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Nutritional deficit as a negative prognostic factor in patients with miliary tuberculosis

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ABSTRACT: The effects of malnutrition on outcomes in miliary tuberculosis (MTB) are not well described. The aim of the present study was to find predictors for the development of acute respiratory failure (ARF) and survival in MTB patients, focusing on parameters reflecting nutritional condition.

Out of the patients from three hospitals who had microbiologically or histopathologically confirmed tuberculosis, 56 patients presenting with typical disseminated pulmonary nodules on radiographs were retrospectively enrolled. A four-point nutritional risk score (NRS) was defined according to the presence of four nutritional factors: low body mass index (BMI; <18.5 kg·m^{-2}), hypoalbuminaemia (<30.0 g·L^{-1}), hypocholesterolaemia (<2.33 mmol·L^{-1}) and severe lymphocytopenia ($<7\times10^5$ cells·L^{-1}).

The male to female ratio was 1:3. ARF developed in 25% of patients (14 out of 56), with a 50% fatality rate. A high NRS (≥3 points) was an independent risk factor for the development of ARF and fatality. In 90-day survival analysis, ARF, severe lymphocytopenia, hypocholesterolaemia, low BMI and higher NRS were risk factors for poor outcome. In multivariate analysis, only high NRS was an independent risk factor for 90-day survival rate in patients with MTB.

A high nutritional risk score was a good predictor of poor outcome in miliary tuberculosis patients. Additional approaches to recover the nutritional deficits may become a focus in future management of miliary tuberculosis.

KEYWORDS: Acute respiratory failure, malnutrition, miliary tuberculosis, prognosis

Miliary tuberculosis (MTB) refers to clinical disease resulting from the uncontrolled haematogenous dissemination of *Mycobacterium tuberculosis*, and develops in 1–2% of patients with tuberculosis (TB) [1]. The clinical implications of MTB are emphasised by the possibility of progression to acute respiratory failure (ARF) and high mortality [1–4]. While the mortality related to MTB is ~25–30% in adults, it is increased to 69% when patients with MTB require mechanical ventilation [4]. This suggests that the identification of risk factors predicting the development of ARF and subsequent survival in patients with MTB will be an important step in overcoming its high mortality.

Various parameters, including platelet count, serum albumin, elevated liver enzymes, lymphocytopenia, hyponatraemia, high Acute Physiology and Chronic Health Evaluation (APACHE) II score and delay in initiation of anti-TB chemotherapy, have been reported as risk factors for the development of ARF due to pulmonary TB or MTB [1, 5–7]. However, these reports were from studies of small numbers of cases or inhomogeneous disease populations including patients with pulmonary TB rather than MTB alone. In addition, the effects of nutritional deficit on the outcome of patients with MTB have rarely been focused upon [8, 9], although being underweight is a well-known predisposing factor for re-activation of TB [10–12]. Loss of both fat and lean tissue can result in reduction of body mass index (BMI) by 13–20% in patients with TB [13], and it can also be a predisposing condition for TB infection [11, 12, 14]. However, its effects on the development of ARF and survival in MTB are not well described. Therefore, the present multicentre study aimed to elucidate whether parameters reflecting nutritional deficits would contribute to the development of ARF and survival in patients with MTB.

MATERIALS AND METHODS

Study subjects

From January 2002 to February 2007, data and case records of patients with MTB were retrospectively reviewed from three hospitals in the Republic of Korea: Seoul National University Hospital (a tertiary referral hospital) and two

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affiliated hospitals, Seoul National University Bundang Hospital and Seoul National University Boramae Hospital. Only patients with typical miliary nodules on radiographs who had been diagnosed with TB microbiologically (*i.e.* positive acid-fast bacilli smear and/or culture for *M. tuberculosis*) or histopathologically (*i.e.* chronic granulomatous inflammation with caseation necrosis) were enrolled. The study was reviewed and permitted by the institutional review boards of each of the three hospitals.

Study design

Retrospectively enrolled patients were classified according to the comparison variables of TB with ARF *versus* TB without ARF and survivor *versus* nonsurvivor. To find the prognostic factors in MTB, further analyses for nutrition-related parameters (cholesterol, albumin, BMI and lymphocyte count), other potential risk factors for ARF discussed in previous reports (elevated liver enzyme and hyponatraemia) and the inflammation marker C-reactive protein (CRP) were performed between groups. Survival analysis was performed with the data acquired over 90 days of patient follow-up because this time covers the duration of intensive care unit stay for severe TB patients requiring mechanical ventilation [15], and the final results of drug susceptibility to anti-TB drugs, which affects the outcome of TB, would become evident at this time.

Definition of ARF

Hypoxaemic or ventilatory ARF was defined when patients met one of the following criteria: 1) arterial oxygen tension <8.0 kPa (60.1 mmHg) despite appropriate oxygen supplement; or 2) presence of a condition requiring mechanical ventilatory support.

Definition of nutritional risk score

Four variables were selected as the components of nutritional risk score (NRS): one anthropometric parameter, the BMI and three blood tests (albumin serum level, cholesterol serum level and lymphocyte count). They were chosen because they are well-known simple parameters related to nutritional status [16–20] and could be acquired routinely and easily without the need for additional questionnaires at the time of hospitalisation. The definitions of each parameter were as follows. 1) Low BMI: BMI <18.5 $kg \cdot m^{-2}$ [16, 17]; 2) hypoalbuminaemia: serum albumin <30.0 $g \cdot L^{-1}$ [5]; 3) hypocholesterolaemia: serum cholesterol <2.33 $mmol \cdot L^{-1}$ [8]; and 4) severe lymphocytopenia: a total lymphocyte count $<7 \times 10^5$ $cells \cdot L^{-1}$ [20]. Each risk factor was assigned a value of 1 if present or 0 if absent; therefore, the NRS ranged from 0 to 4. Patients with three or four points were classed as the high NRS group.

Definition of predisposing medical diseases

Excluding malnutrition, risk factors for TB re-activation, such as diabetes, immunocompromise, a history of gastrectomy and chronic liver disease, were defined as predisposing medical diseases.

Statistical analysis

Univariate analysis was performed using the Chi-squared test (Fisher's exact test for expected number per cell <5) or an unpaired t-test. For multivariate analysis, significant variables in the univariate analysis were entered into the binary logistic regression. The log-rank test with Kaplan–Meier curves and Cox regression tests were applied in survival analysis. Receiver operating characteristics (ROC) analysis was applied to elucidate the diagnostic accuracy of parameters. Statistical significance was determined with $p<0.05$.

RESULTS

Characteristics of study population

Out of the 5,854 patients who were diagnosed as having TB *via* radiographical or microbiological results, 56 patients met the inclusion criteria, and their demographic, clinical, laboratory and nutritional characteristics at the time of initial diagnosis are shown in table 1. The mean age was 52 yrs and male patients were predominant. HIV tests were performed in 49 (87.5%) patients and none of them showed a positive result. The results of the drug susceptibility test for *M. tuberculosis* were available in 18 (32.1%) patients, and there was no patient with multidrug-resistant TB. The mean values of haemoglobin, albumin and sodium were lower than reference values and mean CRP was increased. Of the 56 patients, 10 (17.9%) died during their hospital courses; five deaths were a direct result of MTB and the remainder were a result of systemic inflammatory response syndrome (SIRS) and multi-organ failure caused by ventilator-associated pneumonia or aspiration pneumonia with a significant contribution from MTB.

TABLE 1 Demographic, clinical and laboratory characteristics of the study population

Characteristics	Values
Demographic	
Sex M/F	32 (57.1)/24 (42.9)
Age yrs	51.9±22.4
BMI $kg \cdot m^{-2}$	19.4±2.6
Current or ex-smokers	20 (35.7)
Clinical	
Previous history of TB	4 (7.1)
Predisposing medical disease	9 (16.1)
Presence of ARF	14 (25.0)
ICU care	11 (19.6)
Mortality#	10 (17.9)
Laboratory	
Positive AFB smear or culture	31 (55.4)
Haemoglobin 130–170 $g \cdot L^{-1}$	116.4±21.3
Leukocyte count 4.0–10.0 $\times 10^5$ $cells \cdot L^{-1}$	7.15±3.22
Lymphocytes 20.5–51.1%	16.3±14.0
Total lymphocytes $\times 10^5$ $cells \cdot L^{-1}$	11.3±10.83
CRP 0.0–0.005 $g \cdot L^{-1}$	0.096±0.093
Cholesterol 1.8–6.2 $mmol \cdot L^{-1}$	3.40±1.21
Albumin 33–52 $g \cdot L^{-1}$	30.7±6.9
Serum sodium 135–145 $mmol \cdot L^{-1}$	133.4±5.7
Elevated transaminase¶	11 (19.6)

Data are presented as n (%) or mean±SD. M: male; F: female; BMI: body mass index; TB: tuberculosis; ARF: acute respiratory failure; ICU: intensive care unit; AFB: acid-fast bacilli; CRP: C-reactive protein. #: all causes; ¶: aspartate aminotransferase >40 $IU \cdot L^{-1}$ or alanine aminotransferase >40 $IU \cdot L^{-1}$.

TABLE 2 Results of univariate analysis of the risk factors contributing to the development of acute respiratory failure (ARF) and mortality in patients with miliary tuberculosis (MTB)

Variables	Comparison by presence of ARF			Comparison by fatality		
	Without ARF	With ARF	p-value	Survivors	Nonsurvivors	p-value
Patients n	42	14		46	10	
Clinical presentation						
Sex M/F	24/18	8/6	>0.999	25/21	7/3	0.489
Age yrs	48.7±23.0	61.3±18.4	0.069	49.9±22.9	61.1±18.0	0.153
BMI kg·m^{-2}	19.6±2.69	18.8±2.3	0.315	19.7±2.5	17.7±2.5	0.038
Predisposing medical disease	8 (19.0)	1 (7.1)	0.424	8 (17.4)	1 (10.0)	>0.999
Incorrect initial assessment[#]	3 (7.1)	5 (35.7)	0.018	6 (13.0)	2 (20.0)	0.623
Mortality	3 (7.1)	7 (50.0)	0.001			
Laboratory findings						
Positive AFB smear or culture	20 (50.0)[§]	11 (78.6)	0.115	23 (52.3)[§]	8 (80.0)	0.161
Haemoglobin g·L^{-1}	118.0±18.9	111.4±27.6	0.323	116.5±18.6	115.8±32.2	0.950
Total lymphocytes ×10^5 cells·L^{-1}	13.1±11.9	5.8±3.0	0.001	12.8±11.4	4.7±2.7	0.032
CRP g·L^{-1}	0.075±0.083	0.147±0.10	0.012	0.096±0.095	0.093±0.08	0.942
Cholesterol mmol·L^{-1}	3.65±1.07	2.65±1.34	0.006	3.60±1.14	2.48±1.15	0.007
Albumin g·L^{-1}	32.0±6.8	26.6±5.7	0.009	31.8±6.4	25.4±6.8	0.007
Serum sodium mmol·L^{-1}	134.5±5.3	130.2±5.7	0.012	134.3±5.2	128.5±6.1	0.013
Elevated transaminase[¶]	9 (21.4)	2 (14.3)	0.440	8 (17.4)	3 (30.0)	0.304
Response to anti-TB medication[+]						
Duration of anti-TB medication months	14.3±5.3	17.5±5.9	0.279			
Time to smear negative after initiation of treatment days	40.8±79.9	39.3±26.4	0.975			
Time to culture negative after initiation of treatment days	37.2±70.1	25.5±18.9	0.696			

Data are presented as n (%) or mean± SD, unless otherwise stated. M: male; F: female; BMI: body mass index; AFB: acid-fast bacilli; CRP: C-reactive protein; TB: tuberculosis. [#]: diagnosed with non-MTB diseases at the time of hospitalisation, based on simple chest radiography without full clinical data; five patients with community-acquired pneumonia and three patients with pulmonary oedema. [¶]: aspartate aminotransferase >40 IU·L^{-1} or alanine aminotransferase >40 IU·L^{-1}. [+]: data derived from patients who had completed expected anti-TB medication. [§]: data not available for two patients.

Risk factors for development of ARF in patients with MTB

Out of the 56 patients with MTB, 14 developed ARF, of whom seven died. In the univariate analysis, ARF developed more frequently in patients with decreased lymphocyte count, lower serum cholesterol and albumin levels and higher CRP. Even though there was no statistical difference, there was a trend towards ARF occurring more commonly in older patients. However, the results of AFB smears and/or culture of sputa and the microbiological response to anti-TB treatment were not different between subgroups. In the initial assessment, based on simple chest radiographs without full clinical facts at the time of admission, physicians confused MTB with other diseases such as pneumonia or pulmonary oedema in eight (14.2%) out of the 56 patients, and such confusion was found more frequently in the group with ARF (table 2). However, initial incorrect assessment did not lead to significant delay in starting anti-TB treatment compared with correct assessment (7.57±15.45 days for incorrect assessment *versus* 2.39±3.38 days for correct assessment; p=0.41). Mortality was also statistically similar (eight deaths out of 48 patients *versus* two out eight; p=0.62), although the occurrence of ARF was more frequent in patients who had other non-TB comorbidities at presentation compared with patients who were initially incorrectly assessed (nine out of 48 *versus* five out of eight; p=0.018).

Univariate analysis for the nutritional factors revealed that severe lymphocytopenia, hypocholesterolaemia and increasing NRS were significant risk factors for the development of ARF (table 3). In the multivariate analysis, higher CRP (odds ratio (OR) 1.12, p=0.046) and increasing NRS (OR 2.72, p=0.039) were independent risk factors for the development of ARF.

Results of survival analysis in patients with MTB

Lower BMI, fewer lymphocytes, and lower serum cholesterol, albumin and sodium levels were found in patients who died (table 2). In the 90-day survival analysis, development of ARF (p<0.001), severe lymphocytopenia (<7×10^5 cells·L^{-1}; p=0.001), hypocholesterolaemia (<2.33 mmol·L^{-1}; p<0.001), low BMI (<18.5 kg·m^{-2}; p=0.047) and higher NRS (p<0.001; fig. 1) were statistically significant risk factors. However, in regression analysis using Cox's proportional hazards model, only a high NRS (NRS≥3) was a poor prognostic factor for 90-day survival in patients with MTB (table 4).

TABLE 3 Nutritional risk factors and their effects on the development of acute respiratory failure (ARF) and mortality in patients with miliary tuberculosis

	Total	Comparison by presence of ARF			Comparison by fatality		
		Without ARF	With ARF	p-value	Survivors	Nonsurvivors	p-value
Patients n	56	42	14		46	10	
Nutritional risk factors							
Low BMI[#]	18 (32.1)	12 (29.3)[f]	6 (50.0)[##]	0.298	13 (28.9)	5 (62.5)	0.104
Severe lymphocytopenia[¶]	22 (39.3)	13 (31.0)	9 (64.3)	0.027	14 (30.4)	8 (80.0)	0.009
Hypocholesterolaemia[+]	8 (14.3)	2 (4.8)	6 (42.9)	0.044	3 (6.5)	5 (50.0)	0.002
Hypoalbuminaemia[§]	36 (64.3)	18 (42.9)	10 (71.4)	0.064	21 (45.7)	7 (70.0)	0.163
NRS	0.3±1.1	1.1±1.0	2.1±1.0	0.01	1.1±1.0	2.5±0.9	<0.001
NRS⩾3	10 (17.9)	4 (9.5)	6 (42.9)	0.01	4 (8.7)	6 (60.0)	0.001

Data are presented as n (%) or mean±SD, unless otherwise stated. BMI: body mass index; NRS: nutritional risk score. [#]: BMI <18.5 kg·m^{-2}; [¶]: total lymphocyte count <7×10^5 cells·L^{-1}; [+]: total cholesterol <2.33 mmol·L^{-1}; [§]: serum albumin <30.0 g·L^{-1}; [f]: data not available for one patient; [##]: data not available for two patients.

Diagnostic yield of NRS in predicting the development of ARF and fatality

To evaluate the diagnostic efficacy of NRS in predicting the development of ARF and fatality, ROC analysis was applied. The area under the curve (95% confidence interval) was 0.787 (0.667–0.907; p=0.001) for development of ARF and 0.764 (0.592–0.936; p=0.009) for predicting fatality. When the NRS was 2.5, the sensitivity and specificity for fatality were 0.6 and 0.71, respectively.

DISCUSSION

Various conditions, including TB, may result in ARF because of progression of underlying pulmonary infiltration or comorbidities [2], and high mortality in MTB may be the outcome of ARF itself or of other causes. Therefore, the clinical variables affecting the development of ARF and mortality were elucidated in patients with MTB. As a result, the parameter representing nutritional deficit (*i.e.* high NRS) was a poor prognostic factor in patients with MTB independent of development of ARF. In patients with pulmonary TB requiring mechanical ventilation, nonrespiratory factors including multi-organ failure were reported as the factors contributing to hospital mortality [21]. In addition, nutritional deficit is an important risk factor for nosocomial infection and subsequent multi-organ failure [22, 23], and the synergism of nutrition, infection and immunity are well described [10]. Therefore, sequential steps following nutritional deficit (infection, multi-organ failure and high fatality) may be inferred. In the present study, half the mortality (five out of 10 deaths) was related to combined SIRS and multi-organ failure that occurred due to hospital-acquired pneumonia, suggesting ventilator-associated pneumonia and aspiration pneumonia rather than the progression of the pulmonary lesion in MTB and subsequent respiratory failure. Finally, the current findings may be useful in explaining the relationship between nutritional status and the poor outcome of patients with MTB.

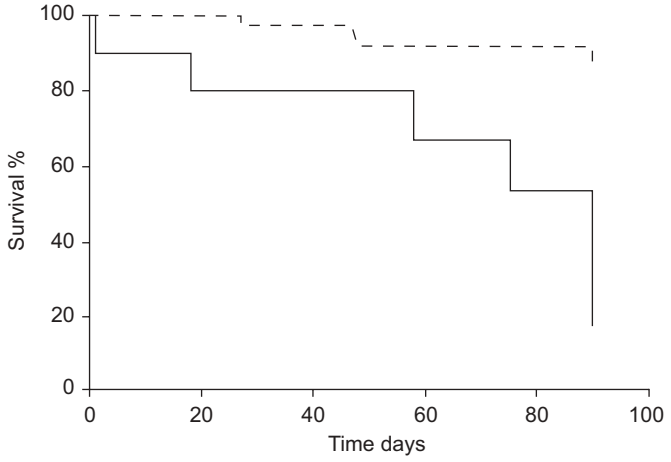

FIGURE 1. A Kaplan–Meier survival curve showing higher 90-day mortality in patients with a high nutritional risk score (NRS ⩾3; ——) compared with those with a lower NRS (<3; ----). A value of p<0.001 was determined using the log-rank test.

In the present study, to include the homogenous cases with MTB, conservative inclusion criteria were applied, which probably resulted in collection of a small number of patients with MTB compared with the number of all cases of TB diagnosed radiographically or microbiologically. The relatively small number may weaken the statistical power of the study.

TABLE 4 Results of Cox regression analysis to determine prognostic factors for 90-day survival[#]

Parameters	OR (95% CI)	p-value
NRS⩾3	11.44 (1.03–127.14)	0.047
Age yrs	1.04 (0.99–1.09)	0.093
Male	0.53 (0.05–5.72)	0.603
Development of ARF	2.84 (0.56–14.37)	0.206
Hyponatraemia	1.00 (0.89–1.11)	0.952

OR: odds ratio; CI: confidence interval; NRS: nutritional risk score; ARF: acute respiratory failure. [#]: variables included in the process were age, sex, site of hospital, development of ARF, serum level of sodium and NRS⩾3.

Even though there were some shortcomings of a retrospective study, including the rather small number of cases and deaths and the variation in sample size according to hospitals, the results from the current study population indicate that malnutrition present before anti-TB chemotherapy is important in the outcome of MTB and could have an impact on clinical practice in the management of MTB. During anti-TB chemotherapy, the cholesterol and albumin serum levels increased significantly by 0.71 ± 1.26 mmol·L^{-1} ($p<0.001$) and 3.7 ± 6.5 g·L^{-1} ($p=0.009$), respectively, in the first 3 months, which may reflect the wasting effects of severe TB (tested using an unpaired t-test to show the change during the 3-month interval). While the dual role of malnutrition as a risk factor and consequence of TB is well known, there have been few previous studies showing that nutritional supplements affect the course of TB [14, 24, 25]. However, recent studies that showed a lower risk of TB in obesity [26] and the effects of a cholesterol-rich diet on bacteriological sterilisation [24] may indirectly support the importance of appropriate nutrition in TB infection. Therefore, interventions to reverse nutritional and immunological dysfunction or to augment anabolic mechanisms in patients with MTB should be emphasised, in order to reduce the high mortality of MTB. Although microbiological cure of TB and recovery from malnutrition will be achieved with anti-TB treatment, it may take many months to reverse the wasting of TB [13] and gain in protein mass may be ineffective [27, 28]. This suggests that new strategies, in addition to simple nutrient supply, are necessary to overcome the malnutrition of patients with TB. A synthetic testosterone analogue has shown beneficial effects on improving body composition during the acute phase postburn [29] and restoring HIV wasting [30]. Since anabolic steroidal effects on improving nutrition in MTB are unknown, further studies are warranted.

The current study has some advantages over previous studies that discussed the prognostic factors of pulmonary TB or MTB [6–9]. First, the present data provide more relevant predictors of outcome in patients with MTB because they were acquired from a larger homogenous population than in previous studies and recruited from multiple centres. In addition to simple binary comparisons between the subgroups, the risk factors related to the survival of patients with MTB were analysed. The baseline characteristics of the present study population, such as age of onset, mortality rate and microbial identification rate in sputa, were similar to those of a previous study [5]. In contrast to the previous study, hyponatraemia and abnormal elevations of transaminase activity did not persist as the risk factors for the development of ARF throughout the statistical analysis. Hyponatraemia has many underlying causes, including malnutrition and syndrome of inappropriate secretion of antidiuretic hormone, and it may also be related to the severity of pulmonary disease. Elevation of transaminase activity is a feature not uncommon to MTB. Therefore, the relative homogeneity of study subjects in the extent of TB (MTB only), might lessen the effect of disease severity on these parameters.

Secondly, the NRS has some advantages in the clinical setting. While various screening methods in adults, such as prognostic nutrition index, prognostic inflammatory and nutritional index, nutritional risk index and subjective global assessment, require questionnaires or complex scoring systems, the current authors used BMI and simple biochemical parameters related to nutritional status. These parameters are routinely measured in hospitalised patients. Therefore, in the setting of hospitalisation, almost all patients have the data collected to determine the NRS, and its diagnostic yield was relatively high in the ROC analysis, suggesting that it can be useful in clinical settings. However, this parameter must be validated in further prospective studies. Among the components of NRS, lymphocytopenia is a common finding in patients with TB and it may be associated with TB severity as well as nutritional deficit. However, considering that study subjects have similar radiographical severity and patients with severe lymphocytopenia have a significantly lower level of albumin (28.2 ± 6.2 *versus* 32.3 ± 6.9 g·L^{-1}; $p=0.029$) and BMI (18.6 ± 2.8 *versus* 20.0 ± 2.3 kg·m^{-2}; $p=0.039$) than patients without severe lymphocytopenia, severe lymphocytopenia may be expected to reveal the nutritional deficit.

In conclusion, the present multicentred retrospective study showed that a simple score calculated from parameters representing nutritional deficits that are easy to obtain was an independent risk factor of survival and of the development of acute respiratory failure in patients with miliary tuberculosis. To reduce the high mortality of miliary tuberculosis, in addition to anti-tuberculosis chemotherapy, approaches aimed at reversing these nutritional deficits should be a focus in management of miliary tuberculosis.

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