Published in final edited form as:

Ann Epidemiol. 2012 July ; 22(7): 466–473. doi:10.1016/j.annepidem.2012.04.007.

Lean Tissue Mass Wasting is Associated with Increased Risk of Mortality among Women with Pulmonary Tuberculosis in Urban Uganda

Ezekiel Mupere, MBChB, M.Med, MS, PhD^{*,1}, LaShaunda Malone, MSPH², Sarah Zalwango, MBChB³, Allan Chiunda, MPH⁴, Alphonse Okwera, MBChB, MSc.³, Isabel Parraga, RD, LD, PhD⁵, Catherine M. Stein, PhD^{2,4}, Daniel J. Tisch, MPH, PhD⁴, Roy Mugerwa, MBChB, M.Med^{3,6}, W. Henry Boom, MD², Harriet Mayanja, MBChB, M.Med, MS^{3,6}, and Christopher C. Whalen, MD, MS⁷

¹Department of Paediatrics & Child Health, College of Health Sciences, Makerere University Kampala, Uganda ²Tuberculosis Research Unit, Department of Medicine, Case Western Reserve University ³Uganda-Case Western Reserve University Research Collaboration ⁴Department of Epidemiology & Biostatistics, Case Western Reserve University ⁵Department of Nutrition, Case Western Reserve University ⁶Department of Internal Medicine, College of Health Sciences, Makerere University ⁷Department of Epidemiology & Biostatistics, College of Public Health, University of Georgia

Abstract

Objective—We assessed the impact of wasting on survival in tuberculosis patients using precise height-normalized lean tissue mass index (LMI) estimated by bioelectrical impedance analysis and body mass index (BMI).

Methods—In a retrospective cohort study, 747 adult pulmonary tuberculosis patients who were screened for HIV and nutritional status were followed for survival.

Results—Of 747 patients, 310 had baseline wasting by BMI (kg/m²) and 103 by LMI (kg/m²). Total deaths were 105. Among men with reduced BMI, risk of death was 70% higher (hazard ratio (HR) = 1.7, 95% CI 1.03, 2.81) than in men with normal BMI. Survival did not differ by LMI among men (HR = 1.1; 95% CI: 0.5, 2.9). In women, both the BMI and LMI were associated with survival. Among women with reduced BMI, risk of death was 80% higher (HR = 1.8; 95% CI: 0.9, 3.5) than in women with normal BMI; risk of death was 5-fold higher (HR = 5.0; 95% CI: 1.6, 15.9) for women with low LMI compared to women with normal LMI.

Conclusion—Wasting assessed by reduced BMI is associated with an increased risk for death among both men and women whereas reduced LMI is among women with tuberculosis.

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*To whom correspondence should be addressed: Mailing Address – Uganda-Case Western Reserve University Research Collaboration, Kampala, Uganda. Telephone: +256-700-451543/or +256-718-490843, Fax: +256-414-5331531, mupez@yahoo.com. This research was performed by the Tuberculosis Research Unit at Case Western Reserve University.

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Conflict of Interest and Sources of Funding

Author disclosures: Mupere E, Malone L, Zalwango S, Chiunda A, Okwera A, Parraga MI, Stein CM, Tisch JD, Mugerwa R, Boom WH, Mayanja KH, and Whalen CC reported no conflict of interest.

Keywords

Tuberculosis; survival; wasting; lean tissue mass index; body mass index; bioelectrical impedance analysis

Introduction

Wasting is a cardinal feature of tuberculosis, an infectious disease associated with worldwide cause of mortality. In Africa, a significant proportion of tuberculosis patients have a marked degree of wasting by the time they present for treatment (1–3). Wasting associated with tuberculosis is likely caused by a combination of decreased appetite and altered metabolism resulting from the inflammatory and immune responses (4, 5). Wasting is associated with impaired physical function (2), longer hospitalization days and increased tuberculosis mortality (3, 6, 7).

Lean tissue mass and fat mass body composition measurements are a precise way to evaluate wasting status (8, 9). Bioelectrical impedance analysis (BIA) has been recommended as a practical and reproducible method for clinical assessment of fat and lean tissue mass (9–11). In this study, we evaluated the effects of wasting on survival using both body mass index (BMI) and BIA measurements among patients with pulmonary tuberculosis in urban Uganda. We considered the role of gender and HIV infection in evaluating the impact of body wasting on survival.

Methods

Study Design

We performed a retrospective cohort study that comprised of 747 adults ≥ 18 years with pulmonary tuberculosis and known HIV sero-status. Data were extracted from the Household Contact study (12–14) and the placebo arm of the prednisolone randomized placebo-controlled clinical trial (15). All participants for the household and prednisolone studies were residents of Kampala district and detailed selection criteria have been published elsewhere (12–15). The household contact study was conducted in two phases (1995 – 1999, and 2002 to present) to describe the epidemiology of tuberculosis in urban African households. The clinical trial was conducted between 1995 to 2000 to determine whether immunoadjuvant prednisolone therapy in HIV-infected patients with tuberculosis was safe and effective at increasing CD4(+) T cell counts (15).

The 747 cohort of adults included 652 participants who were enrolled in the household contact study (312 from phase I and 340 from phase II) and 95 from the placebo arm of the clinical trial. The BIA data were collected only during the second phase of the household contact study; thus, only 311 of the 747 cohort had BIA data. The institutional review boards at Case Western Reserve University in the United States and AIDS Research Council in Uganda reviewed the study protocols and final approval was obtained from the Uganda National Council for Science and Technology. During follow-up, patients were referred to community clinics for further HIV care. Patients with tuberculosis were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health.

Measurements

All participants had socio-demographic information obtained through standardized data collection forms. Active tuberculosis was confirmed by sputum smear microscopy (WHO)

(16) and culture at the Uganda National Tuberculosis Reference Laboratory. HIV-1 infection was diagnosed on the basis of a positive enzyme-linked immunosorbent assay for HIV-1 antibodies (Recombigen; Cambridge Biotech, Cambridge, MA). All participants had posterior-anterior chest X-rays taken at baseline, and readings were performed by one experienced physician.

Nutritional status was assessed using baseline height and weight anthropometric measurements and BIA (RJL Systems, Detroit, MI, Quantum II) before initiation of tuberculosis therapy. Weight was determined to the nearest 0.1 kg using a SECA adult balance, and standing height was determined to the nearest centimeter. BMI was computed as weight (kilograms) divided by height (meters) squared. All BIA measurements were performed by one trained observer using the same equipment and recommended standard conditions (10).

A Single-frequency BIA was performed at 50 kHz and 800 mA with standard tetrapolar lead placement (17) to measure fat and lean tissue mass. Before performing measurements on each participant, the BIA instrument was calibrated using the manufacturer's recalibration device. Resistance and reactance were based on measures of a series circuit (18). BIA measurements were performed in triplicate for each subject and the average was used. Lean tissue mass was calculated from BIA measurements using equations that were previously cross-validated in a sample of patients with and without HIV infection (18) and have been applied elsewhere in African studies (19–21). Fat mass was calculated as body weight minus fat-free mass.

Operational definitions

Baseline wasting was defined using BMI and height-normalized indices (adjusted for height) for lean tissue mass and fat mass as measured by BIA. BMI can be partitioned into height-normalized indices of lean tissue mass index (LMI) and fat mass index (FMI), i.e., $BMI = LMI + FMI$ as previously reported (8, 9, 22) using BMI cutoff for malnutrition $<18.5 \text{ kg/m}^2$ (23). The cutoffs for low LMI and FMI corresponding to a BMI $<18.5 \text{ kg/m}^2$ (9) were as follows: LMI $<16.7 \text{ (kg/m}^2\text{)}$ for men and $<14.6 \text{ (kg/m}^2\text{)}$ for women with corresponding FMI $<1.8 \text{ (kg/m}^2\text{)}$ for men and $<3.9 \text{ (kg/m}^2\text{)}$ for women. LMI and FMI have the advantage of compensating for differences in height and age (11).

Study outcome variable

Observed survival was the main study outcome. It was defined as the time interval between the diagnosis of tuberculosis and death or censoring. Participants were censored at the last clinic visit when they were known to be alive or at the end of study. Mortality was assessed through a standard interview of family members or review of hospital records. When a participant failed to keep a scheduled visit, health visitors visited the participant's home to determine the vital status. Family members also provided the date of death and prominent symptoms at the time of death for those who died at home.

Statistical analysis

For analysis using BMI, data from 747 participants was used and data from 311 participants (a subset of 747) was used for BIA body composition. The overall survival distributions for participants presenting with or without body wasting were estimated using the Kaplan-Meier method and compared using the log-rank test (24). A series of Cox proportional hazards models (25) were fit after testing for the proportional hazards assumptions using graphical methods and goodness of fit Schoenfeld residuals. Observed survival and baseline wasting status as measured by low BMI or LMI were used as the primary dependent and independent variables, respectively in each model. The co-variables included age, sex, HIV sero-status,

prior smoking status, extent of disease on chest radiography, and history of weight loss. Variables that were associated with survival in a univariate analysis or with biological plausibility were evaluated in a series of multivariable models.

Two-way interactions between baseline wasting status and the co-variables were evaluated; significant interactions were demonstrated between sex and low LMI variable for wasting, and between sex and HIV sero-status on survival. Therefore, Cox regression models were fit stratified according to gender. Likelihood ratio tests were used to test the interactions. All analyses were performed using SAS version 9.2 (Cary software, North Carolina SAS Institute Inc. 2004).

Results

Baseline characteristics of tuberculosis patients

Of 747 patients who were included in the analysis for BMI, 310 (42%) had wasting whereas of the 311 participants with BIA measurements, 103 (33%) had lean tissue mass and 135 (43%) fat mass wasting at presentation (Table 1). Overall men had a worse nutritional status at baseline compared to women. Men had significantly greater proportion of individuals with reduced BMI (63%) and reduced LMI (80%) compared to women at presentation (Table 1). Men had significantly lower BMI (18.6 ± 2.1 versus 20.0 ± 3.3 , $p < 0.001$) and lower FMI (2.0 ± 0.8 versus 4.4 ± 2.8 , $p < 0.001$) compared to women, respectively whereas women had significantly lower LMI (15.8 ± 1.1 versus 16.6 ± 1.4 , $p < 0.001$) compared to men at baseline. Of note, there were no differences in body wasting at baseline between HIV positive and HIV negative TB patients regardless of whether BMI, LMI, and FMI cut-off were used to assess wasting.

Datasets for BMI and the subset with BIA measurements had comparable baseline characteristics including wasting as measured by BMI ($p = 0.45$), gender ($p = 0.56$), proportion of anemic individuals (hemoglobin ≥ 10 mg/dl) ($p = 0.59$), current smoking status ($p = 0.95$), and extent of disease on chest radiography ($p = 0.13$).

Effect of baseline wasting on survival

During the mean follow-up period of 31 (SD 23) months for the 747 patients with BMI measurements, 105 deaths occurred, 99 of them among HIV seropositive patients. The overall unadjusted survival for patients with low BMI at presentation was lower than that of patients with normal BMI (Log-rank, $p = 0.002$; Figure 1a). At 6 months, that is the end of tuberculosis treatment, survival among patients with low BMI was 87% compared to patients with normal BMI of 92%; by 12 months, survival among patients with low BMI was 85% compared to patients with normal BMI of 91%. When stratifying by sex, survival proportion was significantly lower among men with low BMI compared to men with normal BMI at diagnosis (Log-rank, $p = 0.033$; Figure 1b). For women with low BMI, the survival proportion was lower than that for women with normal BMI, but this difference was not statistically significant (Log-rank, $p = 0.119$).

During the mean follow-up period of 26 (SD 16) months for 311 patients with BIA measurements, 30 deaths occurred, 29 of them among HIV sero-positive patients. Overall unadjusted survival for 311 patients who presented with low LMI was lower compared to patients with normal LMI (Log-rank, $p = 0.016$; Figure 2a). At 6 months, survival among patients with low LMI was 92% compared to patients with normal LMI of 97%; by 12 months, survival among patients with low LMI was 87% compared to patients with normal LMI of 96%. When stratifying by sex, survival proportion was significantly lower for women who presented with low LMI compared to women with normal LMI at presentation

(Log-rank, $p < 0.001$; Figure 2b). For men with low LMI at presentation, survival proportion was not different from those with normal LMI (Log-rank, $p = 0.65$).

Both low BMI and low LMI at tuberculosis diagnosis were associated with poor survival in univariate and multivariable Cox proportional hazards regression analyses (Tables 2, 3, and 4). The unadjusted HR for death in univariate model among patients with low BMI at diagnosis compared to patients who had normal BMI was 1.80 (95% CI, 1.23, 2.64). Similarly, the unadjusted HR for death among patients with low LMI compared to patients who had normal LMI was 2.34 (95% CI, 1.14, 4.80; Table 2). Other univariate factors that were significantly associated with increased relative hazards of death included male gender, older age group >30 years, HIV sero-positive status, and history of weight loss (Table 2).

The HR for death among patients with low BMI at presentation was 1.83 (95% CI, 1.24, 2.71) after adjusting for age, HIV, prior smoking status, extent of disease on chest x-ray and history of weight loss (Table 3). Because our prior findings (20) showed an interaction between BMI and gender, we fitted Cox regression models stratified by gender (Table 3). Men with low BMI at presentation had a greater risk of death compared with men who had normal BMI (HR = 1.70; 95% CI: 1.03, 2.81). Among women, those presenting with a low compared with a normal BMI had comparable risk of death (HR = 1.83; 95% CI: 0.96, 3.50). Other factors that were associated with the risk of death in this model included older male gender, HIV sero-positive status, and history of weight loss (Table 3).

There was significant interaction between baseline wasting as defined by low BMI and HIV sero-status on survival ($p < 0.001$). In a stratified Cox regression after adjusting for age, prior smoking status, extent of disease on chest x-ray and history of weight loss, HIV-positive patients with reduced BMI had a greater risk for death compared to those with normal BMI (HR = 1.63; 95% CI: 1.09, 2.44). Among HIV-negative patients, the risk of death associated with a reduced BMI was not statistically significant (HR = 6.95; 95% CI: 0.78, 61.89).

When using BIA as the measure of body composition, patients presenting with a low LMI had a greater risk of death compared with patients with normal LMI (HR = 2.36; 95% CI, 1.11, 5.01), after adjusting for age, HIV, prior smoking status, extent of disease on chest x-ray and history of weight loss (Table 4). Because of the significant interaction between LMI and sex on survival ($p = 0.003$), we fitted Cox regression models stratified by gender (Table 4) which showed that women who presented with low LMI had a greater risk of death compared with women presenting with normal LMI (HR = 5.14; 1.56, 16.93), whereas men presenting with low LMI had a similar risk of death as compared with men with normal LMI (HR = 1.05; 95% CI, 0.40, 2.77). HIV sero-positive status among men was another factor associated with risk of death (Table 4).

When we evaluated the effect of baseline fat mass wasting on survival in both unadjusted (Table 2) and adjusted Cox regression models, fat mass wasting was not associated with any risk for death regardless of gender.

Discussion

In this retrospective cohort study of 747 adult patients with pulmonary tuberculosis in urban Uganda, most deaths occurred in HIV-infected persons. Wasting was associated with poor survival, but the effect varied by method of body composition measurement and gender. The impact of wasting varied little between men and women when using the BMI; however, when using the LMI as defined by BIA, the effect of wasting was dramatic in women with reduced lean tissue mass, but not in men. Fat mass wasting appears not to predict survival regardless of gender. This study demonstrates that loss of body mass, especially lean tissue mass, affects the survival of tuberculosis patients, especially when HIV-infected.

Our findings suggest that survival is influenced by BMI in both men and women, but that lean tissue mass is associated with survival only in women. For BMI, the magnitude of effect was similar among men and women and indicated that wasting increased the risk of death by about 80%. We interpret this to mean that loss of body mass in general as measured by BMI is a marker of poor survival. With BIA, we gain insight into potential mechanism that may explain the heightened risk, at least among women. In women, there is preferential loss of fat mass in order to preserve the limited lean tissue as previously described (20). When the energy reserve is spent, the body resorts to the muscle component for survival. Since we did not see any effect of lean tissue on survival in men, we surmise that they had sufficient lean tissue to meet the additional energy requirements of their illness.

Our findings also suggest that the effects of malnutrition on survival are accentuated by co-morbidities (5, 26). In the face of co-morbidities such as HIV, the effects of malnutrition become detectable. HIV sero-positive patients with reduced BMI at time of tuberculosis diagnosis had poor survival compared to HIV sero-positive patients with normal BMI. Yet there was a minimal effect on survival among HIV sero-negative patients with reduced BMI, though the number of deaths in this group were few. Previous studies have also reported similar effect that underweight BMI is associated with increased risk of mortality whereas obese and overweight BMI have reduced risk of both mortality and tuberculosis (27). It is known that malnutrition can cause immune-suppression (28); and thus, tuberculosis in the presence of malnutrition might further exacerbate HIV-associated immune-suppression. These interrelated effects may explain why both tuberculosis and malnutrition are associated with reduced survival among HIV-infected patients (29, 30). It may also account, in part, for the effect of tuberculosis on the natural history of HIV infection.

In this study, most deaths occurred during the first year of follow-up. There are several potential reasons for the early deaths. First, many presented with severe and extensive tuberculosis. More than 75% had moderate/or far advanced disease on chest x-ray. Second, most deaths were HIV-related, indicating that HIV-tuberculosis co-infection may be associated with additional nutritional alterations that lead to poor outcomes. The extra burdens on nutritional status include increased energy expenditure, nutrient malabsorption, reduced intake, micronutrient malnutrition, and increased production of inflammatory cytokines with lipolytic and proteolytic activity (31–33). Third, about a quarter of the study population presented with anemia, which is an HIV-related complication associated with poor outcome (34). Finally, there was substantial wasting at time of tuberculosis diagnosis in our population, yet wasting is associated with increased risk of early death.

The interpretation of findings in this study should be made with caution because the BIA method that was used in measuring body composition is not the reference standard, and the BIA prediction method used has not yet been validated in the local population. As a result, findings of body composition may be biased because of variations in hydration across ethnic groups (10). However, the prediction equations that were used in this study were previously cross-validated in individuals of different races and among men and women who were HIV sero-negative healthy controls and HIV sero-positive patients (18). Moreover, the equations have been used widely in other studies in Africa with meaningful findings (19–21, 35). Our findings are also limited by lack of information on dietary intake. This may contribute to some of the observed difference in body composition and survival by gender. Another limitation is that we did not have data on CD4+ T cell counts to comment on effect of HIV disease severity; however, our findings are consistent with previous studies of mortality in HIV-infected patients in Africa in which the rate of mortality was higher in men than in women (36, 37).

In conclusion, findings in this study indicate that body wasting exerts greatest effect on observed survival among HIV-infected tuberculosis patients with body wasting, and that the effect of wasting on survival varies by gender. A reduced BMI at presentation with tuberculosis is associated with increased risk for death among both men and women whereas reduced lean tissue mass is among women. These observations may need further investigations in other settings, and it may be important to consider use of LMI as part of nutritional assessment to achieve early identification of patients at risk for poor outcomes.

Acknowledgments

We would like to acknowledge the invaluable contribution made by the study medical officers, health visitors, laboratory and data personnel: Dr. Lorna Nshuti, Bonnie Thiel, Mark Breda, Dennis Dobbs, Hussein Kisingo, Mary Rutaro, Albert Muganda, Richard Bamuhimbisa, Yusuf Mulumba, Deborah Nsamba, Barbara Kyeyune, Faith Kintu, Dr. Mary Nsereko, Gladys Mpalanyi, Janet Mukose, Grace Tumusiime, Karen Morgan, Dr. Moses Joloba, Dr. DeoMulindwa, Dr. Brenda Okware, Denise Johnson, Alfred Etwom, and Michael Angel Mugerwa. We acknowledge Prof. Mark Schluchter of Case Western Reserve University for his guidance in analyzing of the project. We would like to acknowledge and thank Dr. Francis Adatu Engwau, Head of the Uganda National Tuberculosis and Leprosy Program, for his support of this project. We would like to acknowledge the medical officers, nurses and counselors at the National Tuberculosis Treatment Centre, Mulago Hospital, the Ugandan National Tuberculosis and Leprosy Program and the Uganda Tuberculosis Investigation Bacteriological Unit, Wandegaya, for their contributions to this study. This study would not be possible without the generous participation of the Ugandan patients and families.

Funding

This work was supported in part by the AIDS International Training Research Program of the Fogarty International Center [grant number TW00011], and the Tuberculosis Research Unit, awards [N01-AI95383, HHSN266200700022C/ N01-AI70022, and AI32414] from the National Institute of Allergy and Infectious Diseases.

List Abbreviations and Acronyms

BMI	Body mass index
LMI	Lean tissue mass index
FMI	Fat mass index
HR	Hazard ratio
BIA	Bioelectrical impedance analysis
WHO	World Health Organization
HIV	Human immune deficiency virus
CI	Confidence interval

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Figure 1.

A. Survival distribution among adult tuberculosis patients presenting with wasting (BMI <18.5 kg/m²) compared to patients without wasting.

B. Survival distribution among adult male tuberculosis patients presenting with wasting (BMI <18.5 kg/m²) compared to men without wasting in urban Uganda.

Figure 2.

A. Survival distribution among adult tuberculosis patients presenting with baseline lean tissue mass wasting ($\text{LMI} < 14.6 \text{ kg/m}^2$) compared to patients without wasting.

B. Survival distribution among adult female tuberculosis patients presenting with lean tissue wasting ($\text{LMI} < 14.6 \text{ kg/m}^2$) compared to female patients without wasting.

Table 1

Baseline characteristics of pulmonary tuberculosis patients with normal BMI or LMI versus patients with low BMI or LMI

Characteristic	Normal BMI (n=437)	Low BMI (n=310)	Normal LMI (n=208)	Low LMI (n=103)
	n (%)	n (%)	n (%)	n (%)
Sex				
Females	236 (54)	116 (37) ^a	126 (61)	21 (20) ^a
Males	201 (46)	194 (63)	82 (39)	82 (80)
Age (years)				
30	257 (59)	177 (57)	135 (65)	59 (57)
>30	180 (41)	133 (43)	73 (35)	44 (43)
HIV status				
Negative	202 (46)	143 (46)	116 (56)	56 (54)
Positive	234 (54)	167 (54)	91 (44)	47 (46)
Hemoglobin (g/dl) ¹				
>10	216 (81)	126 (64) ^a	151 (76)	73 (74)
10	51 (19)	70 (36)	48 (24)	26 (26)
Fat mass index (kg/m ²) ²				
Normal	149 (79)	27 (22) ^a	124 (61)	52 (51)
Low	40 (21)	95 (78)	79 (39)	49 (49)
Chest x-ray disease extent ³	75 (17)	36 (12) ^b	39 (19)	
Normal/mild				10 (10) ^b
Moderate/far advanced	357 (83)	271 (88)	164 (81)	93 (90)
Smoker ⁴				
No	374 (86)	219 (71) ^a	176 (85)	62 (60) ^a
Yes	61 (14)	90 (29)	31 (15)	41 (40)
Takes alcohol ⁵				
No	266 (61)	201 (65)	151 (73)	64 (62) ^b
Yes	170 (39)	109 (35)	56 (27)	39 (38)
History weight loss ⁶				
No	111 (26)	54 (17) ^b	38 (18)	13 (13)
Yes	324 (74)	255 (83)	168 (82)	90 (87)

^a p-value <0.001;

^b p-value <0.05;

LMI = lean tissue mass index; BMI = body mass index;

¹ 284 missed hemoglobin measurement due to lack of blood;

² fat and lean tissue mass was not measured;

³ eight missed extent variable;

⁴ three missed history of ever smoked;

⁵ one missed history of alcohol intake;

⁶ four missed history of weight loss;

LMI low = $<16.7 \text{ kg/m}^2$ for men and $<14.6 \text{ kg/m}^2$ for women; low BMI = $<18.5 \text{ kg/m}^2$; and low fat mass index = $<1.8 \text{ (kg/m}^2\text{)}$ for men and $<3.9 \text{ (kg/m}^2\text{)}$ for women.

Table 2

Univariate Analysis of Factors Associated With Mortality Among Adult Patients With Pulmonary Tuberculosis in Kampala, Uganda.

Characteristic	Deaths n (%)	Relative hazard	95% Confidence Interval
BIA Lean tissue mass index (kg/m ²)			
Normal	14/208 (7)	1	
Low	16/103 (16)	2.34	1.14, 4.80
BIA Fat mass index (kg/m ²)			
Normal	16/176 (9)	1	
Low	14/135 (10)	1.15	0.56, 2.36
Body mass index (kg/m ²)			
Normal	47/437 (11)	1	
Low	58/310 (19)	1.80	1.23, 2.64
Sex			
Female	38/352 (11)	1	
Male	67/395 (17)	1.66	1.12, 2.48
Age (years)			
30	34/434 (8)	1	
>30	71/313 (23)	3.15	2.09, 4.74
HIV sero-status ¹			
Negative	6/345 (2)	1	
Positive	99/401 (25)	16.24	7.13, 37.02
History weight loss ²			
No	11/165 (7)	1	
Yes	94/579 (16)	2.59	1.39, 4.84
Prior smoking status ³			
No	84/593 (14)	1	
Yes	20/151 (13)	0.98	0.60, 1.60
Chest x-ray extent ⁴			
Normal/minimal	19/111 (17)	1	
Moderate/far advanced	86/628 (14)	0.73	0.44, 1.19

¹ One missed HIV status;

² four missed history of weight loss;

³ eight missed chest x-ray disease extent variable; and

⁴ three missed history of prior smoking status.

Low lean tissue mass index=<16.7 kg/m² for men and <14.6 kg/m² for women; low fat mass index = <1.8 (kg/m²) for men and <3.9 (kg/m²) for women; and low body mass index<18.5 kg/m² regardless of gender.

Table 3

Relative Hazards [HR, 95% confidence intervals (CIs)] for Death Among Tuberculosis Patients With Normal Versus Low Body Mass Index (BMI) Adjusted for Age, HIV Status, History of Weight Loss, Prior Smoking Status and Chest X-ray Disease Extent; and Stratified According to Gender in Kampala, Uganda.

Characteristics	Deaths/N (%)	Overall model	Stratified models	
			Women (n=352)	Men (n=395)
			HR (95% CI)	HR (95% CI)
BMI (kg/m ²)				
Normal (≥ 18.5)	47/437 (11)	1	1	1
Low (<18.5)	58/310 (19)	1.83 (1.24, 2.71)	1.83 (0.96, 3.50)	1.70 (1.03, 2.81)
Age (years)				
30	34/434 (8)	1	1	1
>30	71/313 (23)	2.32 (1.53, 3.50)	1.77 (0.93, 3.36)	2.57 (1.45, 4.54)
HIV sero-status ¹				
Negative	6/345 (2)	1	1	1
Positive	99/401 (25)	15.88 (6.94, 36.38)	12.61 (3.84, 41.37)	18.48 (5.76, 59.26)
Prior smoking status ²				
No	84/593 (14)	1	1	1
Yes	20/151 (13)	0.69 (0.42, 1.14)	0.38 (0.05, 2.78)	0.61 (0.35, 1.04)
History weight loss ³				
No	11/165 (7)	1	1	1
Yes	94/579 (16)	3.40 (1.81, 6.37)	2.60 (1.00, 6.76)	4.27 (1.84, 9.95)
Chest x-ray extent ⁴				
Normal/minimal	19/111 (17)	1	1	1
Moderate/advanced	86/628 (14)	0.80 (0.49, 1.32)	0.91 (0.42, 2.99)	0.71 (0.37, 1.37)

¹ One missed HIV status;

⁴ eight missed chest x-ray disease extent variable;

² three missed history of prior smoking status; and

³ four missed history of weight loss.

Table 4

Relative Hazards [HR, 95% Confidence Intervals (CIs)] for Death Among Tuberculosis Patients With Normal Versus Low Lean Tissue Mass Index (LMI) by BIA Adjusted for Age, HIV Status, History of Weight Loss, Prior Smoking Status and Chest X-ray Disease Extent; and Stratified According to Gender in Kampala, Uganda.

Characteristics	Deaths/N (%)	Overall model	Stratified modes	
			Women (n=165)	Men (n=175)
		HR (95% CI)	HR (95% CI)	HR (95% CI)
LMI in kg/m ²				
Normal	14/208 (7)	1	1	1
Low	16/103 (16)	2.36 (1.11, 5.01)	5.14 (1.55, 16.93)	1.05 (0.40, 2.77)
Age (years)				
30	10/194 (5)	1	1	1
>30	20/117 (17)	2.40 (1.10, 5.21)	3.03 (0.90, 10.25)	2.82 (0.94, 8.47)
HIV sero-status ¹				
Negative	1/172 (0.6)	1	1	1
Positive	29/138 (20)	31.84 (4.29, 236.46)		20.3 (2.65, 155.86)
Prior smoking status ²				
No	23/38	1	1	1
Yes	7/72	0.60 (0.25, 1.48)		0.55 (0.20, 1.54)
History weight loss				
No	2/51 (4)	1	1	1
Yes	28/258 (11)	1.70 (0.39, 7.35)	1.86 (0.21, 16.25)	2.24 (0.27, 18.25)
Chest x-ray extent ³				
Normal/minimal	7/49	1	1	1
Moderate/advanced	23/257	0.91 (0.37, 2.20)	.75 (0.22, 2.51)	1.93 (0.41, 9.18)

LMI = lean tissue mass index (kg/m²); LMI low =<16.7 kg/m² for men and <14.6 kg/m² for women;

¹ One missed HIV sero-status and fewer events among HIV negative patients;

² twenty nine missed prior smoking status and fewer events among women; and

³ twenty nine missed chest x-rays.