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Prognostic factors in patients with miliary tuberculosis

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ABSTRACT

Background and purpose: Acute respiratory distress syndrome (ARDS) complication has long been considered a factor associated with poor prognosis in patients with miliary tuberculosis. However, few reports exist on the prognostic factors of miliary tuberculosis including those complicating ARDS.

Subjects and methods: We retrospectively examined prognoses and other clinical information obtained from medical records of a total of 68 patients diagnosed with miliary tuberculosis. Clinical findings were compared between patients who died within three months (non-survivor group) and those who survived beyond three months (survivor group), and risk factors for death within three months of diagnosis were examined using logistic regression analysis.

Results: Fifteen of 68 patients diagnosed with miliary tuberculosis died within three months. Most patients were aged 60 years or older (63 patients; 91.2%), with a peak in the 80 s (32 patients; 47.1%). Of the 68 patients with miliary tuberculosis, 13 (19%) had ARDS. The risk of death within three months increased with increasing age and ARDS onset during the disease course. The results of multivariate analysis revealed that, in addition to age (odd ratio (OR): 15.5) and the presence/absence of ARDS (OR: 12.0), consciousness disturbance (OR: 81.53) and high BUN levels (OR: 5.71) were independent factors for death within three months.

Conclusion: In patients with miliary tuberculosis, old age, ARDS, consciousness disturbance, and high BUN levels were factors associated with poor prognosis.

1. Background

Miliary tuberculosis is a fatal disease caused by hematogenous dissemination of *Mycobacterium tuberculosis* infection. It is also a rare cause of acute respiratory distress syndrome (ARDS). In many cases, the prognosis of miliary tuberculosis can be improved by introducing effective anti-tuberculosis agents; however, elderly patients and patients with ARDS are likely to suffer a poor prognosis. Only a few reports have described ARDS associated with miliary tuberculosis, with mortality reported to be 33–100% [1–9]. Moreover, due to poor prognoses, few cases have been reported in which treatment was found to be effective in improving serious conditions [2–6, 10, 11]. Furthermore, in elderly patients with tuberculosis, older age is considered a risk of mortality, as it relates to decreased function of pulmonary epithelial cells, increased comorbidities, delay in diagnosis due to decreased cognitive ability of patients themselves as well as increased atypical symptoms, and progression of disease state [12]. Many reported studies to date are from high-prevalence countries, targeting relatively young subjects, and few studies have been conducted in elderly patients with tuberculosis. In recent years, a considerably high proportion of patients with tuberculosis in Japan have characteristically been older patients. In this study, we examined prognostic factors in a population of miliary tuberculosis patients including those with ARDS, which predominantly comprised elderly patients.

2. Methods

2.1. Patients

Over a period of 22 years (January 1, 1994–October 1, 2016), 2293 patients were hospitalized at the National Hospital Organization Omuta Hospital with the diagnosis of tuberculosis. Of these, 70 patients were

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diagnosed with miliary tuberculosis. Two patients who did not undergo chest CT were excluded from analysis. All patients who died due to tuberculosis did not survive beyond three months. Therefore, the remaining 68 patients were divided into those who survived longer than three months (survivor group: $n = 53$) and those who died within three months of diagnosis (non-survivor group: $n = 15$).

The following clinical information at hospitalization was collected from medical charts: age, sex, history of smoking, alcohol intake, underlying diseases, symptoms, performance status (PS), microbiological data (including the drug sensitivity pattern of *M. tuberculosis* isolates), PaO2/FiO2 ratio, laboratory findings, time from onset to admission, time from admission to anti-tuberculosis therapy, time from onset to anti-tuberculosis therapy, length of hospital stay, presence or absence of ARDS, and mechanical ventilation. Consciousness disturbance was defined as that with the Glasgow Coma Scale (GCS) of 12 or less.

2.2. Diagnosis of miliary tuberculosis

Miliary tuberculosis was diagnosed by one radiologist and two respiratory physicians, based on the observation of randomly distributed, uniformly sized diffuse bilateral nodules on chest CT. A definitive diagnosis of tuberculosis was made when at least one of the following three criteria was met: (1) positive acid-fast bacilli (AFB) smear and/or culture for *M. tuberculosis* from clinical specimens such as sputum, bronchial lavage fluid, pleural fluid, urine, and bone marrow aspirate; (2) histopathological identification of a tuberculosis granuloma in biopsied tissues of lung, pleura and/or bone marrow; or (3) clinical and radiological improvement after anti-tuberculosis treatment.

2.3. Diagnosis of ARDS

ARDS was diagnosed according to the Berlin definition of ARDS, based on chest x-ray and chest CT findings and the PaO2/FiO2 ratio after having excluded all differential diagnoses, such as heart failure, pneumonia, pulmonary haemorrhage, acute interstitial lung disease, and drug reactions [13].

2.4. Statistical analysis

Age, PS, platelets, CRP, ALP, total bilirubin, and number of days from hospitalization to the initiation of anti-tuberculosis treatment were comparatively examined between the case group (i.e., patients who died within three months of diagnosis) and the control group (i.e., survivors). Statistical tests were performed using the Wilcoxon rank sum (Mann–Whitney) test. With respect to white blood cell count, neutrophils, AST, ALT, LDH, BUN, creatinine, number of days from onset to hospitalization, and number of days from onset to the initiation of anti-tuberculosis treatment, geometric mean values were comparatively examined between the two groups. In the case of 0 days, logarithmic conversion was performed as 0.1 days.

Next, using the case-control study method, risk factors for death within three months of diagnosis were examined. Based on results from previous studies, old age and ARDS onset were suspected to be strongly associated with the risk of death within three months. Since the present study also yielded similar results (described in the following section), analyses of other associated factors were constantly adjusted for age and presence/absence of ARDS, and odds ratios for each factor were obtained using logistic regression analysis.

Furthermore, in order to assess which of the examined factors were strongly associated, clinically relevant factors with a p value < 0.1 in the analysis adjusted for presence/absence of ARDS were incorporated as the first explanatory variables, and thereafter, variables were selected using the stepwise method.

3. Results

3.1. Demographic data and clinical characteristics (Table 1)

The median age of the 68 patients with miliary tuberculosis (18 men and 50 women) was 83.0 years (range, 27–93 years). Most patients were aged 60 years or older (63/68; 91.2%), with a peak in the 80 s (32/68; 47.1%). Ten patients (15%) had a history of smoking, and 8 patients (12%) consumed alcohol. There were 102 underlying diseases in 57 patients: dementia (16), liver disease (8), diabetes (18), connective tissue disease with steroid treatment (9), renal disease (7), heart disease (15), cerebrovascular disease (12), aortic aneurysm (3), neuromuscular disease (3), and malignancy (11). Eight patients (11.8%) had a history of tuberculosis. Symptoms were fever (51/68, 75%), dyspnea (20/68, 29%), cough (19/68, 28%), sputum (14/68, 21%), loss of appetite (44/68, 65%), general malaise (45/68, 66%), consciousness disturbance (8/68, 12%) and lumbar pain (7/68, 10%). The median (range) PS was 3 (1–4). Of the 68 patients with miliary tuberculosis, 13 patients (19%) had ARDS; 11 patients had already developed ARDS at the time of first visit, and the other two developed ARDS during hospitalization.

3.2. Diagnostic findings

Among 26 patients showing only bilateral diffuse nodules on chest CT, 8 had pleural effusion (Fig. 1A). Among 29 patients showing partially fused nodules as well as infiltrations, in addition to bilateral diffuse nodules, 11 had pleural effusion (Fig. 1B). Among 13 patients who fell under the criteria for ARDS imaging diagnosis and showed ground-glass opacities / infiltrations in the entire lungs in addition to bilateral diffuse nodules, 3 had pleural effusion (Fig. 1C).

A definitive diagnosis of tuberculosis was made according to the above-mentioned criteria; 63 patients (93%) were ultimately verified to have *M. tuberculosis*. Of these, 49 had AFB smear-positive clinical specimens during hospitalization, 2 had positive sputum samples by PCR only, and 1 had PCR-positive sputum and bone marrow biopsy tissue showing epithelioid granulomas. Of the AFB smear positive patients, 42 had a positive–PCR for *M. tuberculosis* (MTb) initially. Another 7 patients had a negative–PCR for MTb in the initial investigation, but culture was subsequently positive. The remaining 11 patients had positive cultures during follow-up. In all cases, the presence of *M. tuberculosis* was verified using specimens form the respiratory system or respiratory samples (sputum, fluid from endotracheal tube suction, and bronchial lavage fluid). Moreover, 24 patients also had *M. tuberculosis* culture-positive extrapulmonary specimens (urine, 8; pleural effusion, 6; gastric effusion, 5; blood, 2; and scrotal pus, 12). Subsequently, three patients were confirmed to have tuberculosis by histopathological examination of biopsy tissue (transbronchial biopsy, 1; bone marrow biopsy, 2). As for the remaining two patients, clinical diagnosis was ultimately obtained; these patients had a fever of $\geq 38\,^{\circ}C$, and as antibiotics administered for ≥ 1 week were ineffective, they were referred to our hospital. At the initial visit, one showed only nodules on chest CT, and another showed infiltrations in addition to nodules. Both patients showed improvements in clinical course and imaging findings after treatment with anti-tuberculosis agents was initiated. Based on these courses, the two patients were diagnosed with miliary tuberculosis.

The drug susceptibility test was performed with 57 isolates of *M. tuberculosis*. Of these, 49 isolates (86%) were found to be susceptible to all anti-tuberculosis agents (isoniazid [H], rifampicin [R], ethambutol [E], pyrazinamide [Z], cycloserine, para-aminosalicylic acid [PAS], ethionamide, ofloxacin, streptomycin [S], kanamycin, and enviomycin). On the other hand, the remaining 8 strains (14%) were resistant to at least one agent (3 to H, 1 to S, 3 to E, and 1 to H and S).

The numbers of days from onset to hospitalization, from hospitalization to treatment, and from onset to treatment were 37 days (range,

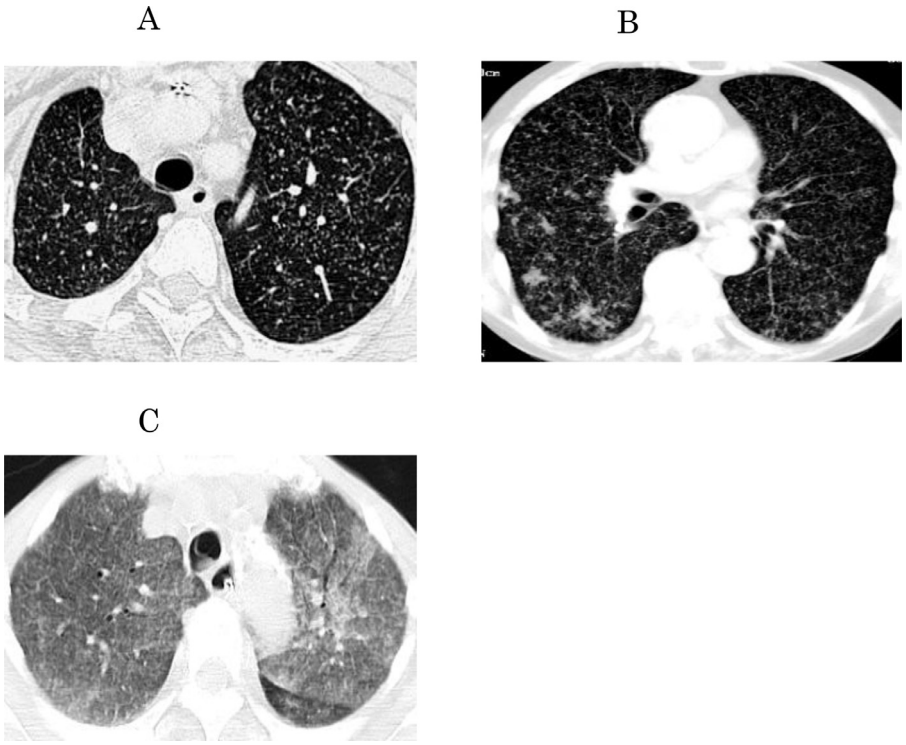

Fig. 1. Chest computed tomographic scans showed three patterns: only diffuse nodules exhibiting a random distribution (A); diffuse nodules exhibiting a random distribution with infiltrations (B); and diffuse nodules exhibiting a random distribution with ground glass opacities (C).

3–361 days), 2 days (range, 0–9 days), and 41 days (range, 3–364 days), respectively.

3.3. Hospital course and prognostic factors

Anti-tuberculosis agents were administered to 67 of 68 patients. One patient died on the second day of hospitalization due to ill condition; therefore, no agent was administered. Sixteen patients received additional treatment with HRZE, 6 with HRZS, 7 with HRS, 33 with HRE, 1 with HRZE and LVFX, 1 with HRE and LVFX, one with HRES, one with HR, and one with H and CFLX (She was treated with injections because of poor general condition. CFLX was used instead of LVFX which had not been released as injection preparation in Japan at that time.). INH resistance was detected in 4 cases and treatment was changed to LVFX in 3 cases and TH in 1 case.

The median time lag from hospitalization to anti-tuberculosis agent administration was 2 days (range, 0–9 days), with no difference between survivors and non-survivors.

Fifteen of 68 patients died due to tuberculosis, with a mortality rate of 22.1%. Of the 15 patients, 6 had ARDS. Compared to the mortality rate of 16% among patients without ARDS, the mortality rate was 46.2% among patients who developed ARDS. With regard to patient characteristics, the risk of death within three months increased with increasing age; however, no steady relationship was observed between the risk of death within three months and sex, smoking history, or alcohol intake. The risk of death within three months also increased with worsening PS. Moreover, ARDS, liver dysfunction, and consciousness disturbance were also associated with an increase in the risk of death within three months. Laboratory findings revealed that an increase in BUN levels was associated with an increase in the risk of death within three months (Table 2). Furthermore, in order to assess which factors were strongly associated, factors with a p value <0.1 (age, PS, ARDS onset, liver dysfunction, consciousness disturbance, and BUN) were incorporated as the initial explanatory variables. In the subsequent examination by the stepwise method, age, ARDS onset, consciousness disturbance, and BUN were four factors that remained significant (Table 3).

4. Discussion

Traditionally, miliary tuberculosis has been commonly observed as a type of primary tuberculosis. Previous reports on the prognosis of patients with miliary tuberculosis, including, especially, those with ARDS, have noted a high prevalence in young people in their 20 s, with many reporting the mean age ranging from 40 to 60 years [1–6, 8–12, 14–23]. In Japan, a publication from more than 20 years ago reported a mean (± SD) age of 45.3 (± 19.3) years [7]. However, in recent years, a remarkably high proportion of the population of patients with tuberculosis in Japan is characteristically elderly, while having a lower proportion of HIV co-infection and multidrug-resistant tuberculosis; a similar trend is starting to appear in the age distribution of extrapulmonary tuberculosis patients [24]. The results of the present study reflected this trend, as those aged 80 years or higher were highest in number (41/68 patients; 60%). In this regard, this study reports valuable findings that shed light on the current status of miliary tuberculosis in Japan.

According to previous studies, ARDS develops in association with miliary tuberculosis at a rate of 16–24% [2, 3, 6]. In the present study as well, ARDS was observed at a similar rate of 19% in patients with miliary tuberculosis.

The rate of disease-specific deaths in patients with miliary tuberculosis with ARDS is reportedly high, at 30–90% [1–11]. In the present study, disease-specific mortality in patients with ARDS was 46.2%, which was significantly higher compared to 16% in patients who did not develop ARDS. These findings suggest the need for a comprehensive study, when considering the prognosis of miliary tuberculosis, that includes patients with ARDS.

Reports on the prognosis of miliary tuberculosis consistently suggest ARDS to be associated with poor prognosis [1–11]. Other reported prognostic factors include old age [16], immunodeficiency [16, 19],

Table 1
Baseline characteristics of patients with miliary tuberculosis ($n = 68$).

Parameters	Results	Parameters	Results
Number of patients	68	AFB-positive sputum: positive/total (%)	
Age, years (range)	83 (27–93)	Smear	49/68 (71%)
Sex: male/female	18/50	PCR	50/66 (76%)
Smoking history: current/former/never	0/10/56	MGIT	47/55 (85%)
Alcohol intake: presence/absence	8/59	Culture	57/68 (84%)
Underlying disease		Culture of AFB in specimens: positive/total (%)	
Heart disease	15 (22%)	Urine	8/31 (26%)
Diabetes	18 (27%)	Gastric effusion	5/9 (56%)
Dementia	16 (24%)	Scrotal pus	12/37 (32%)
Malignancy	11 (16%)	Blood	2/20 (10%)
Cerebrovascular disease	12 (18%)	Cerebrospinal fluid	0/8 (0%)
Renal disease	7 (10%)	Bronchial lavage fluid	4/8 (50%)
Liver disease	7 (10%)	Pleural effusion	6/12 (50%)
Connective tissue disease with steroid treatment	9 (13%)	Ascites fluid	0/0 (0%)
Aneurysm	3 (4%)	Histopathological examination positive/total (%)	
Neuromuscular disease	3 (4%)	Transbronchial biopsy	6/8 (75%)
None	11 (16%)	Bone marrow biopsy	9/14 (64%)
ARDS onset	13 (19%)	Body mass index (kg/m^2)	18.8 (12.6–26.5%)
Symptoms		The period from onset to hospitalization, days (range)	37 (3–361)
Fever (≥38 °C)	51 (75%)		
Cough	19 (28%)	The period from hospitalization to anti-tuberculosis treatment, days (range)	2 (0–9)
Sputum	14 (21%)		
Dyspnea	20 (29%)	The period from onset to anti-tuberculosis treatment, days (range)	41 (3–364)
Loss of appetite	44 (65%)		
General malaise	45 (66%)	Length of hospital stay, days (range)	102 (2–547)
Consciousness disturbance	8 (12%)		
Lumbar pain	7 (10%)		
PS (median)	3 (1–4%)		

Data are presented as median (range) or number (%).
ARDS: acute respiratory distress syndrome; PS:performance status; AFB: acid-fast bacteria; BMI: body mass index.

diabetes [22], delayed discovery [15, 17], psychiatric disorders [8, 20], elevated liver enzymes [15], renal dysfunction [15, 19], malnutrition [15, 21], thrombocytopenia [20, 22], and greater extent of ground glass opacity [23], although no consistent outcomes have been obtained with regard to this aspect. Many previous reports are from high-prevalence countries, with high proportions of subjects being relatively young patients; few reports mention old age as a prognostic predictor [16]. Meanwhile, one of the characteristics of the tuberculosis population in Japan is that the number of elderly patients is remarkably high, and many reports suggest old age as a prognostic predictor [25–27]. In our patients, in addition to the presence/absence of ARDS, age was considered to be strongly associated with the risk of death within three months. Therefore, we conducted analyses by constantly adjusting for age and presence/absence of ARDS to obtain odds ratios for each factor. As a result, ARDS onset, old age, PS, liver dysfunction, consciousness disturbance, and high BUN levels were identified as risk factors for death within three months. We further examined these factors using the stepwise method to assess those showing strong associations, and found ARDS onset, old age, consciousness disturbance, and high BUN levels to be significant factors. With regard to the causes and extent of consciousness disturbance, many aspects remain unclear, as the present study was retrospective in nature. While our subjects likely included those with meningitis and brain tuberculosis, head CT or MRI examinations were not performed, as the condition of patients presenting with consciousness disturbance was poor, with the GCS of 12 or less.

As for high BUN levels, given that no steady relationships were observed between the risk of death within three months and presence/absence of renal disease or serum creatinine levels, our observation might have reflected dehydration tendencies or hypercatabolism.

In Japan, nutritional status is often reported as a prognostic factor for tuberculosis. However, the present study did not find nutritional status to be an independent prognostic predictor. This could be explained by the fact that the nutritional condition of patients with miliary tuberculosis had already deteriorated somewhat at the time of hospital admission, and was thus unlikely to serve as a predictor of prognosis.

Prognostic factor might be not specific to miliary TB: old age, ARDS, consciousness disturbance and high BUN levels would be expected to be predictors of mortality in any condition.

There are some limitations to this study. First, this study was conducted at a single center with a small sample size. In particular, the number of patients with ARDS was quite low. Data on co-morbidities from clinical records were incomplete, but there was no reason to assume a systematic bias for missing information, since they were obtained from the records. Moreover, as the present study used a retrospective design, the degree of consciousness disturbance and the extent of dementia were unclear, and the causes of underlying diseases including renal disease and liver disease were unknown.

In summary, the present study examined prognostic factors in patients with miliary tuberculosis including those with ARDS in Japan, and revealed that ARDS onset, old age, presence/absence of consciousness disturbance, and high BUN levels are independent poor prognostic factors.

5. Conclusion

In patients with miliary tuberculosis, the complication of ARDS was observed in 19%. Old age, ARDS, consciousness disturbance, and high BUN levels were factors associated with poor prognosis.

Ethical considerations

The present study was approved by the Ethics Committee of the National Hospital Organization at Omuta Hospital. The IRB approval number was 29-43.

Availability of data

There are no data other than those included in this article.

Competing interests

The authors declare that they have no competing interests.

Funding

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Author contributions

KW conceived the idea and designed the tool together with NN and HK. SH, MH, AN, NN, KO, KK, MO, EY, TA, SM, SI, MI and MK were involved in the implementation. All authors reviewed and approved the final version of the manuscript.

Table 2
Comparisons of demographic, clinical, and laboratory characteristics between patients with miliary tuberculosis who died within three months (non-survivors) and who survived longer than three months (survivors).

Parameters		Survivors (n = 53)	Non-survivors (n = 15)	Crude odds ratio	95%CI Lower limit	Upper limit	p-value	Adjusted* odds ratio	95%CI Lower limit	Upper limit	p-value
Age (years)	≤72	13	0	3.88†	1.58	9.55	p for trend = 0.003	8.14†	1.98	33.48	p for trend = 0.004
	73–78	11	0								
	79–85	15	6								
	≥86	14	9								
Sex	Female	37	13	1.00	Reference			1.00	Reference		
	Male	16	2	0.36	0.07	1.76	0.206	0.43	0.07	2.60	0.357
Smoking history	Absence	45	11	1.00	Reference		0.465	1.00	Reference		0.287
	Presence	7	3	1.75	0.39	7.89		2.75	0.43	17.72	
	Unknown	1	1	–	–	–	–	–	–	–	–
Alcohol intake	Absence	46	12	1.00	Reference			1.00	Reference		
	Presence	6	2	1.28	0.23	7.15	0.780	1.13	0.15	8.52	0.904
	Unknown	1	1	–	–	–	–	–	–	–	–
PS	1	8	0	1.00	Reference			1.00	Reference		
	2	10	1								
	3	15	3	3.60	0.34	38.30	0.288	3.75	0.29	49.03	0.313
	4	20	11	9.90	1.16	84.47	0.036	7.64	0.71	82.15	0.093
							p for trend = 0.017				p for trend = 0.076
Smear	Negative	17	2	1.00	Reference			1.00	Reference		
	Positive	36	13	3.07	0.62	15.15	0.169	1.81	0.30	10.99	0.518
Drug sensitivity pattern	0**	37	12	–	–	–	0.468 (Fisher's exact test)	–	–	–	–
	1***	7	0	–	–	–		–	–	–	
	2****	1	0	–	–	–		–	–	–	
	N/A	8	3	–	–	–	–	–	–	–	–
PaO2/FiO2ratio	52.9 -	13	7	1.00	Reference			1.00	Reference		
	309 -	26	5	0.36	0.09	1.35	0.128	0.85	0.06	11.15	0.900
	357 -	2	0	0.40	0.08	1.87	0.244	1.61	0.10	25.16	0.736
	378 -	12	3								
							p for trend = 0.191				p for trend = 0.610
PCR	Negative	14	2	1.00	Reference			1.00	Reference		
	Positive	39	11	1.97	0.39	10.03	0.412	0.97	0.14	6.69	0.979
	N/A	0	2	–	–	–	–	–	–	–	–
MGIT	Negative	8	0	–	–	–	0.188 (Fisher's exact test)	–	–	–	–
	Positive	36	11	–	–	–		–	–	–	
	N/A	9	4	–	–	–	–	–	–	–	–
Culture	Negative	10	1	1.00	Reference			1.00	Reference		
	Positive	43	14	3.26	0.38	27.74	0.280	1.56	0.14	17.71	0.719
ARDS onset	Absence	46	9	1.00	Reference			1.00	Reference		
	Presence	7	6	4.38	1.19	16.13	0.026	15.34	2.13	110.25	0.007
Underlying disease	Absence	11	0	–	–	–	0.105 (Fisher's exact test)	–	–	–	–
	Presence	42	15	–	–	–		–	–	–	
Heart disease	Absence	44	9	1.00	Reference			1.00	Reference		
	Presence	9	6	3.26	0.93	11.46	0.066	2.64	0.61	11.48	0.195
Diabetes	Absence	39	11	1.00	Reference			1.00	Reference		
	Presence	14	4	1.01	0.28	3.71	0.984	1.83	0.36	9.26	0.464
Dementia	Absence	41	11	1.00	Reference			1.00	Reference		
	Presence	12	4	1.24	0.33	4.62	0.746	0.30	0.05	1.78	0.187
Malignancy	Absence	44	13	1.00	Reference			1.00	Reference		
	Presence	9	2	0.75	0.14	3.93	0.735	8.09	0.47	139.67	0.150
Cerebrovascular disease	Absence	42	14	1.00	Reference			1.00	Reference		
	Presence	11	1	0.27	0.03	2.31	0.233	0.20	0.02	1.98	0.171
Renal disease	Absence	50	11	1.00	Reference			1.00	Reference		
	Presence	3	4	6.06	1.18	31.03	0.031	4.93	0.62	39.43	0.132
Liver disease	Absence	49	12	1.00	Reference			1.00	Reference		
	Presence	4	3	3.06	0.60	15.55	0.177	12.61	1.03	154.21	0.047
Connective tissue disease with steroid treatment	Absence	45	14	1.00	Reference			1.00	Reference		
	Presence	8	1	0.40	0.05	3.50	0.409	0.58	0.05	6.25	0.657
Aneurysm	Absence	50	15	–	–	–	1.000 (Fisher's exact test)	–	–	–	–
	Presence	3	0	–	–	–		–	–	–	
Neuromuscular disease	Absence	50	15	–	–	–	1.000 (Fisher's exact test)	–	–	–	–
	Presence	3	0	–	–	–		–	–	–	
Symptoms											
Fever (≥38 °C)	Absence	13	4	1.00	Reference			1.00	Reference		
	Presence	40	11	0.89	0.24	3.29	0.866	1.25	0.25	6.23	0.785
Cough	Absence	36	13	1.00	Reference			1.00	Reference		

(*continued on next page*)

Table 2 (*continued*)

Parameters		Survivors (n = 53)	Non-survivors (n = 15)	Crude odds ratio	95%CI Lower limit	Upper limit	p-value	Adjusted* odds ratio	95%CI Lower limit	Upper limit	p-value
	Presence	17	2	0.33	0.07	1.61	0.169	0.58	0.09	3.66	0.562
Sputum	Absence	41	13	1.00	Reference			1.00	Reference		
	Presence	12	2	0.53	0.10	2.66	0.437	0.88	0.13	6.05	0.895
Dyspnea	Absence	40	8	1.00	Reference			1.00	Reference		
	Presence	13	7	2.69	0.82	8.87	0.103	1.47	0.29	7.35	0.637
Loss of appetite	Absence	22	2	1.00	Reference			1.00	Reference		
	Presence	31	13	4.61	0.94	22.53	0.059	4.19	0.70	24.96	0.116
General malaise	Absence	20	3	1.00	Reference			1.00	Reference		
	Presence	33	12	2.42	0.61	9.65	0.209	2.07	0.42	10.05	0.369
Consciousness disturbance	Absence	48	12	1.00	Reference			1.00	Reference		
	Presence	5	3	2.40	0.50	11.48	0.273	9.25	0.82	104.24	0.072
Lumbar pain	Absence	47	14	1.00	Reference			1.00	Reference		
	Presence	6	1	0.56	0.06	5.05	0.605	2.32	0.15	35.66	0.545
Lymphocyte count	2.2-	13	9	1.00	Reference			1.00	Reference		
	416-	13	2	0.22	0.04	1.23	0.085	0.03	1.90	1.23	0.170
	634.5-	13	3	0.33	0.07	1.52	0.156	0.12	4.25	1.52	0.702
	915.2-	14	1	0.10	0.01	0.93	0.043	0.02	2.49	0.93	0.220
							p for trend = 0.024				p for trend = 0.220
Platelet count	2.9-	13	8	1.00	Reference			1.00	Reference		
	15.3-	14	4	0.46	0.11	1.92	0.289	0.40	0.07	2.25	0.300
	23.3-	13	3	0.19	0.04	0.83	0.027	0.39	0.07	2.16	0.027
	32.1-	13	0								
							p for trend = 0.025				p for trend = 0.262
CRP	0.21-	14	3	1.00	Reference			1.00	Reference		
	2.58-	12	1	0.39	0.04	4.25	0.439	0.73	0.05	10.59	0.820
	5.23-	13	3	1.08	0.18	6.32	0.935	1.81	0.23	14.38	0.575
	8.97-	14	8	2.67	0.58	12.19	0.206	3.18	0.49	20.81	0.227
							p for trend = 0.112				p for trend = 0.183
Alb	1.5-	17	10	1.00	Reference			1.00	Reference		
	2.55-	17	3	0.30	0.07	1.29	0.105	0.85	0.14	5.31	0.866
	3.05-	17	2	0.20	0.04	1.05	0.057	0.25	0.04	1.58	0.141
	Missing values	2	0	–	–	–	p for trend = 0.035	–	–	–	p for trend = 0.149
BUN	7-	13	0	1.00	Reference			1.00	Reference		
	13-	9	1								
	14-	16	3	4.13	0.39	43.38	0.238	1.49	0.12	18.55	0.758
	21-	15	11	16.13	1.88	138.47	0.011	6.61	0.59	73.41	0.124
							p for trend = 0.004				p for trend = 0.067
Cr	0.25-	13	2	1.00	Reference			1.00	Reference		
	0.54-	14	1	0.46	0.0	5.7	0.550	0.15	0.0	2.8	0.201
	0.63-	10	6	3.90	0.6	23.6	0.138	0.77	0.1	8.1	0.829
	0.87-	16	6	2.44	0.4	14.2	0.321	0.57	0.1	5.2	0.618
							p for trend = 0.128				p for trend = 0.881
GOT	13-	17	2	1.00	Reference			1.00	Reference		
	29-	18	4	1.89	0.31	11.68	0.494	2.08	0.28	15.29	0.474
	41-	18	8	3.78	0.70	20.38	0.122	4.11	0.49	34.33	0.192
	Missing values	0	1	–	–	–	p for trend = 0.102	–	–	–	p for trend = 0.188
GPT	3-	14	3	1.00	Reference			1.00	Reference		
	17-	20	2	0.47	0.07	3.17	0.435	0.23	0.03	1.96	0.180
	30-	19	9	2.21	0.50	9.69	0.293	3.52	0.37	33.68	0.274
	Missing values	0	1	–	–	–	p for trend = 0.173	–	–	–	p for trend = 0.173
LDH	125-	17	4	1.00	Reference			1.00	Reference		
	205-	18	1	0.24	0.02	2.33	0.217	0.11	0.01	1.31	0.081
	261-	18	9	2.13	0.55	8.21	0.274	0.79	0.12	5.11	0.807
	Missing values	0	1	–	–	–	p for trend = 0.188	–	–	–	p for trend = 0.927

*: Adjusted for age and presence/absence of ARDS. Odds ratios for age and presence/absence of ARDS were only adjusted for other factors mutually. †: Odds ratio for each increase in age group was obtained, when patients were divided into three groups by age.
**: Sensitive to all anti-tuberculosis agents.
***: Resistance to at least one anti-tuberculosis agent.
****: Resistance to two anti-tuberculosis agents.
ARDS: acute respiratory distress syndrome, PS: Performance Status, AFB: Acid-fast bacteria, BMI: body mass index, WBC: white blood cell, Alb: Albumin, CRP: C-reactive protein, Cr: creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase.

Table 3
Relationships between clinical factors and the risk of death within three months of miliary tuberculosis diagnosis: multivariate analysis.

Parameters		Survivors (n = 53)	Non-survivors (n = 15)	Adjusted odds ratio†	95% Confidence interval		P = value
					Lower limit	Upper limit	
Age (years)	≤72	13	0	15.5‡	1.79	134.57	p for trend = 0.013
	73–78	11	0				
	79–85	15	6				
	≥86	14	9				
ARDS onset	Absence	46	9	1.00	Reference		
	Presence	7	6	12	1	141	0.050
Consciousness disturbance	Absence	48	12	1.00	Reference		
	Presence	5	3	81.53	1.26	5258.40	0.038
BUN	7-	13	0	5.71‡	1.13	28.77	p for trend = 0.035
	13-	9	1				
	14-	16	3				
	21-	15	11				

†: Four variables in the table were selected with age, presence/absence of ARDS during the disease course, PS, presence/absence of consciousness disturbance, and presence/absence of liver disease as explanatory variables with a removal probability of 0.1 by backward elimination.
‡: For age and BUN levels, odds ratios for each increase in group were obtained. ARDS: acute respiratory distress syndrome.

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