ERJ Express. Published on May 28, 2008 as doi: 10.1183/09031936.00174907

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

Deog Kyeom Kim MD[1], Hyun Ji Kim MD[2], Sung-Youn Kwon MD[3], Ho-il Yoon MD[3], Choon-Taek Lee[3], Young Whan Kim MD[2], Hee Soon Chung[1], Sung Koo Han MD[2], Yong-Soo Shim MD[2], Jae-Ho Lee MD[3].

1 Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital affiliated Boramae Hospital

2 Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine and Lung Institute, Seoul National University Hospital

3 Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Seoul National University Bundang Hospital

Short title; Nutrition and prognosis of miliary tuberculosis

Corresponding author; Jae-Ho Lee MD.

E-mail; jhlee7@snubh.org

Phone; 82-31-787-7011

Fax; 82-31-787-4052

Department of Internal Medicine, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, Seongnam-si, Geonggi-do, 463-707, Republic of Korea

ABSTRACT

The effects of malnutrition on outcomes in miliary tuberculosis (MTB) are not well described. We aimed to find predictors for the development of acute respiratory failure (ARF) and survival in MTB patients focusing on parameters reflecting nutritional condition.

Of patients from three hospitals with tuberculosis confirmed microbiologically or histopathologically, 56 patients presenting with typical disseminated pulmonary nodules on radiograph were retrospectively enrolled. A 4-points nutritional risk score (NRS) was defined according to the presence of four nutritional factors such as low BMI (<18.5 kg·m^{-2}), hypoalbuminemia (<30.0 g·L^{-1}), hypocholesterolemia (< 2.33 mmol·L^{-1}), and severe lymphocytopenia (<7 x10^{5}cells·L^{-1}).

The male to female ratio was 1.3. ARF developed in 25% (14/56) with a 50% fatality rate. A high NRS (≥3 points) was an independent risk factor for the development of ARF and fatality ($p<0.005$). In 90-day survival analysis, ARF, severe lymphocytopenia, hypocholesterolemia, low BMI, and higher NRS were risk factors for poor outcome ($p<0.005$). In multivariate analysis, only high NRS was an independent risk factor for 90-day survival rate in patients with MTB ($p=0.024$).

A high NRS was a good predictor of poor outcome in MTB patients. Additional approaches to recovery the nutritional deficits may become a focus in future management of MTB.

Key words

Malnutrition, acute respiratory failure, miliary tuberculosis, prognosis

INTRODUCTION

Miliary tuberculosis (MTB) refers to clinical disease resulting from the uncontrolled hematogenous dissemination of *Mycobacterium tuberculosis* and it develops in 1-2% of patients with tuberculosis (TB) [1]. The clinical implications of MTB are emphasized by the possibility of progression to acute respiratory failure (ARF) and its high mortality [1-4]. While the mortality related to MTB is about 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 the platelet count, serum albumin, elevated liver enzymes, lymphocytopenia, hyponatremia, high 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 in 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 [8, 9], while being

underweight is a well-known predisposing factor for reactivation 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, this multi-center study aimed to elucidate whether parameters reflecting nutritional deficits would contribute to the development of ARF and the survival in patients with MTB.

MATERIALS AND METHODS

Study subjects

From Jan. 2002 to Feb. 2007, data and case records of patients with MTB were retrospectively reviewed from three hospitals in Korea Seoul National University Hospital (a tertiary referral hospital), and two affiliated hospitals, Seoul National University Bundang Hospital and Seoul National University Boramae Hospital. We enrolled only patients with typical miliary nodules on radiographs and 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). This study was reviewed and permitted by the institutional review boards of each of the three hospitals.

Study design

Retrospectively enrolled patients were classified with two groups according to the comparison variables of TB with ARF vs. TB without ARF and survivor vs. nonsurvivor. To find the prognostic factors in MTB, further analyses for nutrition

related parameters (cholesterol, albumin, BMI, and lymphocyte count etc), other potential risk factors for ARF discussed in previous reports (elevated liver enzyme, hyponatremia etc.) and 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 ICU care in severe TB patients requiring mechanical ventilation [15] and the final result of drug susceptibility to anti-TB drugs which affects the outcome of TB would become evident at this time.

Definition of acute respiratory failure

Hypoxemic or ventilatory ARF was defined as when patients met one of the following criteria: 1) PaO_2 less than 7,999 Pa despite appropriate oxygen supplement, 2) a condition requiring mechanical ventilatory support.

Definition of nutritional risk score (NRS)

Four variables were selected as the components of nutritional risk score: 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 hospitalization. The definitions of each parameter were as follows: 1) low BMI, BMI <18.5 $kg \cdot m^{-2}$ [16, 17]; 2) hypoalbuminemia, serum albumin < 30.0 $g \cdot L^{-1}$ [5]; 3) hypocholesterolemia, serum cholesterol < 2.33 $mmol \cdot L^{-1}$ [8]; and 4) severe lymphocytopenia, a total lymphocyte count < $7x10^5 cells \cdot L^{-1}$ [20]. Each risk factor was assigned a value of 1 if present or 0 if absent; therefore the nutritional risk score (NRS) ranged from 0 to 4. Patients with 3 or 4 points were classed as the high NRS group.

Definition of predisposing medical diseases

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

Statistical analysis

Data were analyzed with SPSS for Windows systems (Version 11.0, SPSS Inc, Chicago, IL, USA). Univariate analysis was performed using the Chi-square test (Fisher's exact test for expected number per cell less than five) or Student's t test. For multivariate analysis, significant variables in the univariate analysis were entered into the binary logistic regression. The logrank test with Kaplan Meier curves and Cox regression tests were applied in survival analysis. ROC (receiver operating characteristics) analysis was applied to elucidate the diagnostic accuracy of parameters. Statistical significance was determined with $p=0.05$.

RESULTS

Characteristics of study population

Among the 5,854 patients who were diagnosed as TB with radiographic 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. Mean age was 52 years and male patients were predominant. HIV-tests were done in 49 patients (87.5%) s and none of them showed positive result. While the results of the drug susceptibility test for *M. tuberculosis* were available in 18 patients (32.1%), there was no patient with multi-drug resistant TB. The mean value of hemoglobin, albumin, and sodium were lower than reference values and mean CRP was increased. Ten of the 56 patients (17.9%) died during their hospital courses. Of the ten patients who died five were as a direct result of MTB and the remainder were as 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 (year)	51.9±22.4
BMI ($kg \cdot m^{-2}$)	19.4±2.6
Current or ex-smoking*	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)
All cause mortality*	10 (17.9)
Laboratory	
AFB smear or culture positivity*	31 (55.4)
Hemoglobin ($g \cdot L^{-1}$, 130-170)	116.4±21.3
Leukocytes count ($x10^5 cells \cdot L^{-1}$, 4.0-10.0)	7.15±3.22
Lymphocyte (%, 20.5-51.1)	16.3±14.0
Total number of lymphocyte ($x10^5 cells \cdot L^{-1}$)	11.3±10.83
CRP ($g \cdot L^{-1}$, 0.0-0.005)	0.096±0.093
Cholesterol ($mmol \cdot L^{-1}$, 1.8-6.2)	3.40±1.21
Albumin ($g \cdot L^{-1}$, 33-52)	30.7±6.9
Serum sodium ($mmol \cdot L^{-1}$, 135-145)	133.4±5.7
Elevated transaminase *†	11 (19.6)

AFB= Acid fast bacilli, BMI=body mass index, CRP=C-reactive protein

* Data are shown as absolute number (percentage of population) and the others are presented as mean ± SD.

† The number of patients with AST > 40IU/L or ALT >40IU/L

Risk factors for development of ARF in patients with MTB

Fourteen of the 56 patients with MTB developed ARF, of whom seven died. In the univariate analysis, ARF more frequently developed 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 the simple chest radiograph without full clinical facts at the time of admission, physicians confused MTB with other diseases such as pneumonia or pulmonary edema among eight out of the 56 patients (14.2%) and it was found more frequently in the group with ARF (Table 2). But, initial incorrect assessment did not lead to the significant delay in starting anti-TB treatment (2.39 ± 3.38 days vs. 7.57 ± 15.45 days, p=0.41). Mortality was also statistically similar in both groups (8/48 vs. 2/8, p=0.62) although the occurrence of ARF was more frequent in patients who had other non TB comorbidities at presentation (9/48 vs. 5/8, p=0.018)

Univariate analysis for the nutritional factors revealed that severe lymphocytopenia, hypocholesterolemia, and increasing NRS were statistically significant risk factors for the development of ARF (Table 3). In the multivariate analysis, higher CRP (Odds ratio

1.12, p=0.046) and increasing NRS (Odds ratio 2.72, p=0.039) were independent risk factors for the development of ARF.

Table 2. Results of univariate analysis of the risk factors contributing to the development of ARF and mortality in patients with MTB

Variables	Comparison by the presence of ARF			Comparison by fatality		
	TB without ARF (n=42)	TB with ARF (n=14)	P	Survivor (n=46)	Non-survivor (n=10)	P
Clinical presentation						
Sex (M/F) *	24/18	8/6	>0.999	25/21	7/3	0.489
Age (year)	48.7±23.0	61.3±18.4	0.069	49.9±22.9	61.1±18.0	0.153
BMI ($kg \cdot m^{-2}$)	19.6±2.69	18.8±2.3	0.315	19.7±2.5	17.7±2.5	0.038
Predisposing medical disease*	8/42(19.0)	1/14(7.1)	0.424	8/46(17.4)	1/10(10.0)	>0.999
Initial assessment*†	3/42(7.1)	5/14(35.7)	0.018	6/46(13.0)	2/10(20.0)	0.623
Mortality	3/42(7.1)	7/14(50.0)	0.001			
Laboratory findings						
Positive in sputum AFB smear and/or culture*	20/40(50.0)	11/14(78.6)	0.115	23/44(52.3)	8/10(80.0)	0.161
Hemoglobin ($g \cdot L^{-1}$)	118.0±18.9	111.4±27.6	0.323	116.5±18.6	115.8±32.2	0.950

Total number of lymphocytes ($x10^5$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[*‡]	9/42(21.4)	2/14(14.3)	0.440	8/46(17.4)	3/10(30.0)	0.304
Response to Anti-TB medication [§]						
Duration of anti-TB medication (month)	14.3±5.3	17.5±5.9	0.279			
Time to smear negative conversion from initiation of treatment (day)	40.8±79.9	39.3±26.4	0.975			
Time to culture negative conversion from initiation of treatment (day)	37.2±70.1	25.5±18.9	0.696			

AFB= Acid fast bacilli, BMI=body mass index, CRP=C-reactive protein

* Data are shown as absolute number (percentage of population) and the others are presented as mean ± SD.

† The number of patients who diagnosed as non-MTB diseases at the time of hospitalization and it based on simple chest radiography without full clinical data; Five patients with community acquired pneumonia and 3 patiens with pulmonary edema.

‡ The number of patients with AST > 40IU/L or ALT >40IU/L

§ Data were derived from the patients who had completed expected anti-TB medication.

Table 3. Nutritional risk factors and their effects on the development of ARF and mortality in patients with MTB

		Comparison by the presence of ARF			Comparison by fatality		
Nutritional risk factors	Total (n=56)	TB without ARF (n=42)	TB with ARF (n=14)	P	Survivor (n=46)	Non-survivor (n=10)	P
Low BMI*	18 (32.1)	12/41 (29.3)	6/12 (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
Hypocholesterolemia‡	8 (14.3)	2 (4.8)	6 (42.9)	0.044	3 (6.5)	5 (50.0)	0.002
Hypoalbuminemia§	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

BMI=body mass index, NRS=nutritional risk score

* BMI <18.5 $kg \cdot m^{-2}$

† Total lymphocyte count < $7x10^5 cells \cdot L^{-1}$

‡ Total cholesterol < $2.33mmol \cdot L^{-1}$

§ Serum albumin < $30.0g \cdot L^{-1}$

Results of survival analysis in patients with MTB

Lower BMI, fewer lymphocytes, and lower serum cholesterol, albumin, and sodium levels were found in those who died (Table 2). In the 90-day survival analysis, development of ARF ($p<0.001$), severe lymphocytopenia (<$7x10^5 cells \cdot L^{-1}$, $p=0.001$), hypocholesterolemia (<$2.33mmol \cdot L^{-1}$; $p<0.001$), and low BMI (<18.5 $kg \cdot m^{-2}$; $p=0.047$), and higher NRS ($p<0.001$, Figure 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).

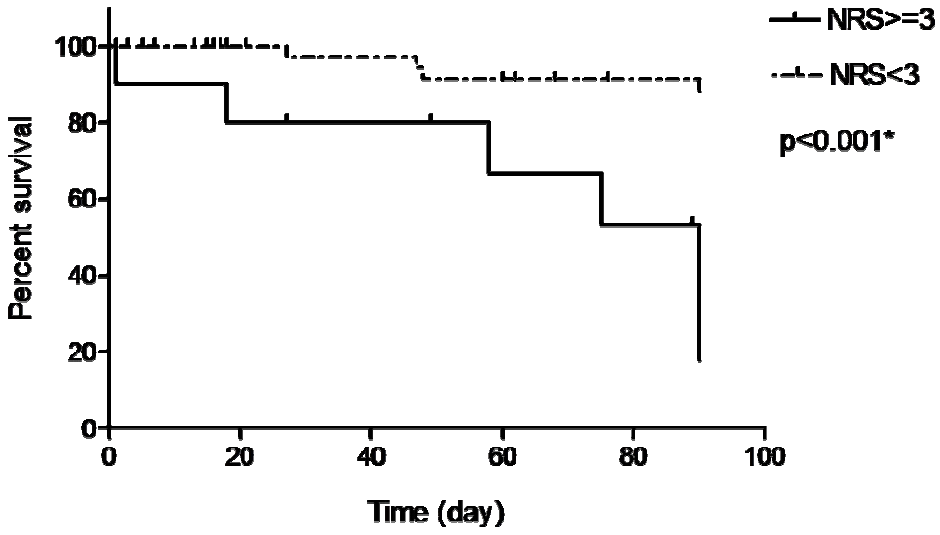

Figure 1. Kaplan-Meier survival curve shows higher 90-day mortality in patients with high NRS (NRS≥3). NRS: nutritional risk score. * P value was determined using the logrank test.

Table 4. Results of Cox regression analysis to determine prognostic factors for 90-day survival *

Parameters	Odds ratio (95% CI)	P
NRS≥3	11.44 (1.03-127.14)	0.047
Age	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
Hyponatremia	1.00 (0.89-1.11)	0.952

* Variables entered on the process were age, sex, site of hospital, development of ARF, serum level of sodium, and NRS≥3

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 was 0.787 (95% CI 0.667-0.907, p=0.001) for development of ARF and 0.764 (95% CI 0.592-0.936, p=0.009) for predicting fatality. When the NRS was 2.5, its sensitivity and specificity for fatality was 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 other causes. Therefore, we elucidated the clinical

variables affecting the development of ARF and the mortality respectively 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, non-respiratory factors including multiorgan 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 multiorgan failure [22, 23] and the synergism of nutrition, infection, and immunity are well described [10]. Therefore, sequential steps following nutritional deficit – infection, multiorgan failure and high fatality – may be inferred. In our study, half of mortality (5 patients) was related to the combined SIRS or multiorgan failure occurred due to hospital acquired pneumonia suggesting ventilator associated pneumonia and aspiration pneumonia rather than the progression of pulmonary lesion itself in MTB and subsequent respiratory failure. Finally, these findings may be useful data explaining the relationship between nutritional status and the poor outcome of patients with MTB.

In this study, to include the homogenous cases with MTB, the conservative inclusion criteria were applied and it probably resulted in collecting small number of patients with MTB comparing with the number of all cases of TB diagnosed radiographically or

microbiogically. The relatively small number may weaken the statistical power of the study. Even though there were some shortcomings of a retrospective study including the rather small number of cases and deaths, the variation in sample size according to hospitals, the results from this study population indicate that malnutrition present before anti-TB chemotherapy is important in the outcome of MTB and it could have an impact on clinical practice in the management of MTB. During anti-TB chemotherapy, the cholesterol and albumin serum levels significantly increased by 0.71 ± 1.26 mmol/L ($p < 0.001$) and 3.7 ± 6.5 g/L ($p=0.009$) in first 3 months and it may reflect the wasting effects of severe TB. While the dual role of malnutrition as a risk factor and consequence of TB is well known, there were few reports showing that the nutritional supplements affect the course of TB [14, 24, 25]. But, recent reports that showed lower risk of TB in obesity [26] and the effects of a cholesterol-rich diet on bacteriological sterilization [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 emphasized to reduce the high mortality of MTB. Although microbiologic 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]. It

suggests that new strategies adjunctive to simple nutrient supply are necessary to overcome the malnutrition of patients with TB. A synthetic testosterone analogue has shown a beneficial effect on improving body composition during the acute phase postburn [29] and restoring HIV wasting [30]. Because anabolic steroidal effects on improving nutrition in MTB are unknown, further studies are warranted.

This study has some advantages over previous reports that discussed the prognostic factors of pulmonary TB or MTB [6-9]. First, we think that our data provide more relevant predictors of outcome in patients with MTB because they were acquired from a larger homogenous population, recruited from multiple centers, than in previous reports. In addition to simple binary comparisons between the subgroups, the risk factors related to the survival of patients with MTB were analyzed. The baseline characteristics of the study population such as age of onset, mortality rate, and microbial identification rate in sputa was similar to those of a previous report [5]. In contrast to the previous report, hyponatremia and abnormal elevations of transaminase activity did not persist as the risk factors for the development of ARF throughout the statistical analysis. Hyponatremia has many underlying causes including malnutrition and SIADH and it may be also 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.

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

In summary, this multi-centered retrospective study showed that a simple score calculated from parameter representing nutritional deficits that are easy to obtain was an independent risk factor of survival and the development of ARF in patients with MTB. To reduce the high mortality of MTB, in addition to the anti-TB chemotherapy, approaches aimed at reversing these nutritional deficits should be focused in management of MTB.

REFERENCES

1. Sharma SK, Mohan A, Sharma A, Mitra DK. Miliary tuberculosis: new insights into an old disease. *Lancet Infect Dis* 2005; 5: 415-430
2. Shneerson JM. Respiratory failure in tuberculosis: a modern perspective. *Clin Med* 2004; 4: 72-76
3. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Experience with ARDS caused by tuberculosis in a respiratory intensive care unit. *Intensive Care Med* 2005; 31: 1284-1287.
4. Penner C, Roberts D, Kunimoto D, Manfreda J, Long R. Tuberculosis as a primary cause of respiratory failure requiring mechanical ventilation. *Am J Respir Crit Care Med* 1995; 151: 867-872
5. Hussain SF, Irfan M, Abbasi M, et al. Clinical characteristics of 110 miliary tuberculosis patients from a low HIV prevalence country. *Int J Tuberc Lung Dis* 2004; 8: 493–499.
6. Kim JY, Park YB, Kim YS, et al. Miliary tuberculosis and acute respiratory distress syndrome. *Int J Tuberc Lung Dis* 2003; 7: 359-364

7. Sharma SK, Mohan A, Banga A, Saha PK, Gungupalli KK. Predictors of development and outcome in patients with acute respiratory distress syndrome due to tuberculosis. *Int J Tuberc Lung Dis* 2006; 10: 429-435
8. Pérez-Guzmán C, Vargas MH. Hypocholesterolemia: A major risk factor for developing pumonary tuberculosis?. *Med Hypothesis* 2006; 66:1227-1230
9. Shin SR, Kim CH, Kim SE, et al. Predictors on in-hopital mortality following in-hospital diagnosis of tuberculosis. *Tuberc Respir Dis* 2006; 61: 233-238
10. Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. *Am J Clin Nutr* 1997; 66: 464s-477s.
11. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States *N Engl J Med*. 2004; 350: 2060-2067.
12. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. *Lancet* 2003; 362: 887-899.
13. Macallan DC. Malnutrition in tuberculosis *Diagn Mirobiol Infect Dis* 1999; 34: 153-157.
14. Schwenk A, Macallan DC. Tuberculosis, malnutrition and wasting. *Curr Opin Clin Nutr Metab Care* 2000; 3: 285-291.

15. Ryu YJ, Koh WJ, Kang EH, et al. Prognostic factors in pulmonary tuberculosis requiring mechanical ventilation for acute respiratory failure. *Repirology* 2007; 12:406-411.

16. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet* 2004; 363: 157-163.

17. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: World Health Organization, 2000.

18. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. *J Clin Epidemiol* 1997; 50: 693-703.

19. Omran ML, Morley JE. Assessment of protein energy malnutrition in older persons, Part II: laboratory evaluation. *Nutrition* 2000; 16: 131–140

20. Bagby GC Jr. Leukopenia and leukocytosis. *In*: Goldman L, Ausiello D, eds. Cecil text book of medicine. 22th Edn. Saunders, Philadelphia, 2003; pp.979-990.

21. Lee PL, Jerng JS, Chang YL, et al. Patient mortality of active pulmonary tuberculosis requiring mechanical ventilation. *Eur Respir J* 2003; 22:141-147

22. Lee S, Choi M, Kim Y, Lee J, Shin C. Nosocomial infection of malnourished patients in an intensive care unit. *Yonsei Med J* 2003; 44:203-209

23. Landi F. Body mass index and mortality among hospitalized patients. *Arch Intern Med* 2000; 160: 2641–2644.

24. Perez-Guzman C, Vargas MH, Quinonez F, Bazavilvazo N, Aguilar A. A cholesterol-rich diet accelerates bacteriologic sterilization in pulmonary tuberculosis. *Chest* 2005; 127: 643-651.

25. Range N, Changalucha J, Krarup H, Magnussen P, Andersen AB, Friis H. The effect of multi-vitamin/mineral supplementation on mortality during treatment of pulmonary tuberculosis: a randomised two-by-two factorial trial in Mwanza, Tanzania. *Br J Nutr*. 2006; 95: 762-770

26. Leung CC, Lam TH, Chan WM, et al. Lower risk of tuberculosis in obesity. *Arch Intern Med* 2007; 167: 1297-1304.

27. Schwenk A, Hodgson L, Wright A, et al. Nutrient partitioning during treatment of tuberculosis: gain in body fat mass but not in protein mass. *Am J Clin Nutr* 2004;79:1006-1012

28. Macallan DC, McNurian MA, Kurpad AV, et al. Whole body protein metabolism in human pulmonary tuberculosis and undernutrition: evidence for anabolic block in tuberculosis. *Clin Sci (Lond)* 1998;94:321-331

29. Jeschke MG, Finnerty CC, Suman OE, Kulp G, Mlcak RP, Herndon DN. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase posburn. *Ann Surg* 2007;246:351-362

30. Hengge UR, Stocks K, Wiehler H, et al. Double-blind, randomized, placebo-controlled phase III trial of oxymetholone for the treatment of HIV wasting. *AIDS* 2003;17:699-710