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Pulmonary tuberculosis with acute respiratory failure in South Korea

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Short title: Tuberculosis with respiratory failure

Abstract

This study evaluated the clinical characteristics, prognoses, and predictors of mortality in patients with pulmonary tuberculosis (TB) with acute respiratory failure (ARF), and investigated the adjunctive use of corticosteroids in such cases.

Ninety TB patients with ARF requiring mechanical ventilation were enrolled retrospectively from 1989 to 2006. The patients were divided into two groups: TB pneumonia (TBp, n = 66) and miliary TB (TBm, n = 24).

The TBp patients were older than the TBm patients (mean age 68.0 vs 54.5 years) and the mean interval from hospital admission to start of anti-TB treatment was longer for the TBp than for the TBm (5.0±7.0 vs 2.8±2.5 days). However, there was no difference in in-hospital mortality rates between the two groups (68.2% vs 58.3%). In TBp patients, multivariate analysis showed that advanced age and shock not related to sepsis were associated with poor outcomes. Even though corticosteroid use was a predictor of survival in TBp patients, it was difficult to conclusively determine the efficacy of corticosteroids in TBp with ARF because of the retrospective study design.

This study shows the need for randomized controlled trials to clarify the role of corticosteroids as adjunctive therapy in the management of TBp with ARF.

Keywords: corticosteroids, mortality, prognostic factors, respiratory failure, tuberculosis

Introduction

Following several decades of decline, the incidence of tuberculosis (TB) has recently begun to increase in many countries. The control of this disease has been impeded by co-infection with human immunodeficiency virus (HIV) [1] and the emergence of multidrug- resistant TB [2]. Active pulmonary TB is a rare primary cause of acute respiratory failure (ARF) [3]; however, high mortality rates have been recently reported in patients with ARF arising from TB [4-6].

Corticosteroids are the most important physiological inhibitors of inflammation. Several randomized studies have shown efficacy and safety of corticosteroid treatment in patients with severe inflammatory conditions, such as catecholamine-dependent septic shock [7, 8], severe community-acquired pneumonia (CAP) [9, 10], and early acute respiratory distress syndrome (ARDS) [11, 12]. With persistent unresolving ARDS, a beneficial effect of corticosteroid treatment was observed in some studies [13] but such improvements were not documented in others [14].

Corticosteroids have also been used as an adjunct in treating TB. The effective use of systemic corticosteroids in this regard is well-documented for several extrapulmonary forms of the disease, such as TB meningitis [15] and TB pericarditis [16]. Several studies have suggested that more rapid radiological resolution of pulmonary infiltrates and closure of cavities accompanied steroid use; these effects may be more pronounced in patients with severe disease [17, 18]. However, use of corticosteroids to modulate the

harmful effects of severe inflammatory responses has not been prospectively investigated in patients with severe TB-induced ARF.

This study was therefore conducted to: (1) evaluate the clinical characteristics of South Korean TB patients who developed ARF requiring mechanical ventilation; (2) determine the mortality rate and predictors of in-hospital mortality; and (3) investigate the status of adjuvant use of corticosteroids and the effect of such therapy on outcomes.

Materials and Methods

Patients

The medical records of all relevant patients (aged > 18 years), who had been admitted to the medical intensive care unit (ICU) of the Asan Medical Center from March 1989 to December 2006, were retrieved according to the following International Statistical Classification of Diseases (ICD) 10 codes: A150–A153 and A160–A162 (TB of lung), and A190–A199 (miliary TB). We reviewed medical records and selected patients who were bacteriologically or histologically diagnosed with active TB. Of these patients, 115 experienced ARF because of associated TB and were managed with invasive mechanical ventilation. Excluding 25 patients whose lungs had been extensively damaged by previous TB episodes, 90 patients were included in the final analysis of this study. Eighteen of these 90 patients had already been diagnosed with TB at other hospitals and were then transferred to our hospital, whereas the rest were diagnosed with TB after admission to our hospital.

Chest radiographs and data collection

Chest radiographs obtained during admission were reanalyzed by a pulmonary radiologist and a pulmonary physician. In case of disagreement, the pulmonary physician's view prevailed. Based on radiographic findings, the patients were divided into the following two groups: TB pneumonia (TBp, n = 66) and miliary TB (TBm, n = 24). TBp was defined as parenchymal consolidation with or without endobronchial spread mimicking bacterial

pneumonia [19]. TBm was defined as the presence of bilateral, diffuse, millet-sized nodules.

Age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) III score, body mass index (BMI), risk factors for TB, underlying diseases, previous history of anti-TB treatment, concomitant extrapulmonary TB, and duration of symptoms before admission were recorded and compared between groups. In addition, a sputum acid-fast bacilli (AFB) smear and culture data, and other diagnostic results such as drug susceptibility, arterial blood gas analysis, serum albumin level, and in-hospital mortality rate were recorded and compared. Furthermore, during hospitalization, the presence of disseminated intravascular coagulation (DIC), concomitant ARDS, shock, and organ failure, were recorded.

We also investigated the status of adjunctive corticosteroid use, including dosage, duration, and interval from commencement of anti-TB treatment to steroid therapy. The use of corticosteroids in patients with severe TB was not formalized in our hospital, being completely at the discretion of the physician-in-charge.

Definitions

The presence or absence of DIC was determined by platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen degradation product (FDP) level, D-dimer assay, and fibrinogen level. Shock was defined as a requirement for vasopressors. The causes of shock were divided into septic shock or shock not related to sepsis, such as heart failure or

cerebrovascular accidents. The diagnosis of ARDS was based on the consensus criteria of the American-European Consensus Conference [20]. Sepsis was considered present when clinical suspicion of infection was combined with evidence of systemic inflammation, based on the criteria decided upon by a recent international consensus conference [21], and septic shock was defined as sepsis combined with hypotension refractory to fluid replacement [21]. Organ failure was diagnosed based on the criteria of Knaus [22], and multiple organ failure (MOF) was defined as the failure of more than one organ.

Statistical analysis

Statistical analysis was performed using a desktop computer with a statistical software package (SPSS for Windows V12.0; SPSS Inc., Chicago, IL). Categorical values, such as sex ratio and mortality rates, were compared between groups using the chi-square and Fisher's exact tests. Continuous values, such as age and APACHE III score, were compared between groups using Student's t-test and the Wilcoxon rank sum test. All values are expressed as means ± standard deviations (SDs) or medians with ranges for continuous variables, and numbers or percentage of the group for categorical values. A stepwise forward multiple logistic regression model was used to evaluate independent risk factors for the prognosis of TB with ARF, including all significant or nearly significant parameters ($p < 0.1$), according to a univariate analysis. A p-value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

The baseline clinical and laboratory characteristics and risk factors for TB are listed in Table 1. The 44 HIV ELISA tests performed were all negative. The median age of all patients was 61.5 (range 22–89) years and the sex ratio was 1.5:1.0 (male:female). The symptom duration before admission was 27 ± 26 days. Diabetes mellitus was the most frequent underlying disease as shown in Table 1. Intra-pulmonary cavities on chest radiographs were present in 25 (27%) patients. Diagnosis was confirmed by sputum AFB smear and/or culture (n = 80), bone marrow biopsy (n = 7), or transbronchial lung biopsy (n = 3). Drug susceptibility data were available on bacterial isolates from 24 patients; isolates from 6 cases showed single-drug resistance, bacteria from 2 patients exhibited multidrug-resistance (MDR), and *Mycobacterium tuberculosis* from the other 16 patients showed pan-susceptibility.

Hospital courses and outcomes

The mean duration of hospitalization, length of ICU stay, and duration of mechanical ventilation were 38 ± 47, 21 ± 27, and 18 ± 26 days, respectively. The mean interval from hospital admission to commencement of anti-TB treatment was 4.3 ± 6.0 days. Systemic corticosteroids were used in 44 patients (49%). The mean daily dosage of prednisolone equivalents was 59 ± 6.7 mg and the median duration of corticosteroid therapy was 20 days (range 7 to 120 days). In 36/44 (81.8%) patients, the reason for using corticosteroids was noted

as treatment of ARDS because of TB. The median interval between start of anti-TB treatment and corticosteroid therapy was 2 days (range 0 to 12 days). In 8/44 patients, systemic corticosteroids were started immediately before the diagnosis of TB for the treatment of another presumed condition such as exacerbation of COPD (n = 6) or presumed cryptogenic organizing pneumonia (n = 2); however, these patients were finally diagnosed with TB and associated ARF. The in-hospital mortality rate was 65.6% (59/90). TB was the direct cause of death in 50 patients (including 34 cases of ARF and 16 cases of shock). Other causes of death were intestinal perforation (n = 1), arrhythmia (n = 4), pulmonary embolism (n =2), massive aspiration (n = 1), and intracranial hemorrhage (n = 1).

Comparison between the tuberculous pneumonia and miliary tuberculosis groups

Comparative data for the two groups are summarized in Table 1. The TBp patients were older than TBm patients (median ages 68.0 and 54.5 years, respectively; $p = 0.009$). The mean interval from hospital admission to start of anti-TB treatment was longer for the TBp group than for the TBm group (5.0 ± 7.0 and 2.8 ± 2.5 days, respectively; $p = 0.048$); in addition, four patients for whom TB treatment was delayed for more than 14 days (15, 25, 28, and 30 days) were in the TBp group. Concomitant extrapulmonary TB, ARDS, or DIC were more common in the TBm group than in the TBp group (all $p < 0.05$). However, there were no significant differences in in-hospital mortality rates between the two groups (68.2% and 58.3%, $p = 0.385$).

Factors predicting in-hospital mortality according to groups

In the TBp group, univariate analysis showed that advanced age, longer duration of symptoms before hospital admission, the presence of shock not related to sepsis, and non-use of steroids, were factors influencing patient survival (Table 2). There were no significant differences in septic shock frequency, MOF, ARDS, number of lobes involved [according to chest radiographs, which indicate the extent of disease; ($p = 0.448$, data not shown)], or the presence of cavitation (70% and 67% respectively; $p = 0.860$), between the survivor and non-survivor groups. Multivariate analysis revealed that advanced age and presence of shock not related to sepsis were independently associated with poor outcomes; however, the use of corticosteroids was a favorable prognostic factor for patients with TBp (Table 3).

In the TBm group, unlike TBp patients, there were no factors predicting non-survival (Table 2).

Comparison between the steroid-use and non-use groups in patients with tuberculous pneumonia

In TBp patients, those receiving corticosteroid therapy had a lower mortality rate (56.7%, 17/30) than those not receiving corticosteroid therapy (77.8%, 28/36) ($p = 0.046$) (Table 4). There were no differences in clinical characteristics such as age, duration of symptoms, and risk factors for TB including diabetes mellitus (20.0% vs. 14.0% respectively, $p = 0.387$, data not shown) between the steroid-use and non-use groups. There were no significant differences in severity indices (such as the oxygenation ratio), shock

not related to sepsis, septic shock, and MOF, between the two groups. Corticosteroids did not affect either the duration of mechanical ventilation ($p = 0.603$), or oxygenation ratio (PaO_2/FiO_2) measured on the seventh day of steroid therapy ($p = 0.182$, data not shown).

Discussion

The present study was performed in a country with an intermediate TB-burden (73.0 per 100,000 general population in 2005) [23] and a low prevalence of HIV infection (the cumulative incidence of HIV infection from 1985 to 2004 was 3,153 individuals in a population of 47 million people) [24], and, to the best of our knowledge, this is the largest study investigating cases of TB with ARF.

In the period following the development of anti-TB drugs, ARF arising because of TB has become relatively rare. However, TB remains a major cause of severe CAP [4-6]. In this study, the mean interval from hospital admission to start of anti-TB treatment was 4.3 ± 6.0 days. This indicates a somewhat shorter treatment initiation interval than in other studies (14.9 days [6] and 7.2 days [25]). The probable reason is that when Korean physicians examine patients with any atypical manifestations, TB is always suspected because there remains a relatively high incidence of TB in Korea and medical professionals are aware that TB can have various manifestations. The overall mortality rate in the present study was 65.6% (59/90), which is similar to those previously reported (66–81%) [4-6]. When it is considered that most patients were prescribed anti-TB treatment immediately after admission, and that most cases had non-MDR-TB without concomitant HIV, the mortality rate was high.

In many previous reports, miliary TB was identified as the main cause of ARF or ARDS [22-28]. Patients with miliary TB were more prone to develop

ARF that required mechanical ventilation and some miliary TB patients presented initially with interstitial infiltration rather than a miliary pattern on a chest radiograph, resulting in delayed diagnosis of TB [5]. In the current study, ARDS was reported in 83.3% of TBm patients but this result may have been biased. In a previous report, despite clinical and radiological features compatible with ARDS in some patients, histology showed confluent TB bronchopneumonia with no evidence of ARDS [29].

In contrast to miliary TB, tuberculous pneumonia has rarely been identified as a cause of ARF [19, 30]. It is difficult to radiologically differentiate between tuberculous pneumonia and severe bacterial pneumonia as causes of ARF, so accurate diagnosis can be delayed. In the present study, the mean interval from hospital admission to commencement of anti-TB treatment was longer in the TBp group than in the TBm group (5.0 ± 7.0 days and 2.8 ± 2.5 days, respectively). The most important factor differentiating TB from other infectious causes was the longer duration of symptoms before admission [19]. In our study, the mean duration of symptoms before admission (29 ± 28 days) was similar to those reported in previous studies [19, 31]. Therefore, AFB sputum examinations should be performed routinely in patients at risk of TB with severe pneumonia, particularly in endemic areas.

The use of corticosteroids to modulate the harmful effects of severe inflammatory responses has not been prospectively investigated in patients with severe TB-induced respiratory failure. Nevertheless, some clinicians prescribe corticosteroids when TB lesions are severe and progressive. Erbes

et al. [30] reported that ARDS developed in 7/58 TB-with-ARF patients, and steroids were used in all 7 cases. Lee et al. [6] also reported that ARDS developed in 25/41 TB-with-ARF patients, and 13/25 patients received > 2mg/kg/day methylprednisolone on the seventh day after the onset of ARDS for the treatment of the fibroproliferative stage. The beneficial effects of corticosteroids in the management of TBp with ARF are suggested by several reports. First, mycobacterial antigen can induce releasing of pyrogens from monocytes, lymphokines from specifically sensitized lymphocytes, and cytokines such as tumor necrosis factor from macrophages and peripheral blood mononuclear cells, which may be responsible for constitutional symptoms and tissue damage [33]. Corticosteroids can inhibit the release and activities of lymphokines and cytokines. Second, the granulomatous host response to TB may paradoxically protect sequestered *M. tuberculosis* from anti-TB therapy. The adjuvant corticosteroids may be beneficial in permitting anti-TB drugs to penetrate into granulomas, by disrupting granuloma formation [32].

In TBp patients, those receiving corticosteroid therapy showed a lower mean mortality rate. However, this may be an epiphenomenon; the data are not sufficiently strong to allow us to conclude that steroids may be useful in TBp patients. In this study, systemic corticosteroid use was based entirely on the attending physician's decision and/or the patient's underlying conditions. The use of corticosteroids was not formalized. The presence of ARDS was more frequent in steroid-use patients than in non-use patients (80% and 44% respectively, $p = 0.003$), suggesting that ARDS presence may be part of the

decision-making process when corticosteroids are prescribed. A history of previous TB may have influenced a decision not to prescribe steroids even though the frequencies of previous TB history did not differ significantly between steroid-use and non-use groups (13.3% vs 33.3% respectively, p = 0.059). A number of patients were already immunosuppressed or had other chronic diseases and these findings may have prevented attending doctors from prescribing corticosteroids. Such patients, denied prescribed corticosteroids because of additional underlying diagnoses, may have had worse outcomes. When a positive bias for prescribing steroids was sought, we observed, for example, that six patients were given steroids in order to relieve exacerbations of COPD but not to ameliorate the severity of TB *per se*. It is conceivable that these patients were more likely to develop respiratory failure because of underlying lung disease, even though they had less severe TB than others, and were in fact more likely to survive.

In the TBm group, corticosteroid therapy did not improve the survival rate; however, this result was inconclusive because of the small sample size. Any benefit of adjuvant corticosteroids in patients with miliary TB is not clear, as only limited evidence with conflicting results is available. A beneficial response was observed in one study [34], but such benefit was not documented in another [35].

This study has some limitations inherent to retrospective studies; some unrecorded bias may be present. Even though large numbers of patients were included over a long period of time, and multivariate analysis was performed,

the data do not permit us to draw final conclusions on best treatment of TB with ARF. In addition, the small number of subjects in the TBm group reduced the statistical power of analysis of these patients. In cases of corticosteroid use in cases of TB with ARF, possible positive or negative biases for steroid use (as described earlier) prevent us from definitively concluding that corticosteroids may be useful. This is so even though the survival rate was higher in the steroid-use group than in the non-use group, and steroid use was a favorable predictor of survival in multivariate analysis.

In conclusion, although South Korean clinicians usually consider TB to be a cause of severe CAP and commence anti-TB treatment promptly, the mortality rate is still high. Factors independently associated with mortality in the TBp group were advanced age and the presence of shock not related to sepsis. Even though multivariate analysis showed that corticosteroid use in TBp patients was a favorable prognostic factor in lowering mortality, the retrospective study design prevents us from concluding that corticosteroids may be useful in the treatment of cases of tuberculous pneumonia with ARF. Further randomized controlled trials are necessary to clarify the role of corticosteroids in the management of tuberculous pneumonia with ARF.

Table 1. Comparison of patient characteristics in the tuberculous pneumonia (TBp) and miliary tuberculosis (TBm) groups.

	Total (%)	TBp (%)	TBm (%)	P value
No.	90	66	24	
Median age, years (range)	61.5 (22-89)	68.0 (23-89)	54.5 (22-81)	0.009

Sex, M:F	1.5:1.0	1.7:1.0	1.0:1.0	0.243
BMI (kg/m^2)	19.2±3.4	19.1±3,4	19.6±3.5	0.241
Previous Hx of TB	20 (22.2)	16 (24.2)	4 (16.7)	0.445
Risk factors for TB	35 (38.9)	25 (37.9)*	10 (41.7)#	0.859
APACHE III score	74.9±24.0	76.3±24.6	71.0±25.0	0.360
PaO_2/FiO_2 ratio	129.8±41.3	127.4±43.6	137.3±33.0	0.341
Duration of MV, days	17.6±25.5	19.7±29.1	11.7±8.0	0.045
Mortality	59 (65.6)	45 (68.2)	14 (58.3)	0.385
Duration of Sx, days	27.1±26.5	29.1±28.8	21.6±18.1	0.235
Time to anti-TB Tx, days	4.3±6.0	5.0±7.0	2.8±2.5	0.048
Extra-pulmonary TB	24 (26.7)	9 (13.6)	15 (62.5)	0.001
Shock not related to sepsis	29 (32.2)	22 (33.3)	7 (29.2)	0.708
Septic shock	32 (35.6)	21 (31.8)	11 (45.8)	0.219
MOF	20 (22.2)	14 (21.2)	6 (25.0)	0.702
ARDS	60 (66.7)	40 (60.6)	20 (83.3)	0.043
DIC	26 (28.9)	13 (19.7)	13 (54.2)	0.001

p-value for comparison between groups.

Data are presented as means ± SDs or n (%).

M: male; F: female; BMI: body mass index; Hx: history; TB: tuberculosis; MV: mechanical ventilation; Sx: symptom; Tx: treatment for tuberculosis; MOF: multiple organ failure; ARDS: acute respiratory distress syndrome; DIC: disseminated intravascular coagulation.

*Diabetes mellitus (n = 11), malignancy (n = 2), gastrectomy (n = 3), immunosuppression (n = 1), chronic lung disease (n = 4), chronic renal failure (n = 2), chronic liver disease (n = 1), pregnancy (n = 1).

#Diabetes mellitus (n = 3); malignancy (n = 1), gastrectomy (n = 1), immunosuppression (n = 3), chronic lung disease (n = 1), chronic liver disease (n = 1).

Table 2. Comparisons between the survivor and non-survivor groups.

	TBp			TBm		
	Decedents (%)	Survivors (%)	P value	Decedents (%)	Survivors (%)	P value

No.	45	21		14	10	
Median age, years	68.0	60.0	0.046	56.5	45.0	0.093
BMI (kg/m^2)	18.9±3.6	19.5±3.1	0.597	20.7±4.4	18.4±1.8	0.316
Albumin, g/dL	2.33±0.6	2.35±0.5	0.701	2.31±0.6	2.51±0.5	0.403
APACHE III score	77.8±24.4	73.2±21.9	0.468	73.8±27.7	67.2±21.6	0.538
PaO_2/FiO_2 ratio	129.0±50.3	124.0±24.3	0.673	139.6±36.3	134.9±30.7	0.757
Previous Hx of TB	10 (22.2)	6 (28.6)	0.575	1 (7.1)	3 (30.0)	0.272
Risk factors for TB	16 (36.0)	9 (43.0)	0.421	7 (50.0)	3 (30.0)	0.263
Duration of Sx, days	33.0±31.0	20.7±21.6	0.043	17.9±12.0	26.7±24.1	0.309
Time to anti-TB Tx, days	5.8±7.6	4.6±6.7	0.566	2.9±2.6	2.7±2.6	0.208
MOF	10 (22.2)	4 (19.0)	0.769	4 (28.6)	2 (20.0)	0.633
Shock not related to sepsis	19 (42.2)	3 (14.3)	0.033	5 (35.7)	2 (20.0)	0.404
Septic shock	16 (35.6)	5 (23.8)	0.128	8 (57.2)	3 (30.0)	0.188
ARDS	27 (60.0)	13 (61.9)	0.791	11 (78.6)	9 (90.0)	0.459
Corticosteroid use	17 (37.8)	13 (61.9)	0.042	7 (50.0)	7 (70.0)	0.327

Data are presented as means ± SDs or n (%).

TBp: tuberculous pneumonia; TBm: miliary tuberculosis; BMI: body mass index; Hx: history; TB: tuberculosis; Sx: symptom; Tx: treatment for tuberculosis; MOF: multiple organ failure; ARDS: acute respiratory distress syndrome.

Table 3. Multivariate analysis of predictors of mortality in the tuberculous pneumonia (TBp) group.

	P value	Odds ratio	95% confidence interval
Old age	0.037	1.052	1.010-1.095
Duration of symptoms	0.079	1.031	0.996-1.067
Shock not related to sepsis	0.014	3.446	1.286-15.102
Use of corticosteroids	0.011	0.544	0.417-0.671

Table 4. Comparisons between the steroid-use and non-use groups.

	TBp			TBm		
	User (%)	Non-user (%)	P value	User (%)	Non-user (%)	P value
No.	30	36		14	10	
Median age, years	65.0	69.0	0.387	52.5	54.5	0.690
BMI (kg/m^2)	19.3±3.2	18.8±3.2	0.113	19.8±3.8	19.4±3.5	0.854
Albumin, g/dL	2.4±0.4	2.3±0.6	0.479	2.3±0.7	2.6±0.4	0.198
APACHE III score	82.4±26.7	71.2±19.5	0.063	75.1±27.7	65.3±20.9	0.332
PaO_2/FiO_2 ratio	128.6±48.9	126.4±39.4	0.843	131.5±35.4	146.8±28.2	0.287
Previous Hx of TB	4 (13.3)	12 (33.3)	0.059	2 (14.3)	2 (20.0)	0.711
Risk factors for TB	14 (47.0)	11 (31.0)	0.316	5 (36.0)	5 (50.0)	0.578
Duration of Sx, days	34.5±34.1	24.6±23.2	0.184	24.6±20.1	17.4±13.5	0.317
Time to anti-TB Tx, days	5.3±7.2	4.7±6.9	0.794	2.7±2.7	2.9±2.4	0.873
MOF	7 (23.3)	7 (19.4)	0.322	4 (28.6)	2 (20.0)	0.633
Shock not related to sepsis	10 (33.3)	12 (33.3)	1.000	4 (28.6)	3 (30.0)	0.939
Septic shock	9 (30.0)	12 (33,3)	0.772	6 (42.9)	5 (50.0)	0.729
Duration of MV, days	18.0±32.2	21.7±25.3	0.603	8.9±7.3	13.6±8.2	0.161
Extra-pulmonary TB	6 (20.0)	3 (8.3)	0.280	8 (57.1)	7 (70.0)	0.521
ARDS	24 (80.0)	16 (44.4)	0.003	12 (85.7)	8 (80.0)	0.711
Mortality	17 (56.7)	28 (77.8)	0.046	7 (50)	7 (70)	0.421

Data are presented as means ± SDs or n (%).

TBp: tuberculous pneumonia; TBm: miliary tuberculosis; BMI: body mass index; Hx: history; TB: tuberculosis; Sx: symptom; Tx: treatment for tuberculosis; MOF: multiple organ failure; MV: mechanical ventilation; ARDS: acute respiratory distress syndrome.

References

1 Rosen MJ, Clayton K, Schneider RF, *et al.* Intensive care of patients with HIV infection: utilization, critical illnesses, and outcomes. Pulmonary complications of HIV Infection Study Group. *Am J Respir Crit Care Med* 1997; 155: 67-71.

2 Pablos-Mendez A, Raviglione MC, Laszlo A, *et al.* Global surveillance for antituberculosis-drug resistance, 1994-1997. *N Engl J Med* 1998; 338: 1641-1649.

3 Keim LW, Schuldt S, Bedell GN. Tuberculosis in the intensive care unit. *Heart Lung* 1977; 6: 624-634.

4 Frame RN, Johnson MC, Eichenhorn MS, *et al.* Active tuberculosis in the medical intensive care unit: a 15-year retrospective analysis. *Crit Care Med* 1987; 15: 1012-1014.

5 Penner C, Roberts D, Kunimoto D, *et al.* Tuberculosis as a primary cause of respiratory failure requiring mechanical ventilation. *Am J Respir Crit Care Med* 1995; 151: 867-872.

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

7 Keh D, Boehnke T, Weber-Cartens S, *et al.* Immunologic and hemodynamic effects of low-dose hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003; 167: 512-520.

8 Annane D, Sebille V, Bellissant E. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med* 2006; 34: 22-30.

9 Moton C, Ewig S, Torres A, *et al.* Role of glucocorticoids on inflammatory response in nonimmunosuppresed patients with pneumonia: a pilot study. *Eur Respir J* 1999; 14: 218-220.

10 Confalonieri M, Urbino R, Potena A, *et al.* Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171: 242-248.

11 Bernard GR, Luce JM, Sprung CL, *et al.* High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J Med* 1987; 317: 1565-1570.

12 Meduri GU, Golden E, Freire AX, *et al.* Methylprednisolone infusion in early severe ARDS: result of a randomized controlled trial. *Chest* 2007; 131: 954-963.
13 Meduri GU, Headley A, Golden E, *et al.* Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled tiral. *JAMA* 1998; 280: 159-165.
14 Steinbreg KP, Hudson LD, Goodman RB, *et al*. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354: 1671-1684.
15 Thwaites GE, Bang ND, Dung NH, *et al.* Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004; 351: 1741-1751.
16 Strang JIG, Gibson DG, Nunn AJ, *et al.* Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *The Lancet* 1987; 330: 1418-1422.
17 Bilaceroglu S, Perim J, Buyuksirin M*, et al.* Prednisolone: a beneficial and safe adjunt to anti-tuberculous treatment: A randomized controlled trial. *Int J Tuberc Lung Dis* 1999; 3: 47-54.
18 Smego RA, Ahmed N. A systematic review of the adjunctive use of systemic corticosteroids for pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2003; 7: 208-213.
19 Septimus EJ, Awe RJ, Greenberg SD, Raleigh JW. Acute tuberculous pneumonia. *Chest* 1977; 71: 774-775.
20 Bernard GR, Artigas A, Brigham KL, *et al.* The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149: 818-824.
21 Levy MM, Fink MP, Marshall JC, *et al.* 2001 SCCM/ESICM/ACCP/ATS/SIS International sepsis definition conference. *Crit Care Med* 2003; 31: 1250-1256.
22 Knaus WA, Draper EA, Wagner DP, *et al.* Prognosis in acute organ-system failure. Ann Surg 1985; 202: 685-696.
23 Korea Center for Disease Control and Prevention, Korean Institute of Tuberculosis. Annual report on the notified tuberculosis patients in Korea, 2005
24 Korea Center for Disease Control and Prevention. The prevalence of human immunodeficiency virus (HIV) infection in Korea, 2004.

25 Heffner JE, Strange C, Sahn SA. The impact of respiratory failure on the diagnosis of tuberculosis. *Arch Intern Med* 1988; 148: 1103-1108.
26 Homan W, Harman E, Braun NM, *et al.* Miliary tuberculosis presenting as acute respiratory failure: treatment by membrane oxygenator and ventricle pump. *Chest* 1975; 67: 366-369.
27 Dyer RA, Chappell WA, Potgieter PD. Adult respiratory distress syndrome associated with miliary tuberculosis. *Crit Care Med* 1985; 13: 12-15.
28 Lintin SN, Isaac PA. Miliary tuberculosis presenting as adult respiratory distress syndrome. *Intensive Care Med* 1988; 14: 672-674.
29 Levy H, Kallenbach JM, Feldman C, et al. Acute respiratory failure in active tuberculosis. *Crit Care Med* 1987; 15: 221-225.
30 Erbes R, Oettel K, Raffenberg M, *et al.* Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. *Eur Respir J* 2006; 27: 1223-1228.
31 Zahar JR, Azoulay E, Klement E, *et al.* Delayed treatment contribute to mortality in ICU patients with severe active pulmonary tuberculosis and acute respiratory failure. *Intensive Care Med* 2001; 27: 513-520.
32 Wallis RS. Reconsidering adjuvant immunotherapy for tuberculosis. *Clin Infect Dis* 2005; 41: 201-208.
33 Muthuswamy P, Hu TC, Carasso B, *et al.* Prednisone as adjunctive therapy in the management of pulmonary tuberculosis. Report of 12 cases and review of the literature. *Chest* 1995; 107: 1621-1630.
34 Sun TN, Yang JY, Zheng LY, *et al.* Chemotherapy and its combination with corticosteroids in acute miliary tuberculosis in adolescents and adults: analysis of 55 cases. *Chin Med J* 1981; 94: 309–314.
35 Massaro D, Katz S, Sachs M, Choroidal tubercles. A clue to hematogenous tuberculosis, *Ann Intern Med* 1964; 60: 231–241.