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ORIGINAL RESEARCH

Undernutrition and Treatment Success in Drug-Resistant Tuberculosis in Uganda

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Background: Undernutrition is associated with unfavourable treatment outcomes among people with drug-resistant tuberculosis (DRTB). Factors influencing the treatment outcomes among undernourished people with DRTB are not well characterised. The aim of this study was to determine factors associated with treatment success among undernourished people with DRTB in Uganda.

Methods: We analysed data from a retrospective cohort of people with DRTB from 16 treatment sites in Uganda. We included participants with a pre-treatment body mass index (BMI) of <18.5 kilograms/meters^2 (kg/m^2). Participants were categorised as having mild (BMI of 18.5–17 kg/m^2), moderate (BMI of 16.9–16.0 kg/m^2) or severe (BMI of <16.0 kg/m^2) undernutrition. We performed logistic regression analysis to determine factors associated with treatment success.

Results: Among 473 people with DRTB, 276 (58.4%) were undernourished (BMI < 18.5 Kg/m^2) and were included in the study. Of these, 92 (33.3%) had mild, 69 (25.0%) had moderate and 115 (41.7%) had severe undernutrition. The overall treatment success rate (TSR) for the undernourished was 71.4% (n = 197). Although the TSR was similar among participants with mild (71.7%), moderate (78.3%) and severe (67.0%) undernutrition (p = 0.258), all treatment failure cases (n =6) were among participants with severe undernutrition (p = 0.010). Cigarette smoking (odds ratio (OR) = 0.19, 95% CI 0.07–0.47, p < 0.001), urban residence (OR = 0.31, 95% CI 0.14–0.70, p = 0.005) and moderate (OR = 0.14, 95% CI 0.06–0.35, p < 0.001) and severe anaemia (OR = 0.06, 95% CI 0.01–0.29, p = 0.001) were associated with lower odds of treatment success.

Conclusion: Most undernourished people with DRTB have severe undernutrition. Smoking and anaemia are modifiable factors which upon appropriate intervention could improve treatment success. The effect of urban residence on the TSR needs to be evaluated further.

Keywords: MDR TB, undernutrition, malnutrition, drug resistant, tuberculosis, anaemia

Background

About 10 million cases of tuberculosis (TB) occurred in 2019.[1] While the End TB strategy aims to reduce new TB cases by 90% and TB deaths by 95% between 2015 and 2035, most high-burdened countries are not on course to achieve these targets.[2,3] Moreover, the emergence of drug-resistant tuberculosis (DRTB) is a threat to the global TB control efforts. About 19 million people are estimated to have latent multidrug-resistant tuberculosis (MDRTB) infection globally.[4] In 2019, half-a-million people developed rifampicin resistant/MDR TB and the treatment success rate (TSR) was only 57% for the 2017 cohort.[1] Concerted efforts are needed to reduce TB cases and deaths for us to realise the End TB strategy.

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Undernutrition accounts for almost half of the TB cases attributed to the five major risk factors of TB: undernutrition, HIV infection, alcohol, smoking and diabetes.[4] A body mass index (BMI) of < 18.5 kilograms/meters^2 is a cheap and reproducible measure of undernutrition used among adults with TB.[5–7] The relationship between TB and undernutrition is bidirectional. On the one hand, undernutrition affects innate and adaptive immune responses by impairing phagocytosis, antigen presentation and functions of the complement system.[8] Consequently, undernutrition increases the risk of developing TB in individuals with and without HIV co-infection.[9,10] Conversely, nutritional supplementation accelerates sputum smear and culture conversion when given alongside TB therapy.[11,12] On the other hand, TB can cause undernutrition by modulating the appetite mediators; leptin and ghrelin.[13] Because of this bi-directional relationship, the prevalence of undernutrition in people with TB in low-income settings is high (30–80%).[7,14,15] There are growing calls to address the problem of undernutrition to reduce TB incidence at population level and to improve treatment outcomes among people with active TB.[16]

In DRTB, undernutrition is associated with unfavourable treatment outcomes across several cohorts in low-, middle - and high-income countries.[17–27] Moreover, undernutrition is associated with TB relapse and mortality even after DRTB treatment completion.[28] Unfortunately, few studies have explored factors associated with unfavourable treatment outcomes in undernourished people with DRTB, yet the prevalence of undernutrition in DRTB is high (35–65%), particularly in sub-Saharan Africa.[26,29,30]

The prevalence of undernutrition in DRTB in Uganda is not well documented. However, the prevalence of undernutrition in TB was estimated to be 46% at a national referral hospital in Uganda.[31] The objective of this study was to determine factors associated with treatment success among undernourished people with DRTB in Uganda, a TB and TB/HIV high-burdened country.[32]

Methods

Study Setting and Population

We performed a secondary analysis of data from a large retrospective cohort[33] of people with DRTB from 16 DRTB treatment sites in Uganda. We included people with laboratory confirmed DRTB, a treatment outcome documented between 2013 and 2019 and undernutrition defined as a pre-treatment BMI of < 18.5 kg/m^2. DRTB was confirmed by either the Xpert MTB/RIF® assay and/or a culture-based phenotypic drug susceptibility test performed at the treatment sites and the National Tuberculosis Reference Laboratory, respectively. Participants in the primary study were drawn from 16 DRTB treatment sites in Uganda comprising of one national referral hospital, 11 regional referral hospitals and four district hospitals. The management of DRTB in Uganda during the period under evaluation is described elsewhere.[33–35]

Study Measurements

Sociodemographic and clinical data were extracted from the participants' charts using a data abstraction form. Sociodemographic variables collected included year of enrolment in care, age, sex, employment status, level of hospital (national referral, regional referral, and district hospitals), residence (rural and urban), marital status and any history of alcohol and/or cigarette use. Clinical characteristics included the baseline weight and height, history of previous TB treatment, HIV serological status, other comorbidities (cancer, hearing impairment, heart failure, hypertension and diabetes mellitus), haemoglobin, hepatic transaminase and creatinine levels, TB resistance profiles, time from diagnosis to treatment initiation, number and type of drugs in the DRTB treatment regimen, treatment duration, time to sputum culture conversion, and treatment outcomes. Anaemia was defined as a haemoglobin level of <13.0 grams per decilitre (g/dl) for males and <12.0 g/dl for females. Anaemia was further graded as mild (11.0–12.9 g/dl for men and 11.0–11.9 g/dl for females), moderate (8.0–10.9 g/dl for both sexes) and severe (<8.0 g/dl for both sexes).[36] The BMI was calculated by dividing the weight in kilograms by the square of height in metres. Participants were categorised as having mild (BMI of 18.5–17 kg/m^2), moderate (BMI of 16.9–16.0 kg/m^2) or severe (BMI of <16.0 kg/m^2) undernutrition.[37] Treatment success was the sum of TB cure and treatment completion as defined by the WHO.[38] An unfavourable outcome was a composite of treatment failure, loss-to-follow-up and death. A full description of the study measurements is available from the primary study.[33]

Data Analysis and Sample Size Estimation

All participants in the primary study with undernutrition were included. Data were entered in EpiData 4.4.0 and analysed with STATA 16.0 (STATA, College Station, Texas, USA). Clinical and sociodemographic characteristics were compared among participants with mild, moderate and

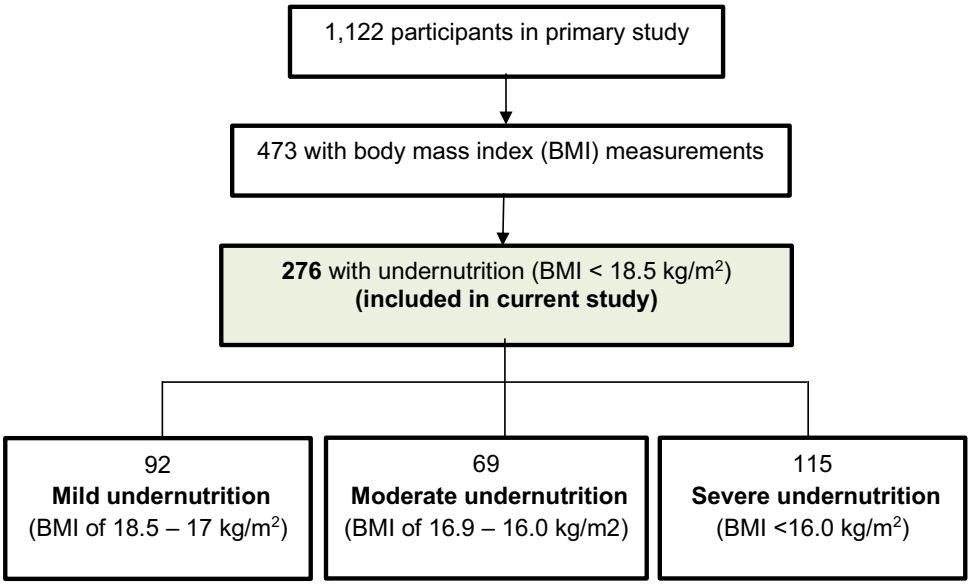

Figure 1 Study flow diagram.

severe undernutrition using Pearson's chi-square test or Fisher's exact test for categorical variables and one-way analysis of variance for continuous variables. The median test was used to compare the medians across the different groups of undernutrition. We performed bivariable logistic regression analysis for factors associated with treatment success. All factors with p<0.2 were considered for the multivariable logistic regression model. We used stepwise backward regression, controlling for severity of undernutrition, to select variables for the final multivariable regression model for factors associated with treatment success. We also compared time to an unfavourable outcome between the three categories of undernutrition using Kaplan Meier survival curves.

Results

Of 1122 people with DRTB in the primary study, 473 had pre-treatment baseline BMI measurements. Of these, 276 (58.4%) were undernourished and were thus included in the study. Figure 1 shows the study flow diagram. There were no significant differences between participants with and without pre-treatment BMI measurement with regard to sex (p = 0.890), HIV co-infection (p = 0.052), grade of anaemia (p = 0.160), and smoking (p = 0.318). The two groups differed with regard to age (p = 0.003) and this was because nutritional assessment is by mid upper arm circumference and not BMI in most paediatric cases (< 15 years).

Characteristics of Undernourished People with DRTB in Uganda

Of 276 people with DRTB and undernutrition, 92 (33.3%) had mild, 69 (25.0%) had moderate and 115 (41.7%) had severe undernutrition. Among the participants, the mean (standard deviation (SD)) age was 39.0 (14) years, 179 (64.9%) were male, and 145 (52.5%) were co-infected with HIV.

People with severe undernutrition were more frequently managed at district hospitals (47.0%, p<0.001) and had higher frequency of baseline resistance to ethambutol (32.2%, p = 0.026) than people with moderate and mild undernutrition. People with moderate undernutrition had higher frequency of cigarette use (42.9%, p=0.005) and history of a previous TB episode (66.7%, p=0.039) than people with mild and severe undernutrition. Table 1 shows characteristics of people with DRTB with severe, moderate and mild undernutrition.

Treatment Outcomes Among Undernourished People with DRTB in Uganda

The overall treatment success rate (TSR) was 71.4% (n = 197). Although the TSR was similar among people with DRTB and mild (71.7%), moderate (78.3%) and severe (67.0%) undernutrition (p = 0.258), all treatment failure cases (n = 6) were among people with severe undernutrition (p = 0.010). The overall (n = 79) median (95% CI) time to an unfavourable outcome (treatment failure, death

Table 1 Characteristics of People with DRTB with Severe, Moderate and Mild Undernutrition in Uganda

Characteristic	Total n (%)	Severe Undernutrition	Moderate Undernutrition	Mild Undernutrition	p-value
Level of hospital					<0.001
National referral hospital	15 (5.4)	9 (7.8)	2 (2.9)	4 (4.3)	
Regional Referral	170 (61.6)	52 (45.2)	48 (69.6)	70 (76.1)	
District hospital	91 (33)	54 (47.0)	19 (27.5)	18 (19.6)	
Residence					0.764
Rural	187 (70.8)	76 (69.1)	49 (74.2)	62 (70.5)	
Urban	77 (29.2)	34 (30.9)	17 (25.8)	26 (29.5)	
Age, mean (SD) (Years)	39.0 (14.0)	37.0 (13)	41.0 (13)	39.0 (13)	0.182
Sex					0.517
Male	179 (64.9)	75 (65.2)	48 (69.6)	56 (60.9)	
Female	97 (35.1)	40 (34.8)	21 (30.4)	36 (39.1)	
Nature of Employment					0.066
Unemployed	112 (41.8)	55 (49.5)	26 (38.8)	31 (34.4)	
Self employed	121 (45.1)	47 (42.3)	33 (49.3)	41 (45.6)	
Employed	35 (13.1)	9 (8.1)	8 (11.9)	18 (20.0)	
Married	144 (53.3)	55 (48.2)	38 (57.6)	51 (56.7)	0.260
Alcohol use	103 (42.9)	40 (38.8)	32 (31.1)	31 (30.1)	0.274
Cigarette use	49 (20.4)	13 (26.5)	21 (42.9)	15 (30.6)	0.005
History of TB treatment	164 (59.4)	73 (63.5)	46 (66.7)	45 (48.9)	0.039
HIV co-infection	145 (52.5)	53 (46.1)	37 (53.6)	55 (59.8)	0.143
Diabetes	20 (29)	6 (27.3)	10 (41.7)	4 (17.4)	0.182
Hypertension	7 (4.7)	2 (3.3)	2 (5.4)	3 (5.8)	0.798
Cancer	5 (1.8)	2 (1.7)	1 (1.4)	2 (2.2)	0.941
Hearing Impairment	74 (31.3)	24 (24.5)	21 (34.5)	29 (37.2)	0.358
Type of DRTB at baseline					0.298
Rifampicin resistant	159 (57.6)	65 (56.5)	35 (50.7)	59 (64.1)	
MDRTB	109 (39.5)	48 (41.7)	30 (43.5)	31 (33.7)	
Pre-XDRTB	4 (1.4)	1 (0.9)	2 (2.9)	1 (1.1)	
Poly resistant TB	3 (1.1)	0 (0)	2 (2.9)	1 (1.1)	
Mono resistant TB (other than rifampicin)	1 (0.4)	1 (0.9)	0 (0)	0 (0)	
DST profile at baseline					
Rifampicin	275 (99.6)	114 (99.1)	69 (100)	92 (100)	0.495
Isoniazid	119 (43.1)	58 (50.4)	29 (42.0)	32 (34.8)	0.160
Pyrazinamide	8 (2.9)	6 (5.2)	0 (0)	2 (2.2)	0.153
Ethambutol	65 (23.6)	37 (32.2)	13 (18.8)	15 (16.3)	0.026
Streptomycin	62 (22.5)	32 (27.8)	15 (21.7)	15 (16.3)	0.219
Aminoglycoside	4 (1.5)	1 (0.9)	3 (4.4)	0 (0)	0.063
Fluoroquinolone	1 (0.4)	0 (0)	1 (1.5)	0 (0)	0.257
Days from diagnosis to treatment, Median (IQR)	6 (3, 18)	5.5 (2, 10)	7 (3, 25)	6 (3, 18)	0.067

(*Continued*)

Table 1 (Continued).

Characteristic	Total n (%)	Severe Undernutrition	Moderate Undernutrition	Mild Undernutrition	p-value
Months to culture conversion, Median (IQR)	2 (1, 3)	2 (1, 3)	2 (1, 3)	2(1, 2)	0.620
Number of drugs in regimen, Mean (SD)	6.1 (1.1)	6.2 (1.1)	6.0 (1.1)	6.2 (1.2)	0.436
Drugs in treatment regimen					
Bedaquiline	18 (6.5)	7 (6.1)	8 (11.6)	3 (3.3)	0.129
Levofloxacin	204 (73.9)	86 (74.8)	50 (72.5)	68 (73.9)	0.942
Moxifloxacin	71 (25.7)	29 (25.2)	18 (26.1)	24 (26.1)	0.987
Kanamycin	227 (82.3)	98 (85.2)	53 (76.8)	76 (82.6)	0.350
Amikacin	1 (0.4)	1 (0.9)	0 (0)	0 (0)	0.495
Capreomycin	42 (15.2)	11 (9.6)	11 (15.9)	20 (21.7)	0.052
Ethionamide	270 (97.8)	111 (96.5)	68 (98.6)	91 (98.9)	0.577
P-Amino salicylic acid	2 (0.7)	1 (0.9)	1 (1.5)	0 (0)	0.721
Clofazimine	75 (27.2)	31 (27.0)	18 (26.1)	26 (28.3)	0.952
Linezolid	7 (2.5)	3 (2.6)	4 (5.8)	0 (0)	0.055
High dose Isoniazid	75 (27.2)	31 (27.0)	16 (23.2)	28 (30.4)	0.591
Ethambutol	77 (27.9)	32 (27.8)	16 (23.2)	29 (31.5)	0.506
Pyrazinamide	265 (96.0)	108 (93.9)	67 (97.1)	90 (97.8)	0.388
Serum creatinine, Median (IQR)	70.4 (54.3, 91.3)	60.7 (44.2, 90.9)	73.3 (59.2, 90.0)	70 (63, 80)	0.062
Serum ALT, Median (IQR)	19.5 (11.5, 41.3)	18.2 (10.2, 45.0)	19.5 (11.4, 39.2)	21.0 (12.3, 39.0)	0.710
Serum AST, Median (IQR)	38.3 (31.4, 54.7)	37.0 (30.1, 55.0)	42.1 (32.2, 73.8)	36.4 (31.4, 52.5)	0.151
Serum GGT, Median (IQR)	51.0 (31.0, 121.0)	60 (31, 121)	57.9 (37.9, 259.5)	44 (30.5, 116.0)	0.479
Serum ALP, Median (IQR)	154.0 (111.0, 254.5)	151.5 (109, 204.3)	149.5 (123.6, 306.7)	166 (106, 254.5)	0.694
Serum bilirubin, Median (IQR)	0.5 (0.3, 0.9)	0.5 (0.3, 0.9)	0.4 (0.3, 0.7)	0.5 (0.3, 0.9)	0.245
Mean Hb, Mean (SD)	12.6 (2.5)	12.2 (2.5)	12.1 (2.1)	12.7 (2.5)	0.104

Abbreviations: AST, aspartate aminotransferase; GGT, gamma-glutamyl aminotransferase; ALT, alanine aminotransferase; ALP, alkaline aminotransferase; Hb, haemoglobin; MDRTB, Multi-drug-resistant tuberculosis; XDRTB, extensively drug-resistant tuberculosis; IQR, interquartile range; SD, standard deviation.

and loss-to-follow-up combined) was 5 (2–7) months. There was no statistical difference in the median (95% CI) time to an unfavourable outcome in mild (2 (1.8–6) months), moderate (4 (0.6–7) months) and severe undernutrition (9 (3–11) months) ($P_{wilcoxon}$ = 0.097). A Kaplan Meier survival curve is shown in Figure 2. Table 2 compares the individual treatment outcomes across mild, moderate and severe undernourished groups.

Factors Associated with Treatment Success Among Undernourished People with DRTB in Uganda

Cigarette smoking (odds ratio (OR) = 0.19, 95% CI 0.07–0.47, p < 0.001), urban residence (OR = 0.31, 95% CI 0.14–0.70, p = 0.005) and moderate (OR = 0.14, 95% CI 0.06–0.35, p < 0.001) and severe anaemia (OR = 0.06, 95% CI 0.01–0.29, p = 0.001) were associated with lower odds of treatment success. Table 3 shows a multivariable model for factors associated with treatment success.

Discussion

People with DRTB and undernutrition consistently post unfavourable treatment outcomes. The aim of this study was to determine factors associated with treatment success among people with DRTB and undernutrition. Cigarette smoking, urban residence and moderate and severe anaemia were associated with lower odds of treatment success.

We found that 42% of undernourished people with DRTB have severe undernutrition. This is concerning

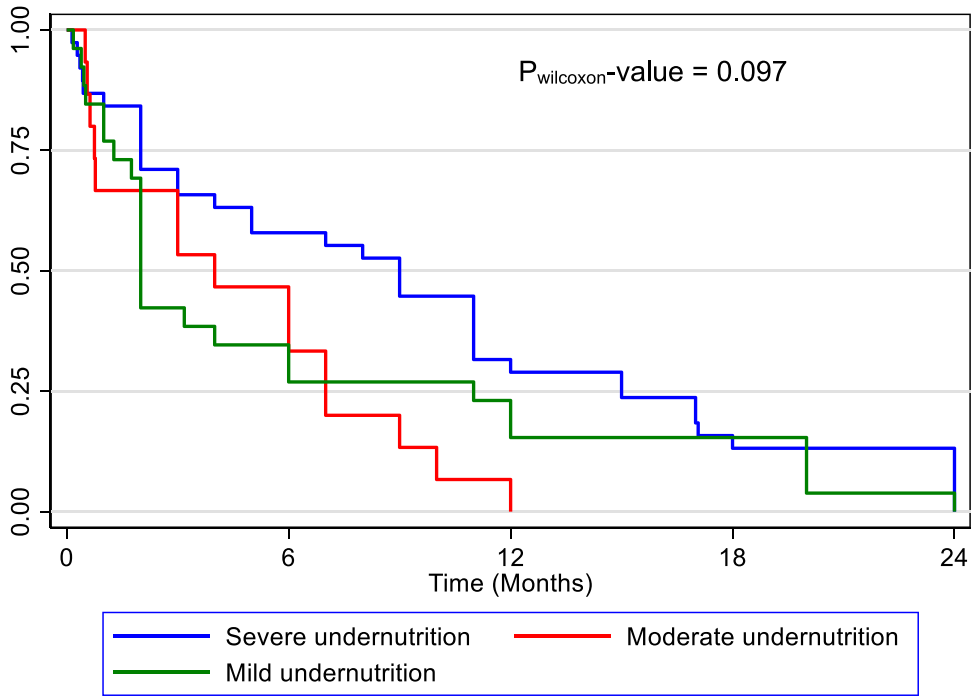

Figure 2 Kaplan Meier survival curve for time to unfavourable outcome among undernourished people with DRTB in Uganda.

considering that there are no clear management approaches for undernutrition among people with DRTB. While nutritional supplementation could improve weight gain during TB therapy and accelerate sputum conversion, there is insufficient evidence for the effect of supplementation on TB treatment outcomes.[11,39] High quality randomised controlled trials are needed to determine management strategies for undernutrition in DRTB.

The overall TSR was similar across categories of undernutrition. This was supported by the time to unfavourable outcome analysis. These findings suggest that there is no clear linear relationship between the TSR and baseline BMI. Rather, the rate of change of BMI during therapy may be a better predictor of treatment success.[40] However, from our study, treatment failure was observed only among participants with severe undernutrition. There are several factors that could account for this. Almost half of participants with severe undernutrition were unemployed, the highest frequency of the three groups. Further, >30% of them had TB strains that were resistant to ethambutol in addition to RR/MDR TB. Moreover, most of the participants with severe undernutrition were managed at lower-level hospitals (district hospitals) which have inadequate resources to closely monitor these individuals. These social, biological and system factors could influence outcomes among people with DRTB and severe undernutrition. It is therefore important to address socio-economic barriers, individualise treatment regimens to susceptibility profiles and closely monitor sputum cultures among people with DRTB and severe undernutrition.

From our study, there were two modifiable and one non-modifiable factors that could improve the TSR. Cigarette use and anaemia were modifiable factors associated with a reduction in the odds of treatment success. Urban residence was also associated with a 67% reduction in the odds of

Table 2 A Comparison of Treatment Outcomes Among People with DRTB and Mild, Moderate and Severe Undernutrition

Treatment Outcome	Total	Severe Undernutrition	Moderate Undernutrition	Mild Undernutrition	p-value
Cured	175 (63.4)	71 (61.7)	48 (69.6)	56 (60.9)	0.467
Treatment Completion	22 (8.0)	6 (5.2)	6 (8.7)	10 (10.9)	0.318
Loss to follow up	17 (6.2)	6 (5.2)	3 (4.3)	8 (8.7)	0.507
Treatment Failure	6 (2.2)	6 (5.2)	0 (0)	0 (0)	0.010
Death	56 (20.3)	26 (22.6)	12 (17.4)	18 (19.6)	0.680

Table 3 Multivariable Model for Factors Associated with Treatment Success Among People with DRTB and Undernutrition in Uganda

Characteristic	Bivariable Analysis			Multivariable Analysis		
	Crude Odds Ratio	95% Confidence Interval	p-value	Odds Ratio	95% Confidence Interval	p-value
Cigarette use						
No	1 (base)			1 (base)		
Yes	0.56	0.29 1.10	0.091	0.19	0.07–0.47	<0.001
Residence						
Rural	1 (base)			1 (base)		
Urban	0.62	0.35 1.10	0.100	0.31	0.14–0.70	0.005
Haemoglobin level						
Normal	1 (base)			1 (base)		
Mild anaemia	0.71	0.33 1.53	0.380	0.65	0.25–1.69	0.374
Moderate anaemia	0.27	0.13 0.56	<0.001	0.14	0.06–0.35	<0.001
Severe anaemia	0.14	0.04 0.50	0.002	0.06	0.01–0.29	0.001
Severity of undernutrition						
Mild	1 (base)			1(base)		
Moderate	1.42	0.68 2.94	0.348	2.07	0.73–5.90	0.598
Severe	0.80	0.44 1.45	0.460	0.80	0.34–1.85	0.173

treatment success. Interestingly, all these are known risk factors for active tuberculosis alongside undernutrition.[41,42] Nicotine in tobacco affects innate immune responses against TB by attenuating the expression of toll-like receptors and production of cytokines (IL – 6 and 8 and TNFα) and chemokines by lung epithelial cells, macrophages and type 2 pneumocytes.[43,44] Anaemia is associated with low CD4+ T-lymphocyte counts, delayed sputum culture conversion, and severe forms of TB.[45–47] Therefore, smoking, anaemia and undernutrition can be expected to synergistically increase the risk of unfavourable TB outcomes. While the optimal management of anaemia in DRTB is not known, barriers to integrating smoking cessation programs in DRTB care should be addressed.[48] Anaemia in TB is complex and multifactorial. Although the most common cause of anaemia in TB is inflammation, anaemia does not invariably resolve on TB therapy.[49,50] Obviously, nutritional causes are likely to be contributory in our study population. Therefore, moderate and severe anaemia forms of anaemia need further characterisation and appropriate treatment in addition to DRTB therapy. It is unclear why urban residence would be associated with unfavourable outcomes, although it is a known risk factor for TB. The association of urban residence and unfavourable DRTB treatment outcomes is equivocally reported in literature.[51,52] It is possible that urban residents have little social support and food security, both of which can affect treatment adherence. The effect of residence status on DRTB TSR should be evaluated by a meta-analysis of existing studies. Nonetheless, DRTB programs should be tailored to address context-specific needs in rural and urban settings.

Our study has limitations. First, the small size could have affected the validity of the comparisons of the three groups. Therefore, the differences in the comparisons should be interpreted with caution. Relatedly, more than 50% of participants in the primary database did not have BMI measurements. This could cause selection bias if health workers preferentially took these measurements for relatively healthy individuals (able to stand on the weighing scale) or those whom they presumed to be very ill – to guide dosing of medications. However, we found that participants in the primary database with and without BMI measurements had several baseline characteristics that were similar. The study, nevertheless, analysed data from a representative country-wide cohort. To our knowledge, it is the first study to report factors associated with treatment success among people with DRTB and undernutrition. We therefore provide relevant baseline data to inform design and implementation of future studies.

Conclusion

A high proportion of people with DRTB and undernutrition have severe undernutrition. Moreover, severe undernutrition may be associated with treatment failure in this population.

Therefore, there is an urgent need for high quality randomised controlled trials to evaluate efficacious and cost-effective management approaches for undernutrition in DRTB. Anaemia and cigarette smoking reduce the odds of treatment success. Cigarette cessation programs when integrated in DRTB care could improve DRTB treatment outcomes. Correcting moderate and severe anaemia, which may not be amenable to TB therapy only, is likely to increase treatment success among undernourished people with DRTB.

Data Sharing Statement

Datasets used in this analysis are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The Mulago Hospital Research and Ethics Committee (#MHREC 1679) approved the primary study. Waiver of consent for the use of secondary data was provided by the same committee. The study was conducted in accordance with the Declaration of Helsinki.

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Disclosure

The authors declare no competing interests in this work.

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