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Effect of malnutrition on tuberculosis microbiologic severity in India

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EFFECT OF MALNUTRITION ON TUBERCULOSIS MICROBIOLOGIC SEVERITY IN INDIA

by

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ABSTRACT

The relationship between malnutrition and tuberculosis disease (TB) severity is understudied. This study analyzed data collected by a large cohort study to investigate the effect malnutrition, measured by BMI, had on TB mycobacterial burden.

A study population of 538 subjects was utilized for this secondary data analysis. Multivariate negative binomial regression was used to evaluate relationships between body mass index (BMI) categories and mycobacterial growth indicator tube (MGIT) days to positive.

Of the 538 subjects, 79% were male and 21% were female. The median age was 45 years of age. One subject was HIV seropositive and was excluded from the final analysis. There were incomplete outcome data for 63 subjects, who were excluded from the final analysis. BMI was categorized as severe malnutrition (BMI<16.5 kg/m^2), malnutrition (16.5≤BMI<18.5), normal (18.5≤BMI<25), and overweight/obese (BMI≥25), with 27%, 32%, 36%, and 5% of the population comprising these categories, respectively. The median MGIT days to positive was 8 days. After adjusting for confounders, individuals who had severe malnutrition or malnutrition had an adjusted RR of 1.05 (95% CI, 0.90–1.23) and 1.08 (95% CI, 0.94, 1.24), neither measure was significant for the association between TB disease burden and MGIT. Overweight/obese individuals had an 8% decreased risk (RR=0.92, 95% CI, 0.79–1.19) of shorter time to result compared to those with normal BMI, after adjusting for confounders.

The results of this study indicate that there is no significant association between BMI and MGIT in an adjusted model. However, there are several limitations to this result including, lack of cavitation data and failure to account for collinearity in the final model.

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Introduction

Tuberculosis (TB) is an airborne transmitted respiratory disease caused by *Mycobacterium tuberculosis* (MTB). The World Health Organization estimates 9.6 million new cases of TB in 2014, with 23% of those cases occurring in India[16]. In 2015, India reported a TB mortality of 36 deaths/100,000 people in the population per year, excluding those co-infected with HIV[16]. Immunocompromising conditions, malnutrition, diabetes, and chronic kidney disease have been specifically related to increased risk of progression from infection to active TB disease[5,16].

Malnutrition is of particular concern in India as among adults age 15–49 and children aged under 15 years, 34% of men, 36% of women and 48% of children are categorized as having malnutrition (body mass index (BMI)<18.5kg/m^2)[8]. In India among adults over 15 years of age, malnutrition was associated with 8.3 times the risk of culture positive pulmonary TB (PTB), compared to those with a BMI ≥18.5 kg/m^2.[4] A study used National Family Health Survey (NFHS-3) and a previously reported unadjusted risk ratio of 4.49 for the risk of TB among individuals with malnutrition to calculate the population attributable fraction of TB to malnutrition; 55.49% of all active TB cases in women and 54.4% of all active cases in men were attributable to malnutrition[1].

Similarly, malnutrition has been associated with increased mortality among persons with TB. Early death was associated with BMI <17 kg/m^2 (OR=1.8) compared to those who were of normal BMI (BMI≥18.5), in Malawi after adjusting for gender, type of TB, HIV status, co-trimoxzole administration, and baseline BMI[18]. These results were paralleled by a study that found an odds ratio of 2.14 for the risk of TB specific mortality in patients with malnutrition controlling for age, sex, gender, comorbidities, and TB status characterized by acid-fast bacilli (AFB) smear, TB culture, and chest radiograph[17].

A clear association between malnutrition and TB exists, but there are limited data on the impact of malnutrition on TB disease severity. Previous studies have demonstrated that low BMI is associated with higher colony counts on both AFB smear and culture[10,15]. Individuals identified with malnutrition were registered in the Latvian national multi-drug resistant TB (MDR-TB) database who were over 18 years of age, with MDR-TB, and started treatment between January 2000 and June 2004 had 2.7 times the odds of having a culture with 3+ grade (200–500 colonies on LJ media), compared to those who were normal or overweight, but multivariable analyses were not done[10]. Mid-upper arm circumference (MUAC), a measure of malnutrition assessed by determining the circumference of the left-upper arm, was significantly related to AFB grade in a Tanzanian study[15]; lower MUAC was associated with increased AFB smear density. The association was determined controlling for sociodemographic factors, but not comorbidities or patient symptoms. While an association between malnutrition and TB disease severity has been demonstrated, the majority of the data presented on the relationship was generated as secondary analyses within larger studies. These analyses are largely univariate in nature, and fail to properly control for confounding within the association.

Further distinction of the role malnutrition plays in TB burden is necessary to determine the most effective method for intervention and improving TB treatment outcomes in low-income nations. Of the studies centering on TB severity, no distinctions are made for the extent of malnutrition (e.g., severe vs moderate malnutrition) and the studies do not control for significant confounders of the association between malnutrition and TB (e.g., poverty leading to delays in TB care). The objective of this analysis is to use existing cross-sectional data to determine the relationship between malnutrition and TB severity

Methods

Study Design

A secondary analysis was conducted using data collected from a cohort of subjects enrolled in the Indo-US Regional Prospective Observational Research in TB (RePORT) study. Participants are pooled from three sources, one city in the Puducherry union territory (Pondicherry) and two districts in the state of Tamil Nadu: Villupuram, and Cuddalore. The goals of the primary study are to: identify biomarkers for risk of TB disease development and treatment relapse and to determine the impact of risk factors on treatment outcome of PTB and development of latent TB infection (LTBI) among household contacts. All cases are placed on standard of care drug therapy through the TB control program of India. Index cases are assessed at baseline by sputum analysis, clinical questionnaire, and anthropometric measurements (BMI, MUAC). After two months, study personnel follow-up with the participants and administer a symptom questionnaire, collect sputum (if feasible), and assess treatment compliance. The final follow-up at the end of treatment includes analysis of disease status (i.e., treatment failure) and questionnaire administration.

Participant Identification

Enrollment is ongoing and started in 2014. For this analysis, data collected on subjects enrolled as of July 2016 were used. Individuals suspected of having TB at their primary health center (PHC) are screened using a set of two sputum samples evaluated by AFB microscopy. Persons with a Ziehl-Neelsen sputum stain positive for AFB ($\geq 1+$) are suspected as having TB and added to a list of potential index cases. Study personnel followed up with the potential cases and conducted an interview to determine enrollment eligibility based on the criteria detailed below.

Inclusion Criteria

1. At least 6 years old
2. Sputum Ziehl-Neelsen stain positive for AFB($\geq 1+$)
3. Culture positive for Mtb; those who were smear positive but ultimately culture negative, were included until their culture results returned at which time they were retrospectively removed from the study
4. No history of TB treatment (partial or completed treatment course from previous Tb episode)
5. Intended to complete TB therapy for recommended duration
6. Planned to enroll in Directly Observed Therapy (DOTS) program for treatment

7. Intended to reside in the study area for duration of treatment

Exclusion Criteria

1. Received >1 week (5 daily or 3 intermittent) doses of multi-drug TB therapy in the preceding 30 days
2. Known MDR or extensively drug resistant (XDR-TB) at diagnosis or known contact of MDR or XDR-TB case
3. Chose not to initiate or complete the treatment course
4. Received more than 7 days of fluoroquinolone therapy or other drugs with anti-TB activity for any reason in the preceding days
5. Too sick to enroll (Karnofsky score of ≤ 10)
6. Fail to consent to HIV test, or no proof of HIV test in the last 3 months

Primary Explanatory and Outcome Variables

The primary explanatory variable was nutrition status, defined by baseline BMI (reported in units of kg/m^2). BMI was categorized into 4 groups: severe malnutrition (BMI <16), malnutrition (BMI 16–18.4), normal (18.5–25), and overweight/obese (BMI>25) as per standard WHO categorizations. In children, severe malnutrition was defined as BMI less than 3 standard deviations below the mean BMI. Malnutrition was defined as BMI greater than or equal to 3 standard deviations below the mean BMI and less than or equal to 2 standard deviations below the mean BMI. Normal nutrition status was considered less than 2 standard deviations above or below the mean BMI.

Overweight/obese was defined as greater than 2 standard deviations above the mean.

The outcome variable was liquid mycobacterial growth indicator tube (MGIT). Sputum samples were collected for culture confirmation of disease diagnosis. Cultures are performed on all identified cases. The liquid MGIT culture was quantified as time to positive culture (days).

Statistical Analysis

Descriptive variables were stratified by BMI category. Chi-square tests were conducted to determine associations between categorical variables and BMI. ANOVA tests were used to compare BMI with continuous variables. Univariate negative binomial regression models were used to determine unadjusted associations between descriptive variables and MGIT.

To identify the adjusted risk ratio for the association between BMI and MGIT, negative binomial regression was used. Confounding variables were added to the unadjusted model one at a time. Variables that were associated with both BMI and MGIT were added in first, in order of decreasing magnitude of effect. Those variables thought to be biologically relevant were then added in based on magnitude of effect. Variables associated with BMI and MGIT with a high magnitude of effect, or those that had biological relevance, were considered confounders and included in the final multivariate model. After addition of each new variable, the risk ratio was assessed for a 10% change in estimate in any of the BMI categories. If a 10% or greater change was found in any one of the BMI categories, the variable was retained in the final adjusted model as a confounder. A less than 10% change resulted in the conclusion that the variable was not a confounder, and the variable was dropped from the final model. All data analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

Characterization of Study Population

A study population of 538 subjects was identified for descriptive analysis. One subject was HIV seropositive and was excluded from analysis. Sixty-three subjects were excluded from the final analytic dataset due to missing outcome data. The final dataset used for model construction included 474 subjects. The study population was 79% male and 21% female. The median age was 45 years (range 14–81 years). Eighty percent of the population was employed, with 50% of the cohort having a monthly household income of less than 5000 rupees (<79 USD). The majority (59%) of subjects had a BMI <18.5kg/m2, 27% percent of subjects were characterized as having severe malnutrition, 32% had malnutrition, 36% were of normal BMI, and 5% were obese or overweight. The median MGIT time to result was 8 days (range 1–28 days, IQR=4 days) (Table 1).

Identification of Confounders and Multivariate Analysis

Table 1 displays univariate analysis for risk factors and their relationship with MGIT. Table 2 shows descriptive variables stratified by BMI category, and their univariate association with BMI. Factors identified as potential confounders were: gender, age, marital status, employment, years of education and mother's years of education, household income, diabetes, alcohol use, and smoking status. Symptoms considered in multivariate analysis for confounding were: cough, cough duration, coughing up blood, fever, night sweats, unexpected weight loss, loss of appetite, asthma, chest pain, fatigue, stomach removal, Chronic Obstructive Pulmonary Disease (COPD), hepatitis, maximum symptom duration.

Risk factors retained in the final multivariate analysis as confounders were household income, diabetes, loss of appetite, age, marital status, smoking, alcohol use, coughing blood, weight loss, mother's education, cough duration, asthma, stomach removal, COPD. Individuals who had severe malnutrition or malnutrition had an adjusted RR of 1.05 (95% CI, 0.90–1.23) and 1.08 (95% CI, 0.94, 1.24) respectively for risk of one day longer MGIT time to result, compared to those of normal BMI after adjusting for confounders. Overweight/obese individuals had an 8% decreased risk (RR=0.92, 95% CI, 0.79–1.19) of a one day longer time to result compared to those with normal BMI, after adjusting for confounders.

Discussion

The purpose of this study was to determine if a relationship exists between malnutrition, categorized by BMI, and TB disease severity measured by MGIT time to positive. This analysis found that among this cohort of individuals, malnutrition was not significantly associated with TB disease burden, as measured by days to positive MGIT result. Subjects who had severe malnutrition (BMI<16.5) and non-severe malnutrition (16.5≤BMI<18.5) had an essentially null (and not significant) increased risk of less severe disease burden, after controlling for confounders in multivariate analysis. Subjects who were overweight/or obese had essentially the same severity of disease compared to those with normal BMI after controlling for confounders.

It has been suggested that undernutrition has been linked to defective cell mediated immune function and may lead to increased TB disease severity, thought this relationship is not a definitive[19]. However, the results of this study found that malnutrition was not statistically significantly associated with TB mycobacterial burden.

Unlike many other studies on the association between malnutrition and TB disease severity, this analysis approached the question in a multivariate analysis. Because of the in-depth surveys administered, a wide range of potential confounders were assessed and used in the final adjusted model. This study also had no participants with HIV, thereby eliminating the strong effect that HIV has on TB. Children in this study were categorized based on a standard deviation distribution, accounting for their innate difference in developmental status, thereby addressing potential misclassification of malnutrition associated with using traditional BMI categories. The strength of this study was in the ability to consider a breadth of confounders in the context of a multivariate analysis.

The major limitation of this study is the lack of data on cavitation status. It is likely that among those with TB, disease severity is confounded by extent of cavitation, as cavities lead to an increase in expectorated bacilli. Including data on cavitation status would allow for more precise categorization of disease severity, and may lead to development of a more clear association between malnutrition and disease severity. Data on cavitation is being collected by this consortium and will be available for inclusion in future analyses. This study included many confounders in the construction of the final model that most likely are collinear. Further review will be done to minimize collinearity and address biological importance of variables to strengthen the validity of the final model.

Additionally, the data used in this analysis are cross-sectional; therefore no inferences about causation can be drawn. In order to draw conclusions about causality and mechanism of the role malnutrition plays in TB disease severity it is critical to understand if TB preceded malnutrition, or if malnutrition/wasting occurred as a result of TB. In this study, self-reported data on disease duration and weight loss were collected to try to parse out this time sequence. However, although these data may provide some insight into the pathway, self-report data, specifically data that required recall of time periods, is inherently biased. Therefore, the conclusions about malnutrition and disease time are not completely reliable to use as a basis of inference. Ideally, a cohort of subjects could be enrolled prior to the onset of disease to determine which comes first in this pathway, disease or malnutrition.

Future studies could focus on using longitudinal data to determine if duration of TB disease plays a role in the association between malnutrition and mycobacterial load. These studies could also aim to collect more in-depth clinical information and perform immunologic studies to better characterize the role immune suppression plays on clinical course of the disease. Importantly longitudinal studies could inform the causal pathway and interplay between TB infection, malnutrition, progression to TB disease, and TB disease severity. It is necessary to not only determine if malnutrition preceding disease relates to greater mycobacterial burden, but also if more severe malnutrition post-infection correlates with poorer outcomes.

Overall, the results of this study did not demonstrate a significant association between malnutrition and TB disease severity, and our hypothesis that those who have severe malnutrition will have more severe disease was not confirmed. A more critical look at the causal pathway to address confounders and interaction needs to be employed to get a more reliable risk assessment. If future analyses show an association between malnutrition and TB disease severity, nutritional supplementation and a more directed treatment algorithm could be instituted with the aim of improving health outcomes. Specifically, identification of a high impact, low cost intervention such as nutritional intervention could mean improved treatment outcomes in an impoverished nation.

Table 1a. Characteristics of TB cases, data on mycobacterial growth indicator tube (MGIT), and RR for MGIT time to positive

N=537	N (%)	Median MGIT time to positive days Median (range)	Unadjusted RR (95%CI)*** p-value
BMI (n=537)			
Severe Underweight (BMI < 16kg/m2)	145 (27.0)	7 (2,28)	0.96 (0.86, 1.06) p=0.37
Underweight (16<=BMI <18.5)	172 (32.03)	8 (2,28)	1.02 (0.93, 1.13) p=0.61
Normal (18.5<=BMI <25)	195 (36.31)	8 (1,27)	Ref
Overweight/Obese (BMI >=25)	25 (4.66)	7.5 (4,13)	0.95 (0.77, 1.17) p=0.62
BMI (continuous) median (range) (n=533)	17.54 (11.38,37.40)		1.00 (0.99, 1.02) p=0.82
Characteristics			
Gender (n=537)			
Male	412 (76.72)	8 (1,28)	0.95 (0.86,1.04) p=0.26
Female	125 (23.28)	8 (2,26)	Ref
Age (n=536)			
<10yrs	0		
10–20yrs	47 (8.75)	8 (3,28)	1.28 (0.51, 3.17) p=0.60
21–30yrs	66 (12.29)	8 (2,26)	1.59 (0.52, 3.17) p=0.60
31–40 yrs	94 (17.5)	8 (3,22)	1.20 (0.49, 2.97) p=0.69
41–50 yrs	143(26.63)	7 (1,28)	1.10 (0.45, 2.72) p=0.83
51–60 yrs	117 (21.79)	8 (2,27)	1.59 (0.49, 3.00) p=0.67
61–70 yrs	60 (11.17)	8 (4,18)	1.17 (0.47, 2.89) p=0.74
71–80 yrs	8 (1.49)	8 (4,13)	1.12 (0.43, 2.94) p=0.82
>80 yrs	1 (0.19)	7 (7,7)	Ref
Marital status (n=537)			
Never married	97 (18.06)	8 (3,28)	Ref
Married/living together	369 (68.72)	8 (1,28)	0.92 (0.83, 1.02) p=0.13
Separated/divorced	19 (3.54)	7 (4,22)	0.93 (0.74, 1.16) p=0.51
Widowed	52 (9.68)	8 (2,18)	0.91 (0.77, 1.06) p=0.22
***Caste (n=537)**			
Scheduled Caste	143 (26.63)	7.5 (1,26)	1.31 (0.75, 2.28) p=0.34
Scheduled Tribe	1 (0.19)	8 (8,8)	133 (0.48, 3.71) p=0.58
Other backwards caste	382 (71.14)	8 (2,28)	1.42 (0.82, 2.47) p=0.21
Don't Know	5 (0.93)	6 (5,7)	Ref
None	6 (1.12)	7 (5,11)	1.33 (0.68, 2.61) p=0.40

Economic Indicators			
Employment Status (n=537)			
Employed	433 (80.63)	8 (1,28)	0.99 (0.88, 1.11) p=0.84
Student	39 (7.26)	8.5 (3,28)	1.15 (0.96, 1.38) p=0.12
Unemployed	65 (12.10)	8 (2,24)	Ref
Years of Education (n=534)			
9 years or less	349 (65.36)	8 (1,28)	1.07 (1.01, 1.14) p=0.02
10–13 years	143 (26.78)	8 (2,27)	1.01 (1.00, 1.02) p=0.006
>13 years	42 (7.87)	8 (4,28)	Ref
Years of Education of Mother (n=515)			
9 years or less	492 (95.53)	8 (1,28)	1.23 (1.05, 1.44) p=.009
10–13 years	21 (4.08)	10 (5,28)	1.02 (1.01, 1.03) p=0.002
>13 years	2 (0.39)	9 (7,11)	Ref
Monthly Household Income (n=537)			
<Rs 3000 (less than 48 USD)	71 (13.22)	7 (2,22)	0.75 (0.52, 1.09) p=0.14
Rs 3000–5000 (48–79 USD)	189 (35.20)	8 (3,26)	0.80 (0.56, 1.15) p=0.23
Rs 5001–10000 (79–158 USD)	186 (34.64)	8 (1,28)	0.82 (0.57, 1.18) p=0.29
> Rs 10000 (>158 USD)	74 (13.78)	8 (2,17)	0.78 (0.54, 1.14) p=0.20
Refused to Answer	5 (0.93)	9 (8,16)	Ref
Unknown	12 (2.23)	8 (3,15)	
Building material of external house wall (n=241)			
Cement/Brick	201 (83.40)	8 (2,28)	1.20 (0.50, 2.87) p=0.68
Mud	20 (8.30)	6 (3,17)	1.09 (0.45, 2.66) p=0.85
Thatch	18 (0.41)	8 (3,18)	1.18 (0.48, 2.89) p=0.72
Polythene	1 (0.41)	14 (14,14)	2.0 (0.67, 6.09) p=0.22
Other	1 (7.47)	7 (7,7)	Ref
Comorbidities			
Stomach Removal (n=537)			
Yes	2 (0.37)	4.5 (2,7)	0.54 (0.25, 1.14) p=0.11
No	535 (99.63)	8 (1,28)	Ref
COPD (n=537)			
Yes	3 (0.56)	8 (3,9)	0.80 (0.47, 1.36) p=0.41
No	534 (99.44)	8 (1,28)	Ref

Hepatitis (n=537)			
Yes	31 (5.77)	8 (4,18)	1.02 (0.86, 1.21) p=0.83
No	506 (94.23)	8 (1,28)	Ref
Asthma (n=342)			
Yes	7 (2.04)	8 (3,13)	0.96 (0.61, 1.50) p=0.85
No	333(97.37)	8 (1,28)	Ref
Unknown	2(0.58)	10 (3,17)	
Diabetes Mellitus (n=532)			
Random Blood Sugar >200	183 (34.40)	8 (3,28)	1.02 (0.93, 1.12) p=0.64
Random Blood Sugar<200	349(65.60)	8 (1,28)	Ref
****Risky Alcohol Use- based on AUDIT-C score (n=537)**			
yes	220 (40.97)	8 (2,28)	0.99 (0.91, 1.07) p=0.84
no	317(59.03)	8 (1,28)	Ref
Smoking (n=537)			
yes (current)	87 (16.20)	7 (1,22)	0.84 (0.75 ,0.93) p=0.002
Yes(former)	175 (32.59)	7 (2,28)	0.90 (0.83, 0.98) p=0.02
No(never)	275 (51.21)	8 (2,28)	Ref

*Scheduled castes and tribes are among the most disadvantaged socio-economic groups in India. Other backwards castes are individuals of a slightly higher-ranking demographic than those in scheduled castes. These groups have been designated by the Government of India to receive special programming and legislation to promote empowerment and development.
**The AUDIT-C score is a composite score from a screening test to identify individuals with excessive drinking behaviors. The test consists of a series of questions that are quantified to classify hazardous patterns of alcohol use. A score of 8 or more indicates the individual partakes in risky alcohol behavior.
*** Negative Binomial Regression with TTPDAYS Univariate

Table 1b. Symptoms of TB and Symptom Durations among TB patients.

N=537	N (%)	Median. MGIT time to positive days Median (range)	Unadjusted RR (95%CI)* p-value
Cough (n=537)			
yes	534 (99.44)	8 (1,28)	1.19 (0.71, 2.01) p=0.51
no	3 (0.56)	5 (5,11)	Ref
Cough Duration (n=537)			
≥3 weeks	439 (82.06)	8 (1,28)	1.11(1.00, 1.23) p=0.05
< 3 weeks	94 (17.57)	7 (3,24)	Ref
Unknown	1 (0.19)		
Coughing up blood (n=537)			
yes	130 (24.21)	8 (3,28)	1.07 (0.98, 1.17) p=0.14
no	401 (74.67)	8 (2,28)	Ref
Fever (n=537)			
yes	457 (85.10)	8 (1,28)	0.94 (0.84, 1.05) p=0.23
no	80 (14.90)	8 (4,24)	Ref
Night sweats (n=537)			
yes	344 (64.06)	8 (1,28)	0.94 (0.87, 1.02) p=0.16
no	191 (35.57)	8 (3,26)	Ref
Unknown	2 (0.37)	9 (3,15)	
Unexpected weight loss(n=537)			
yes	491 (91.43)	8 (1,28)	0.84 (0.72, 1.03) p=0.02
no	35 (6.52)	9 (4,24)	Ref
unknown	11 (2.05)	11 (3,16)	
Loss of appetite(n=537)			
yes	400 (74.49)	8 (1,28)	1.03 (0.94, 1.13) p=0.45
no	137 (25.51)	8 (2,18)	Ref
Fatigue(n=537)			
yes	448 (83.43)	8 (1,28)	0.99 (0.89, 1.10) p=0.84
no	88 (16.39)	8 (3,26)	Ref
Unknown	1 (0.19)		
Chest Pain(n=537)			
Yes	365 (67.97)	8 (1,28)	1.03 (0.94, 1.12) p=0.60
No	172 (32.03)	7 (3,28)	Ref
Maximum Symptom Duration(weeks) (continuous) median (range) (n=536)	4 (1,36)		1.01 (1.00, 1.02) p=0.19
MGIT Culture(n=474) (continuous) median (range)			
Time to Result (days)	8 (1,28)		

* Negative binomial regression with MGIT time to positive days.

Table 2a. Stratification of subject characteristics by BMI category.

	Severe Malnutrition (n=145)	**Malnutrition (n=172)**	**Normal (n=195)**	**Overweight/ Obese (n=25)**	**P values for univariate association with BMI*** **
Characteristics					
MGIT Culture median (range)					
Time to Result (days) median (range)	7 (2, 28)	8 (2, 28)	8 (1, 27)	7.5 (4, 13)	0.64
Male	117(80.69)	136 (79.07)	145 (74.36)	11 (44.00)	0.04
Female	28(19.31)	36(20.93)	50 (25.64)	14 (56.00)	
Age					0.01
<10yrs	0	0	0	0	
10–20yrs	14 (9.66)	11 (6.40)	21 (10.77)	1 (4.00)	
21–30yrs	20 (13.79)	33 (19.19)	13 (6.67)	0	
31–40 yrs	18 (12.41)	33 (19.19)	37 (18.97)	6 (24.00)	
41–50 yrs	45 (31.03)	35 (20.35)	55 (28.21)	8 (32.00)	
51–60 yrs	29 (20.00)	36 (20.93)	46 (23.59)	6 (24.00)	
61–70 yrs	18 (12.41)	17(9.88)	21 (10.77)	4 (16.00)	
71–80 yrs	1 (0.69)	6 (3.49)	1 (0.51)	0	
>80 yrs	0	1 (0.58)	0	0	
Marital status					0.21
Never married	28 (19.31)	36 (20.93)	31 (15.90)	2 (8.00)	
Married/living together	104 (71.72)	112 (65.12)	136 (69.74)	17 (68.00)	
Separated/divorced	4 (2.76)	9 (5.23)	4 (2.05)	2 (8.00)	
Widowed	9 (6.21)	15 (8.72)	24 (12.31)	4 (16.00)	
***Caste**					0.99
Scheduled Caste	45 (31.03)	53 (30.81)	38 (19.49)	6 (24.00)	
Scheduled Tribe	0	0	1 (0.51)	0	
Other backwards caste	92 (63.45)	115(66.86)	153 (78.56)	18 (72.00)	
Don't Know	2 (1.38)	2 (1.16)	1 (0.51)	0	
None	1 (0.69)	2 (1.16)	2 (1.03)	1 (4.00)	

Economic Indicators					
Employment Status					0.004
Employed	120 (81.08)	144 (83.72)	155 (79.49)	14 (56.00)	
Student	9 (6.21)	8 (4.65)	20 (10.26)	2 (8.00)	
Unemployed	16 (11.03)	20 (11.63)	20 (10.26)	9 (36.00)	
Years of Education					0.21
9 years or less	106 (73.10)	112 (65.12)	116 (59.49)	15 (60.00)	
10–13 years	29 (20.00)	43 (25.00)	63 (32.31)	8 (32.00)	
>13 years	9 (6.21)	15 (8.72)	16 (8.21)	2 (8.00)	
Years of Education of Mother (Median, Range)					0.58
9 years or less	132 (91.03)	158 (91.86)	180 (92.31)	22 (88.00)	
10–13 years	4 (2.76)	8 (4.65)	7 (3.59)	2 (8.00)	
>13 years	1 (0.69)	1 (0.58)	0	0	
Monthly Household Income					<0.0001
<Rs 3000 (less than 48 USD)	31 (21.38)	24 (13.95)	15 (7.69)	1 (4.00)	
Rs 3000–5000 (48–79 USD)	51 (35.17)	68 (39.53)	63 (32.31)	7 (28.00)	
Rs 5001–10000 (79–158 USD)	46 (31.72)	60 (34.88)	74 (37.95)	6 (24.00)	
> Rs 10000 (>158 USD)	11 (7.59)	16 (9.30)	36 (18.46)	11 (44.00)	
Refused to Answer	2 (1.38)	1 (0.58)	2 (1.03)	0	
Don't Know	4 (2.76)	3 (1.74)	5 (2.56)	0	
Building material of external house wall					0.06
Cement/Brick	56 (38.62)	64 (37.21)	74 (37.95)	6 (24.00)	
Mud	9 (6.21)	10 (5.81)	1 (0.51)	0	
Thatch	4 (2.76)	5 (2.91)	8 (4.10)	0	
Polythene	1 (0.69)	0	0	0	
Other	0	1 (0.58)	0	0	

Comorbidities					
Stomach Removal					
Yes	1 (0.69)	1 (0.58)	0 (0.00)	0 (0.00)	0.57
No	144 (99.31)	171 (99.42)	195 (100.00)	25 (100.00)	
COPD					
Yes	0 (0.00)	1 (0.58)	2 (1.03)	0 (0.00)	0.81
No	145 (100.0)	171 (99.42)	193 (98.97)	25 (100.00)	
Hepatitis					
Yes	8 (5.52)	10 (5.81)	11 (5.64)	2 (8.00)	0.91
No	137 (94.48)	162 (94.19)	184 (94.36)	23 (92.00)	
Asthma					
Yes	2 (1.38)	2 (1.16)	2 (1.03)	1 (4.00)	0.59
No	88 (60.69)	111 (64.53)	120 (61.54)	14 (56.00)	
Diabetes Mellitus					
Yes	13 (8.96)	40 (23.26)	109 (55.90)	21 (72.00)	<0.0001
No	131 (90.34)	130 (75.58)	84 (43.08)	4 (28.00)	
****Risky Alcohol Use- based on AUDIT-C score**					
Yes	78 (53.79)	72 (41.86)	66 (33.85)	4 (16.00)	0.0001
No	67 (46.21)	100 (58.14)	129 (66.15)	21 (84.00)	
Smoking					
yes (current)	32 (22.07)	31 (18.02)	23 (11.79)	1 (4.00)	<0.0001
Yes(former)	59 (40.69)	61 (35.47)	51 (26.15)	4 (16.00)	
No(never)	54 (37.24)	80 (46.51)	121 (62.05)	20 (80.00)	

* Scheduled castes and tribes are among the most disadvantaged socio-economic groups in India. Other backwards castes are individuals of a slightly higher-ranking demographic than those in scheduled castes. These groups have been designated by the Government of India to receive special programming and legislation to promote empowerment and development.
** The AUDIT-C score is a composite score from a screening test to identify individuals with excessive drinking behaviors. The test consists of a series of questions that are quantified to classify hazardous patterns of alcohol use. A score of 8 or more indicates the individual partakes in risky alcohol behavior.
*** Univariate analysis for the association between BMI and predictors using chi-square and ANOVA.

Table 2b. Patient symptoms stratified by BMI category.

	Severe Malnutrition (n=145)	Malnutrition (n=172)	Normal (n=195)	Overweight/ Obese (n=25)	P values for univariate association with BMI***
Cough					
Yes	143 (98.62)	171 (99.42)	195 (100.00)	25 (100.00)	0.30
No	2 (1.38)	1 (0.58)	0	0	
Cough Duration					
Greater than 3 weeks	121 (83.45)	140 (81.40)	156 (80.00)	22 (88.00)	0.62
Less than 3 weeks	22 (15.17)	30 (17.44)	39 (20.00)	3 (12.00)	
Coughing up blood					
Yes	33 (22.76)	32 (18.60)	54 (27.69)	11 (44.00)	0.02
No	109 (75.17)	139 (80.81)	139 (71.28)	14 (56.00)	
Fever					
Yes	132 (91.03)	139 (80.81)	166 (85.13)	20 (80.00)	0.07
No	13 (8.97)	33 (19.19)	29 (14.87)	5 (20.00)	
Night sweats					
Yes	100 (68.97)	93 (54.07)	135 (69.23)	16 (64.00)	0.02
No	44 (30.34)	78 (45.35)	60 (30.77)	9 (36.00)	
Unexpected weight loss					
Yes	139 (95.86)	155 (90.12)	117 (60.00)	20 (80.00)	0.01
No	2 (1.38)	14 (0.81)	15 (7.69)	4 (16.00)	
Loss of appetite					
Yes	119 (82.07)	135 (78.49)	133 (68.21)	13 (52.00)	0.0009
No	26 (17.93)	37 (21.51)	62 (31.79)	12 (48.00)	
Fatigue					
Yes	136 (93.79)	142 (82.56)	151 (77.44)	19 (76.00)	0.002
No	9 (6.21)	29 (16.86)	44 (22.56)	6 (24.00)	
Chest Pain					
Yes	107 (73.79)	124 (72.09)	123 (63.08)	11 (44.00)	0.006
No	38 (26.21)	48 (27.91)	72 (36.92)	14 (56.00)	
Maximum Symptom Duration (weeks)	4 (1, 36)	4 (1, 18)	4 (1, 24)	4 (2,7)	0.58

*** Univariate analysis for the association between BMI and predictors using chi-square and ANOVA.

Table 3. Final Model Construction Scheme. Variables were added to the model one at a time. Variables were retained in the model if a 10% change in estimate in any one of the BMI categories was observed. The reference values used to assess 10% change are denoted in the reference model column and correspond the model number. Values presented in the BMI category columns refer to the log scale estimates, followed by the percent change in estimate compared to the reference model in parenthesis.

Model Number	Variable Added	Reference Model	Severe Malnutrition Estimate	Malnutrition	Overweight/ Obese	Variable Retained in the model?
1	BMI		-0.0412	0.0244	-0.0539	
2	Household Income	1	-0.0355 (16)	0.0285 (14)	-0.0452 (19)	Yes
3	Diabetes	2	-0.0151 (135)	0.0426 (33)	-0.0683 (34)	Yes
4	Loss of Appetite	3	-0.0176 (14)	0.0403 (6)	-0.0657 (4)	Yes
5	Age	4	-0.0004 (4300)	0.0424 (5)	-0.0456 (44)	Yes
6	Marital Status	5	-0.0014 (71)	0.0423 (0.2)	-0.0448 (2)	Yes
7	Smoking	6	0.0155 (109)	0.0554 (24)	-0.0683 (34)	Yes
8	Alcohol Use	7	0.0131 (18)	0.0520 (6)	-0.0537 (27)	Yes
9	Coughing Blood	8	0.0151 (13)	0.0499 (4)	-0.0697 (23)	Yes
10	Fever	9	0.0189 (20)	0.0460 (8)	-0.0662 (5)	Yes
11	Weight Loss	10	0.0334 (43)	0.0497 (7)	-0.1059 (37)	Yes
12	Night Sweat	11	0.0340 (2)	0.0475 (5)	-0.1083 (2)	No
13	Gender	11	0.0339 (1)	0.05 (0.6)	-0.0979 (8)	No
14	Amount of Education	11	0.0344 (3)	0.0514 (3)	-0.1007 (205)	Yes
15	Mother's Amount of Education	14	0.0310 (8)	0.0432 (15)	-0.1145 (8)	Yes
16	Cough	15	0.0314 (1)	0.0468 (8)	-0.1161 (1)	No
17	Cough Duration	16	0.0352 (12)	0.0353 (22)	-0.1290 (11)	Yes
18	Asthma	17	0.0695 (49)	0.0693 (49)	-0.0578 (123)	Yes

19	Chest Pain	18	0.0694 (0.1)	0.0691 (0.2)	-0.0576 (0.3)	No
20	Fatigue	18	0.068 (2)	0.0684 (1)	-0.0594 (3)	No
21	Stomach Removal	18	0.0673 (3)	0.0807 (14)	-0.0589 (2)	Yes
22	COPD	21	0.0535 (26)	0.0772 (5)	-0.0820 (28)	Yes
23	Hepatitis	22	0.0540 (0.9)	0.0781 (1)	-0.0820 (0)	No
24	Maximum Symptom Duration	22	0.0499 (0.9)	0.0785 (2)	-0.0779 (5)	No

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Curriculum Vitae

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