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Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death

R. Zachariah[1], M. P. Spielmann[1], A. D. Harries[2] and F. M. L. Salaniponi[2] *[1]Médecins Sans Frontières–Luxembourg, Thyolo District, Malawi; [2]National Tuberculosis Control Programme of Malawi, Community Health Science Unit, Private Bag 65, Lilongwe 3, Malawi*

Abstract

A study was conducted in new patients registered with tuberculosis (TB) in a rural district of Malawi to determine (i) the prevalence of malnutrition on admission and (ii) the association between malnutrition and early mortality (defined as death within the first 4 weeks of treatment). There were 1181 patients with TB (576 men and 605 women), whose overall rate of infection with human immunodeficiency virus (HIV) was 80%. 673 TB patients (57%) were malnourished on admission (body mass index [BMI] <18·5 kg/m^2). There were 259 patients (22%) with mild malnutrition (BMI 17·0–18·4 kg/m^2), 168 (14%) with moderate malnutrition (BMI 16·0–16·9 kg/m^2) and 246 (21%) with severe malnutrition (BMI < 15·9 kg/m^2). 95 patients (8%) died during the first 4 weeks. Significant risk factors for early mortality included increasing degrees of malnutrition, age >35 years, and HIV seropositivity. Among all the 1181 patients, 10·9% of the 414 patients with moderate to severe malnutrition died in the first 4 weeks compared with 6·5% of the 767 patients with normal to mild malnutrition (odds ratio 1·8, 95% confidence interval 1·1–2·7). In patients with TB, BMI < 17·0 kg/m^2 is associated with an increased risk of early death.

Keywords: tuberculosis, *Mycobacterium tuberculosis*, human immunodeficiency virus, malnutrition, mortality, Malawi

Introduction

The association between tuberculosis (TB) and malnutrition has been recognized for a long time. Malnutrition may predispose to TB, and in turn TB often causes malnutrition (MACALLAN, 1999). By the time African patients with TB present for registration and treatment, a significant proportion have a marked degree of nutritional impairment (HARRIES *et al.*, 1988; KENNEDY *et al.*, 1996). Since the 1980s, many countries in sub-saharan Africa have been affected by a severe epidemic of human immunodeficiency virus (HIV) infection. Malawi, a small country situated in the southern region of Africa, is no exception, and in 1999 it was estimated that there were 800 000 adults and children living with HIV/AIDS (acquired immune deficiency syndrome) in a total population of approximately 10·6 million (UNAIDS, 2000). TB is one of the most common opportunistic infections arising as a result of HIV immunosuppression, and in Malawi 77% of TB patients registered country-wide were found to be HIV seropositive in 2000 (KWANJANA *et al.*, 2001). Weight loss is a characteristic feature of HIV/AIDS, and malnutrition in TB patients is likely to be further exacerabated by the concomitant effects of HIV (KOTLER, 2000).

Case fatality rates in TB patients in sub-saharan Africa have risen in the last 10 years, and are highly associated with HIV infection. A substantial proportion of these deaths occur early in the course of treatment (NUNN *et al.*, 1992; GARIN *et al.*, 1997; WOOD & POST, of 1997; CONNOLLY *et al.*, 1998; HARRIES *et al.*, 1998). Factors associated with early mortality are at present not well characterized. We hypothesized that malnutrition in TB patients, by further compromising host immunity and predisposing to life-threatening nutritional deficiencies and superadded infections, is a risk factor for early mortality. We conducted a study in a rural district of Malawi to determine the prevalence of malnutrition in TB patients at the time of initial registration, and to examine the association between malnutrition and early mortality.

Address for correspondence: Dr R. Zachariah, Head of Mission (Mission Malawi), Médecins Sans Frontières–Luxembourg, 70 Rue de Gasperich, L-1617, Luxembourg; phone +265 644409, fax +265 641468 (Malawi), +352 335133 (Luxembourg), e-mail zachariah@internet.lu

Materials and Methods

Study setting and management of TB

The study was carried out on new patients who were registered with TB between November 1999 and March 2001 in Thyolo district, a rural region of southern Malawi. There are 2 hospitals, one government district hospital and one mission hospital, in the district which register and treat patients with TB. New TB patients, as soon as they are registered, are started on standardized anti-TB treatment. In brief, these regimens during the study period in Thyolo were as follows. New patients with smear-positive pulmonary tuberculosis (PTB) and serious forms of extra-pulmonary tuberculosis (EPTB) were given an 8 months' regimen consisting of 2 months' daily supervised streptomycin, rifampicin, isoniazid and pyrazinamide in hospital followed by 6 months of daily unsupervised isoniazid and ethambutol in the community (2SRHZ/6EH). New patients with smear-negative PTB and less serious forms of EPTB were given a 12 months' regimen consisting of one month of daily supervised streptomycin, isoniazid and ethambutol in hospital followed by 11 months of daily isoniazid and ethambutol, which is self-administered (1SEH/11EH). All new patients therefore, regardless of the type of TB, spent the first month of treatment in hospital.

Since mid-1999, all TB patients in Thyolo have been offered voluntary counselling and HIV testing, and those who are HIV seropositive and have no contraindication are offered co-trimoxazole prophylaxis at a dose of 480 mg (400 mg of sulfamethoxazole and 80 mg of trimethoprim) twice daily. All TB patients (while in hospital) also receive a daily nutritional supplement of 1250 kcal in the form of a premix of Likuni-Phala™ (a mixture of maize flour, soya, oil and sugar) in addition to a routine hospital ration of 1200 kcal.

Study population and data collection

A structured questionnaire and record form were used to gather information on basic demographic data, HIV status, length of symptoms before being diagnosed as a case of TB, and type of TB. All patients were weighed on admission, without shoes and with minimum clothing, between 09:00 and 10:00. The same weighing scale was used for all patients, and calibration was carefully controlled. Height was measured (on admission) with the patient standing upright and looking straight ahead. With patients who could not stand unassisted, height was estimated using knee height

(DENKE & WILSON, 1998). A normal body mass index (BMI; weight in kg divided by height in m^2) was defined as 18·5–24·9 kg/m^2. Malnutrition was defined as BMI < 18·5 kg/m^2. Different degrees of malnutrition were defined as follows: mild malnutrition, BMI = 17·0–18·4 kg/m^2; moderate malnutrition, BMI = 16·0–16·9 kg/m^2; and severe malnutrition, BMI < 16·0 kg/m^2 (DENKE & WILSON, 1998). Personnel conducting these measurements were well trained, and the same personnel were used throughout the study. All patients gave voluntary informed consent to participate in the study. All deaths occurring between registration and the first 4 weeks of treatment were recorded, and were regarded as 'early mortality'.

Statistical analysis

Data analysis was done using Epiinfo software (Centres for Disease Control, Atlanta, Georgia, USA), and the Logistic™ software (ANONYMOUS, 1994). The χ^2 test and χ^2 test for linear trend were used to test for differences in proportions and linear trends, respectively. A non-parametric test (the Kruskal–Wallis test for 2 groups) was used to verify differences in means between groups. Crude odds ratios (OR) and adjusted odds ratios (adjusted OR) were used to assess whether BMI and other factors were associated with early mortality. ORs were adjusted using multivariate logistic regression, the level of significance being set at $P \leq 0{\cdot}05$, and 95% confidence intervals were calculated throughout.

Results

Characteristics of the study population

There were 1319 new adult TB patients who registered during the study period. Of these, 138 patients were excluded from the study: HIV status was unknown in 83, there were spinal deformities in 12 and oedema in 8, and 35 patients died before undergoing height and weight measurements. Of the 1181 patients in the study, 576 were men and 605 (51%) were women; the mean age was 37 years. There were 624 patients (53%) with smear-positive PTB, 250 (21%) with smear-negative PTB, and 307 (26%) with EPTB. 943 (80%) patients were HIV positive. 922 were given co-trimoxazole chemoprophylaxis, which was started as soon as a positive HIV result was available. HIV positive patients with TB had a mean age of 32 years, which was less than the mean age of HIV negative TB patients, 38 years ($P < 0{\cdot}001$).

Nutritional status on admission.

The mean BMI on admission for all TB patients was 18·2 kg/m^2; for males it was 18·4 and for females 17·9 ($P < 0{\cdot}001$). 673 TB patients (57%) were malnourished on admission with 414 (35%) having moderate or severe malnutrition (BMI < 17·0 kg/m^2) (Figure).

Nutritional status and early mortality.

Ninety-five patients (8%) in the study died during the first 4 weeks of treatment (early mortality). Factors associated with early mortality are shown in Table 1. Significant risk factors were age >35 years, HIV seropositivity and increasing degrees of malnutrition. Early mortality was 6·3% in patients with normal nutrition, 6·9% in those with mild malnutrition, 10·1% in those with moderate malnutrition and 11·4% in those with severe malnutrition (χ^2 test for trend = 6·8, $P < 0{\cdot}01$).

A BMI of 17·0 kg/m^2 was used as the cut-off value to determine whether patients with normal nutrition/mild malnutrition and moderate/severe malnutrition had an increased risk of early death. This assessment was used for all patients, and in relation to the factors listed in Table 1. The results are shown in Table 2. For all patients, there was a significantly higher rate of early mortality amongst patients with moderate to severe malnutrition than for those who had normal nutrition or mild malnutrition. This significantly higher early mortality rate was found in relation to male sex, age >35 years, symptoms >3 months' duration, smear-positive PTB, HIV seropositivity, and co-trimoxazole prophylaxis.

Discussion

This study showed that over half of all TB patients in a rural district of Malawi were malnourished at the time of registration, and over one-third had moderate to severe malnutrition; 8% of patients in the study died during the first 4 weeks of treatment. Factors associated with early mortality included increasing degrees of malnutrition, age >35 years and HIV seropositivity. Patients with moderate to severe malnutrition, (BMI <17·0 kg/m^2) had higher rates of early death compared with those whose nutritional status was normal or mildly impaired, and these differences were found regardless of age, HIV serostatus and other factors.

The strengths of this study are that a large number of patients were studied, all patients were offered counselling and HIV testing, the same personnel and the same equipment were used for performing measurements of

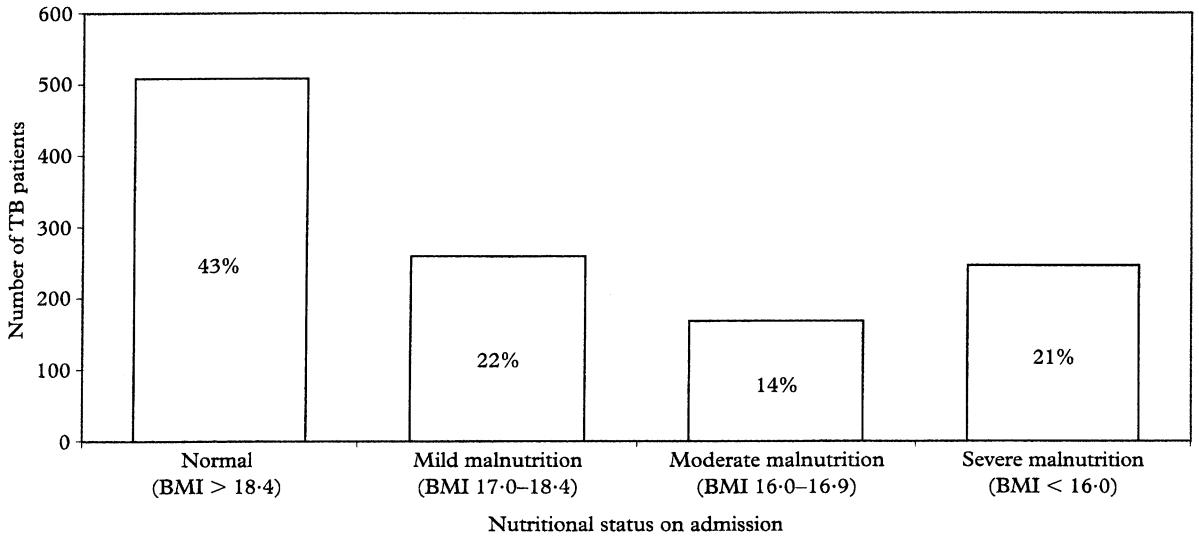

Figure. Nutritional status of patients with tuberculosis (TB) categorized by body mass index (BMI) in Thyolo district, Malawi. (Source: National Tuberculosis Control Programme of Malawi and Médecins sans Frontières–Luxembourg.)

Table 1. Risk factors associated with early mortality (during first 4 weeks of treatment) of patients with tuberculosis

Variables	Early deaths (%)	OR[a]	Adjusted OR[b]	*P*
Gender				
Female	42/605 (6·9)	1	1	
Male	53/576 (9·2)	1·3	1·4 (0·9–2·2)	0·15
Age (years)				
≤35	45/660 (6·8)	1	1	
>35	50/521 (9·6)	1·4	1·5 (1·0–2·4)	0·05
Type of TB[c]				
Smear positive	43/624 (6·9)	1	1	
Others (smear negative, EPTB[d])	52/557 (9·3)	1·4	1·3 (0·9–2·1)	0·20
HIV[e] status				
Negative	12/238 (5·0)	1	1	
Positive	83/943 (8·8)	1·8	4·8 (1·3–17·1)	0·01
Period of symptoms (months)				
<3	63/768 (8·2)	1	1	
>3	32/413 (7·7)	0·9	1·0 (0·6–1·5)	0·87
Co-trimoxazole				
Yes	16/259 (8·6)	1	1	
No	79/922 (6·2)	0·7	2·7 (0·8–8·3)	0·09
BMI on admission (kg/m^2)[f]				
>18·5	32/508 (6·3)	1	1	
17·0–18·4	18/259 (6·9)	1·1	1·2 (0·6–2·2)	0·59
16·0–16·9	17/168 (10·1)	1·4	1·8 (1·0–3·5)	0·05
<15·9	28/246 (11·4)	1·7	2·2 (1·3–3·8)	<0·01

[a]Odds ratio.
[b]Adjusted for gender, type of tuberculosis, human immunodeficiency virus status, co-trimoxazole administration and body mass index on admission; 95% confidence intervals in parentheses.
[c]Tuberculosis.
[d]Extrapulmonary tuberculosis.
[e]Human immunodeficiency virus.
[f]Body mass index; χ^2 for trend = 6·8, P = <0·01.

Table 2. Early mortality (during first 4 weeks of treatment) and nutritional status of patients with tuberculosis

	Normal/mild malnutrition (BMI ≥ 17·0 kg/m^2)		Moderate/severe malnutrition (BMI < 17·0 kg/m^2)			
	No.	Deaths (%)	No.	Deaths (%)	OR[a]	*P*
All patients	767	50 (6·5)	414	45 (10·9)	1·8 (1·1–2·7)	<0·01
Gender						
Female	241	13 (5·4)	243	21 (8·6)	1·5 (0·8–3·0)	0·10
Male	405	29 (7·2)	171	24 (14·0)	2·1 (1·2–3·9)	<0·01
Age (years)						
≤35	407	24 (5·9)	253	21 (8·3)	1·4 (0·8–2·8)	0·20
>35	360	26 (7·2)	161	24 (14·9)	2·3 (1·2–4·2)	<0·01
Symptoms (months)						
< 3	525	37 (7·0)	243	26 (10·7)	1·6 (0·9–2·8)	0·08
> 3	242	13 (5·4)	171	19 (11·1)	2·2 (1·0–4·9)	0·03
Type of TB[b]						
Smear positive PTB	386	19 (4·9)	238	24 (10·1)	2·2 (1·1–4·2)	0·01
Smear negative PTB	160	15 (9·4)	90	9 (10·0)	1·1 (0·4–2·8)	0·87
EPTB	221	16 (7·2)	86	12 (14·0)	2·1 (0·9–4·9)	0·07
HIV[c] status						
Negative	159	9 (5·7)	79	3 (3·8)	0·7 (0·1–2·8)	0·75
Positive	608	41 (6·7)	335	42 (12·5)	2·0 (1·2–3·2)	<0·01
Co-trimoxazole						
Yes	594	40 (6·7)	328	39 (11·9)	1·9 (1·2–3·1)	<0·01
No	173	10 (5·8)	86	6 (7·0)	1·2 (0·4–3·9)	0·70

[a]Odds ratio; 95% confidence intervals in parentheses.
[b]TB = tuberculosis; PTB = pulmonary TB; EPTB = extrapulmonary TB.
[c]Human immunodeficiency virus.

height and weight and, as all patients spent the first 4 weeks in hospital, deaths could be reliably ascertained. However, one of the limitations of the study was the fact that 35 TB patients (who died soon after admission and before any BMI measurements could be carried out) were excluded. We do not know the nutritional status of these patients, but their deaths comprised nearly 30% of the total deaths occurring between registration and the first 4 weeks of treatment. The results in this study do not therefore apply to very early mortality occurring soon after admission.

There are several potential reasons for early deaths of patients with TB: for example, late presentation of patients with severe and extensive TB; life-threatening

HIV-related complications such as severe anaemia and bacteraemia (GILKS *et al.*, 1990; MADEBO *et al.*, 1997; NIYONGABO *et al.*, 1999; GORDON *et al.*, 2001); and the occurrence of a Herxheimer-type reaction due to rapid killing of tubercle bacilli by anti-TB drugs (ELLIS & WEBB, 1983). We have shown that moderate to severe malnutrition is also a risk factor for early death. However, we do not know whether such nutritional impairment in its own right predisposes to early death, or whether it is a marker for extensive TB, severe HIV-related complications or Herxheimer reactions.

Preventing early death of patients with TB will be a major challenge in resource-poor countries such as Malawi (HARRIES *et al.*, 2001). Identification of bacteraemia in many African hospitals is difficult, because of lack of access to blood culture facilities, and ill patients may require an empirical course of antibiotics to treat commonly occurring infections due to *Streptococcus pneumoniae* and non-typhoidal *Salmonella*. Corticosteroids have been suggested as one way to reduce early deaths due to a Herxheimer-type reaction by reducing the toxicity of the disease (ELLIS & WEBB, 1983). Prospective controlled trials have shown a treatment benefit of corticosteroids in tuberculous meningitis and pericardial and pleural disease (ALZEER & FITZGERALD, 1993). However, trials of the use of corticosteroids in sick, malnourished TB patients, especially those with HIV infection, have yet to be carried out and published. Non-antibiotic nutritional interventions such as multivitamins may improve cell-mediated immunity in HIV positive patients (TANG *et al.*, 1997), but efficacy in this group has yet to be assessed in placebo-controlled trials. Anti-retroviral therapy is likely to have a major effect in reducing deaths from TB in HIV positive individuals, but, despite the pressure for widespread introduction of these therapies in sub-saharan Africa, it is likely to be some time before the infrastructure or the funds are available to turn this rhetoric into action.

The results of this study may help in finding solutions to this problem. BMI is a simple measurement for most hospitals to perform. TB patients with BMI < 17·0kg/m^2 form a group which has a higher risk of early death compared with patients whose BMI is 17·0 kg/m^2 or greater.

Although it is unclear what impact interventions in patients with BMI < 17·0 kg/m^2 might have in reducing overall TB mortality, this is nevertheless a group which could be targeted with interventions such as empirical antibiotics, corticosteroids and nutritional supplements in an operational research setting while awaiting the definitive results of phase III randomized controlled trials.

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