reviewed, 332 (86.2%) met the study inclusion criteria. Of these, 226 (68.1%) were men and 193 (58.1%) were HIV-positive. A total of 73 participants (22.7%) had unfavorable treatment out-

comes (treatment failure, loss to follow-up or death). History of cigarette smoking (OR 5.10, 95% CI 2.4–11.4; $P < 0.001$), age >60 years (OR 6.32, 95% CI 2.2–18.6; $P < 0.001$), anemia (OR 2.38, 95% CI 1.1–5.3; $P = 0.02$) and thrombocytopenia (OR 3.60, 95% CI 1.6–8.1; $P < 0.001$) were independent predictors of unfavorable treatment outcomes.
C O N C L U S I O N : There is a high prevalence of unfavorable treatment outcomes among patients with DR-TB. Further research is required to design a prognostic model for DR-TB patients in a resource-limited setting.
K E Y W O R D S : TB; drug resistance; treatment outcomes; predictors; HIV; Uganda; Africa

Drug-resistant TB (DR-TB) remains a public health threat and a major hindrance to global TB control strategies.[1] The emergence of DR-TB has been linked to weak TB control programs and suboptimal TB case management,[2] with approximately 465,000 new cases of rifampin-resistant or multidrug-resistant TB (RR/MDR-TB) estimated to emerge globally each year.[3] The prevalence of DR-TB in sub-Saharan Africa (SSA) is currently not well-documented due to poor reporting and case notification.[3] In 2019, more than 65,000 TB cases were notified in Uganda, with the WHO estimating that 1% of the new cases and 12% of previously treated cases were drug-resistant.[4] Compared to drug-susceptible TB (DS-TB) treatment, DR-TB requires a longer course of treatment with second-line anti-TB drugs, a higher pill burden, and use of medicines with a higher incidence of adverse events, all of which translate into low treatment success rates.[5]

Recent improvements in diagnostics and treatment have increased detection and improved cure rates among DS-TB patients in several settings.[6] However, treatment outcomes among patients with DR-TB in

SSA are still documented to be poor, and treatment success rates were recently documented to be only 59%,[3] considerably below the WHO target of 75%.[7] TB disease burden has previously been described as heterogenous among African countries,[1] thereby calling for a targeted response in different African countries as opposed to a one-size-fits-all approach.

Previous studies have suggested that chest radiograph findings,[8] regimen modification,[9] baseline body weight,[10] older age,[11] and previous exposure to second-line TB drugs[12] were associated with unsuccessful treatment outcomes in patients with DR-TB. A systematic review and meta-analysis previously described TB risk factor modification by geographic area;[13] the identification of country-specific risk factors is thus needed for developing optimal intervention strategies for DR-TB control. However, despite the high burden of TB and TB-HIV in Uganda, there is still limited information on predictors of treatment outcomes in patients with DR-TB.[14] This study sought to describe treatment outcomes and identify predictors of unfavorable outcomes among patients with DR-TB in Uganda.

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METHODS

Study design, setting and population

This was a retrospective review of patient records conducted at the TB treatment unit of Mbarara Regional Referral Hospital (MRRH) in Mbarara, Uganda. MRRH is a government-funded and teaching hospital for Mbarara University of Science and Technology (MUST) and has the largest TB treatment unit in the western part of the country. Data were collected from adults ($\geq$18 years) who had been admitted to the TB unit and had evidence of DR-TB either based on Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) results or a positive sputum culture. We excluded patients who were on treatment under active follow-up (as they do not have treatment outcomes), and those who had been switched back to first-line treatment following drug susceptibility testing (DST) that showed DS-TB.

Variables

We collected sociodemographic data; age (in years), sex at birth (described as male or female), and the number of dependents (including children). The clinical variables collected were HIV status, prior history of TB, baseline body mass index (BMI), mid-upper arm circumference (with a cut-off of 23 used to describe nutritional status), regimen used by the patient (short-term, long-term, or modified short), DST results (MDR- or RR-TB), history of smoking (yes, no) and alcohol use (yes, no). Data on the laboratory variables routinely collected at the TB treatment unit were extracted. These included the values obtained from the complete blood count done at baseline: hemoglobin concentration (characterized as anemia if <12 g/dL for males and <13 g/dL for females), total leukocyte count, neutrophil count and platelet count (characterized as thrombocytopenia if $<150 \times 10^3$ cells/μL). The levels of sodium, potassium, total bilirubin, liver enzymes (alanine transaminase and aspartate transaminase) measured at baseline were collected. We also recorded the documented outcomes of interest. The WHO defines DR-TB treatment outcomes as cured (where a patient has had smear or culture conversion), completed treatment (patient who has completed treatment but does not meet the definition for cure or treatment failure), died, loss to follow-up and treatment failure (if two or more of the five cultures recorded in the final 12 months are positive, or if any one of the final three cultures is positive or if a clinical decision has been made to terminate treatment early due to poor response or adverse events). In this study, we grouped cured and completed as favorable outcomes, whereas died, loss to follow-up and treatment failure were grouped as unfavorable outcomes.

Data analysis

Data was imported into RStudio statistical software (R Computing, Vienna, Austria) for cleaning and analysis. Categorical variables were expressed as proportions and percentages. In contrast, continuous variables were expressed as means and standard deviations if normally distributed and medians with interquartile ranges for skewed data to describe the sociodemographic and laboratory characteristics of the patients. Two analyses were done: one among all DR-TB patients and another among only DR-TB patients living with HIV to identify if predictors of unfavorable outcomes differed among the subpopulation of PLHIV. In the bivariate analysis, each independent variable (baseline demographics and laboratory values) was regressed with the dependent variable (treatment outcome). We set up the analysis so that for each variable, the reference category was that which was hypothesized to have the lowest risk of an unfavorable outcome; for example, not smoking was hypothesized to have a better clinical outcome and was therefore the reference category.
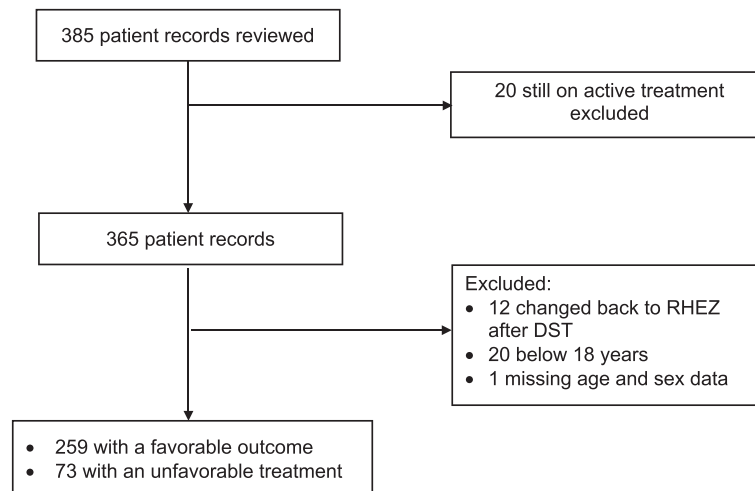
Crude odds ratios (cORs) with the associated 95% confidence intervals (CIs) were calculated. The multivariable regression analysis only included factors with a $P < 0.05$. Considered variables for multivariable regression were tested for multicollinearity, and those with a variance inflation factor (VIF) < 4, were included in the final model. Adjusted ORs (aORs) with the associated 95% CIs were calculated. Factors that had a $P < 0.05$ were considered to be significant. Backward stepwise regression analysis was performed and only statistically significant variables were included in the final model. All statistical inferential frameworks were based on the two-sided P value and a 5% error margin.

RESULTS

Of the 385 reviewed records, 332 (86.2%) records met the inclusion criteria for the study. Of these, 259 (77.3%) were described as having a favorable treatment outcome that is either completed treatment or had a negative sputum culture at the time of review and 73 were recorded as having an unfavorable outcome (Figure).

Baseline characteristics and factors associated with unfavorable outcomes

The mean age of patients with an unfavorable outcome (40.9 $\pm$ 15 years) was higher than that of patients with a favorable treatment outcome (37.9 $\pm$ 11.2 years). Of the 73 patients with unfavorable outcomes, 42 (57.5%) were men. The regimen used by the patients was found to be associated with the type of outcome; with the majority of patients

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Figure   Study flow diagram. RHEZ = rifampin, isoniazid, ethambutol and pyrazinamide; DST = drug susceptibility testing.

(74.6%) having used the long-term regimen. A smoking history was also found to be significantly associated with outcome in the patients.

Among the laboratory values, the mean hemoglobin concentration in patients with unfavorable outcomes was 9.9 ± 2.5 g/dL as compared to 12.0 ± 2.42 g/dL in those with favorable treatment outcomes. Total lymphocyte count was also different in the group with unfavorable outcomes (1.34 ± 0.99

x10^3) compared to those with a favorable outcome (1.72 ± 0.82 × 10^3) (Table 1).

Predictors of unfavorable outcomes in patients with DR-TB

In multivariate analysis, participants older than 60 were at a higher risk of unfavorable outcomes (aOR 6.3, 95% CI 2.2–18.6; $P < 0.001$). A participant with anemia was also at higher risk of unfavorable outcomes (aOR 2.4, 95% CI 1.1–5.3; $P = 0.02$).

Table 1   Baseline characteristics of study participants

Variables	Overall (n = 332) n (%)	Treatment outcomes		P value
		Favorable (n = 259, 78%) n (%)	Unfavorable (n = 73, 22%) n (%)	
Age, years, mean ± SD	38.53 ± 12.16	37.9 ± 11.2	40.9 ±15	0.06
Male	226 (68.1)	184 (71.0)	42 (57.5)	0.03
MUAC, cm	23.0	23.36 ± 3.0	21.40 ± 3.1	<0.01
HIV-positive	193 (58.1)	144 (55.6)	49 (67.1)	0.08
History of TB	168 (51.2)	135 (52.1)	33 (45.2)	0.30
Drug susceptibility testing				
MDR-TB	128 (38.5)	99 (38.2)	29 (39.7)	0.11
RR-TB	199 (60.1)	158 (61.0)	41 (56.2)	
Pre-XDR-TB	5 (1.5)	2 (0.01)	3 (0.04)	
Regimen used by patient (n = 323)*				
Long	180 (55.7)	130 (50.8)	50 (74.6)	<0.01
Short	103 (31.9)	90 (35.2)	13 (19.4)	
Modified short	40 (12.4)	36 (14.1)	4 (0.1)	
MTB bacillary load on Xpert†				
High	56 (20.3)	44 (20.2)	12 (20.7)	0.15
Medium	92 (33.3)	67 (30.7)	25 (43.1)	
Low	128 (46.4)	107 (49.1)	21 (36.2)	
History of smoking	40 (14.3)	20 (0.1)	20 (32.8)	<0.01
History of alcohol use	109 (39.1)	81 (37.2)	28(45.9)	0.22
Hemoglobin, g/dL, mean ± SD	11.54	12.0 ± 2.42	9.9 ± 2.5	<0.01
Platelet count, x10^3/μL, mean ± SD	297.1	308.04 ± 136.9	253.3 ± 149.3	0.01
Potassium levels, mmol/L, median [IQR]	4.4 [4.00–4.70]	4.33 ± 0.71	4.30 ± 0.59	0.81
Sodium levels, mmol/L, median [IQR]	132.0 [129.0-138.0]	130.13 ± 14.83	126.52 ± 10.43	0.13
Total lymphocyte count, 10^3 cells/mcL, mean ± SD	1.50	1.72 ± 0.82	1.34 ± 0.99	<0.01

* Regimens named according to the changing WHO treatment guidelines.
† Determined by cycle threshold values.
SD = standard deviation; MUAC = mid-upper arm circumference; MDR-TB = multidrug-resistant TB; RR-TB = rifampin-resistant TB; XDR-TB = extensively drug-resistant TB; MTB = *M. tuberculosis.*

Table 2   Predictors of unfavorable outcomes in patients with drug-resistant TB in Uganda

Characteristic	OR (95% CI)	P value	aOR (95% CI)	P value
Age, years				
<60	Reference	<0.01	1	
>60	5.46 (2.21–13.95)		6.32 (2.18–18.57)	<0.01
Sex				
Male	Reference			
Female	1.81 (1.05–3.09)	0.03		
HIV serostatus				
Negative	Reference			
Positive	1.63 (0.95–2.85)	0.08		
History of TB				
No	Reference			
Yes	0.76 (0.45–1.27)	0.30		
History of smoking				
No	1		1	
Yes	4.85 (2.40–9.89)	<0.01	5.10 (2.36–11.36)	<0.01
Regimen				
Long	1			
Short	0.38 (0.19–0.71)	<0.01		
Modified short	0.29 (0.08–0.77)	0.02		
GeneXpert severity				
High	1			
Medium	1.37 (0.63–3.08)	0.44		
Low	0.72 (0.33–1.62)	0.42		
Drug susceptibility testing				
Pre-XDR-TB	Reference			
MDR-TB	0.19(0.02,1.23)	0.08		
RR-TB	0.17 (0.02–1.08)	0.06		
MUAC, cm				
>23	Reference			
<23	2.83 (1.46–5.65)	<0.01		
History of alcohol use				
No	Reference			
Yes	1.44 (0.81–2.55)	0.22		
Hemoglobin				
Normal	Reference		1	
Anemia	2.95 (1.49,6.31)	<0.01	2.38(1.14–5.34)	0.02
Platelet count, 10^3 cells/mcL				
>150	Reference		1	
<150	3.08(1.46–6.36)	<0.01	3.60(1.58–8.09)	<0.01

OR = odds ratio; CI = confidence interval; aOR = adjusted OR; XDR-TB = extensively drug-resistant TB; MDR-TB = multidrug-resistant TB; RR-TB = rifampin-resistant TB; MUAC = mid-upper arm circumference.

Smoking was identified as a predictor of unfavorable outcomes in these participants (aOR 5.1, 95% CI 2.4–11.4; $P < 0.001$), and so was having thrombocytopenia (aOR 3.6, 95% CI 1.6–8.1; $P < 0.001$) (Table 2).

Among patients living with HIV, smoking (aOR 9.2, 95% CI 3.2–28.0; $P < 0.001$), anemia (aOR 3.3, 95% CI 1.2–10.3; $P = 0.02$) and thrombocytopenia (aOR 4.4, 95% CI 1.6–12.3; $P < 0.01$) were identified as independent predictors of unfavorable outcomes (Table 3).

DISCUSSION

This study aimed to determine the predictors of unfavorable treatment outcomes among patients with DR-TB in Uganda. The treatment success rate in this study was 77%, higher than a WHO estimate of 59% and the recommended treatment success rate of 75%.[15] The treatment success rate in this study was also higher than that in a previous Ugandan study (72%), possibly due to the inclusion of only patients with multiple poor prognostic indicators in the cited study.[12] In our study, we also identified age, history of cigarette smoking, thrombocytopenia, and anemia as significant predictors of unfavorable outcomes.

Tobacco smoking has previously been associated with an increased risk of acquiring TB.[16] In our study, patients with a history of cigarette smoking had a five-fold risk of dying or being lost to follow-up. In contrast, among patients co-infected with HIV, cigarette smoking presented a nine-fold risk of having unfavorable treatment outcomes. These findings are similar to a systematic review that described a history of smoking as a strong risk factor for DR-TB.[17] This negative effect of smoking has been attributed to the fact that smokers are less likely to complete anti-TB treatment[18] and the pre-existing lung parenchyma

Table 3 Predictors of unfavorable outcomes in HIV-positive patients with drug-resistant TB in Uganda

Characteristic	OR (95% CI)	P value	aOR (95% CI)	P value
Age, years				
<60	Reference			
>60	3.07 (0.55–17.06)	0.18		
MUAC				
>23	Reference			
<23	3.03 (1.33–7.30)	0.01		
Sex				
Male	Reference			
Female	1.30 (0.66–2.51)	0.44		
Smoking				
No	Reference		Reference	
Yes	6.91 (2.79–18.10)	<0.001	9.18 (3.23–28.01)	<0.01
Regimen				
Long	Reference			
Modified short	0.10 (0.01–0.52)	0.03		
Short	0.27 (0.11–0.60)	<0.01		
Hemoglobin				
Normal	Reference		Reference	
Anemia	4.44 (1.83–12.54)	<0.01	3.31 (1.21–10.34)	0.03
Platelet count, 10^3 cells/mcL				
>150	Reference		Reference	
<150	4.61 (1.89–11.37)	<0.01	4.40 (1.61–12.31)	<0.01
History of TB				
No	Reference			
Yes	0.89 (0.46–1.70)	0.72		
GeneXpert severity				
High	Reference			
Low	0.43 (0.16–1.18)	0.10		
Medium	1.50 (0.58–4.05)	0.41		
Drug susceptibility testing				
Pre-XDR-TB	Reference			
MDR-TB	0.38 (0.04–3.35)	0.35		
RR-TB	0.30 (0.04–2.63)	0.25		
Alcohol use				
No	Reference			
Yes	1.62 (0.80–3.30)	0.18		

OR = odds ratio; CI = confidence interval; aOR = adjusted OR; MUAC = mid-upper arm circumference; XDR-TB = extensively drug-resistant TB; MDR-TB = multidrug-resistant TB; RR-TB = rifampin-resistant TB.

damage, which increases one's susceptibility to other lung infections that may negatively affect treatment outcomes.[19]

Increasing age is commonly associated with unfavorable treatment outcomes in several other infectious diseases.[20] In this study, patients aged ≥60 years were more likely to have unfavorable outcomes than their counterparts. This is similar to findings in other studies in which age was identified as an independent risk factor for mortality among DR-TB patients.[16,21] In contrast, among patients co-infected with HIV, age was not identified as a significant predictor for unfavorable outcomes, unlike in other studies done in Ethiopia[22] and China.[23] This could be because there are few people above 60 years living with HIV in the current study population.

Anemia is a common comorbidity at TB diagnosis. Anemia has been previously associated with mortality in patients with DR-TB,[24] delayed sputum smear conversion,[25] and severe clinical forms of TB such as meningeal and disseminated TB.[26] In these patients, anemia may result from undernutrition,[27] chronic inflammation,[28] or adverse effects of anti-TB drugs.[29] Therefore, poor treatment outcomes among patients with anemia and TB, such as those identified in this study, may be caused by an impaired host T-cell immunity, increased susceptibility to adverse drug reactions, and secondary infections due to compromised immunity.

Thrombocytopenia was identified as a significant predictor of unfavorable treatment outcomes in this study, having a three-fold risk of unfavorable treatment outcomes. This is in line with a study done in India that found thrombocytopenia associated with poor treatment outcomes.[30] Additionally, thrombocytosis may be protective against severe pulmonary TB disease by promoting type 1 collagen degradation and engendering less interleukin (IL) 1β, tumor necrosis factor-α, IL-6 and interferon-γ production.[31,32] There is robust clinical evidence for the role of platelets in TB progression, for example, upregulated platelet-associated gene transcripts and

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increased platelet activity have been shown to occur in TB patients.[33] Thrombocytopenia may represent a more advanced stage in the interaction between platelets and TB infection. In addition, treatment regimens for DR-TB contain drugs such as linezolid which has been described to cause both thrombocytopenia and anemia.[34] This poorly understood association may undermine recent efforts to use antiplatelet agents as anti-TB therapies.[35] The association between thrombocytopenia and DR-TB treatment outcomes warrants further research.

In this study, we provide data on a large cohort of patients with DR-TB. However, this was a retrospective study, and the effect of confounding variables on the outcome could not be all be controlled for. Therefore, we could not account for the effect of radiological abnormalities, performance status, and adverse drug reactions on the outcome. It is important that each of the predictors of unfavorable DR-TB identified in this study is explored further to provide an in-depth understanding of the magnitude of their effect on treatment outcomes.

CONCLUSION

Anemia, age, smoking, and thrombocytopenia are modifiable predictors of unfavorable treatment outcomes among people with DR-TB in Uganda. Smoking cessation programs and early correction of hematological abnormalities could improve treatment outcomes in similar settings. Furthermore, the predictors of unfavorable outcomes among DR-TB patients do not differ depending on whether or not a patient is co-infected HIV. Clinicians should consider the predictors of unfavorable outcomes identified in this study during patient management to allow intensified treatment and increase treatment success rates. There remains a need to analyze data of multinational cohorts to design a prognostic tool for DR-TB.

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RÉSUMÉ

CONTEXTE : La TB résistante aux médicaments (DR-TB) reste un fardeau important pour la santé publique et une menace pour les progrès réalisés dans la lutte contre la TB et la prévention en Afrique subsaharienne.

OBJECTIF : Déterminer les facteurs de risque pour les mauvais résultats de traitement chez les patients atteints de DR-TB en Ouganda.

MÉTHODES : Nous avons examiné de manière rétrospective les dossiers médicaux d'adultes Ougandais qui ont été traités pour la DR-TB au Mbarara Regional Referral Hospital (MRRH) en Ouganda.

RÉSULTATS : Parmi les 385 dossiers examinés, 332 (86,2%) répondaient aux critères d'inclusion de l'étude. Parmi eux, 226 (68,1%) étaient des hommes et 193 (58,1%) étaient positifs pour le VIH. Au total, 73 participants (22,7%) ont eu des résultats de traitement défavorables (échec du traitement, perte de suivi ou décès). L'historique de fumeur de cigarette (OR 5,10 ; IC 95% 2,4–11,4 ; $P < 0,001$), l'âge >60 ans (OR 6,32 ; IC 95% 2,2–18,6 ; $P < 0,001$), l'anémie (OR 2,38 ; IC 95% 1,1–5,3 ; $P = 0,02$) et la thrombocytopénie (OR 3,60 ; IC 95% 1,6–8,1 ; $P < 0,001$) étaient des prédicteurs indépendants des résultats de traitement défavorables.

CONCLUSION : Il existe une forte prévalence de résultats de traitement défavorables chez les patients atteints de DR-TB. Des recherches supplémentaires sont nécessaires pour concevoir un modèle pronostique pour les patients atteints de DR-TB dans un environnement limité en ressources.

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