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 \textit{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 Omura Hospital with the diagnosis of tuberculosis. Of these, 70 patients were...
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 = 32) and those who died within three months of diagnosis (non-survivor group: n = 36).

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 80s (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 partial 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 ≥ 38 °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 enniomycin). 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,
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 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 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 20s, 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],

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).
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 con-
sidered 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 con-
sciousness 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 ex-
aminations 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 ex-
plained 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 con-
ducted 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 as-
ssume a systematic bias for missing information, since they were ob-
tained from the records. Moreover, as the present study used a retro-
spective design, the degree of consciousness disturbance and the extent
of dementia were unclear, and the causes of underlying diseases in-
cluding renal disease and liver disease were unknown.
In summary, the present study examined prognostic factors in pa-
ients with miliary tuberculosis including those with ARDS in Japan,
and revealed that ARDS onset, old age, presence/absence of con-
sciousness 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* | Adjusted odds ratio | 95%CI Lower limit | Upper limit | p-value |
|-----------------------------|--------------------|------------------------|------------------|-------------------|-------------|-------------------|---------------------|-------------------|-------------|---------|
| Age (years)                | 13 0 3.88†         | 15 0 1.58 9.55         | 95%CI            | 1.00              | Reference   | 0.003             | 1.00                | Reference         |
| ≥ 86                       | 14 9              |                        |                  |                   |             |                   |                     |                   |             |         |
| Sex                        | Female 37 13 1.00  | Male 16 2 0.36 0.07    | 95%CI            | 1.76              | Reference   | 0.006             | 0.43                | 0.07              | 2.60       | 0.357   |
| Smoking history            | Absence 45 11 1.00 | Presence 7 3 1.75 0.39 | 95%CI            | 7.89              | Reference   | 0.006             | 2.75                | 0.43              | 17.72      | 0.287   |
| PS                         | 1 8 0 1.00         |                        | 95%CI            |                   |             | 0.017             | 1.00                | Reference         |
| Alcohol intake             | Absence 46 12 1.00 | Presence 6 2 1.28 0.23 | 95%CI            | 7.15              | Reference   | 0.006             | 1.13                | 0.15              | 8.52       | 0.904   |
| Drug sensitivity pattern   | 0** 37 12         | 1*** 7 0              | 95%CI            | 0.468 (Fisher’s  | Reference   | 1.00              | 1.00                | Reference         |
| PaO2/FiO2 ratio            | 52.9 - 13          | 389 - 26               | 95%CI            | 0.36              | Reference   | 0.017             | 1.00                | Reference         |
| PCR                        | Negative 17 2 1.00 | Positive 36 13 3.07 0.62 | 95%CI            | 15.15             | Reference   | 0.006             | 1.00                | Reference         |
| ARDS onset                 | Absence 46 9 1.00  | Presence 7 6 4.38 1.19 | 95%CI            | 16.13             | Reference   | 0.006             | 1.00                | Reference         |
| Underlying disease         | Absence 11 0       | Presence 42 15         | 95%CI            |                   |             | 0.191             | 1.00                | Reference         |
| Heart disease              | Absence 44 9 1.00  | Presence 9 6 3.26 0.93 | 95%CI            | 11.46             | Reference   | 0.006             | 2.64                | 0.61              | 11.48      | 0.195   |
| Diabetes                   | Absence 39 11 1.00 | Presence 14 4 1.01 0.28 | 95%CI            | 3.71              | Reference   | 0.006             | 1.83                | 0.36              | 9.26       | 0.464   |
| Malignancy                 | Absence 44 9 1.00  | Presence 12 4 1.24 0.33 | 95%CI            | 4.62              | Reference   | 0.006             | 0.30                | 0.05              | 1.78       | 0.187   |
| Cerebrovascular disease    | Absence 42 14 1.00 | Presence 8 1 0.40 0.05 | 95%CI            | 3.50              | Reference   | 0.006             | 0.58                | 0.05              | 6.25       | 0.657   |

*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**                          | 41                 | 13                     | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **Dyspnea**                         | 12                 | 2                      | 0.53             | 0.10               | 2.66        | 0.437   | 0.88                 | 0.13               | 6.05        | 0.895   |
| **Loss of appetite**                | 40                 | 8                      | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **General malaise**                 | 31                 | 13                     | 4.61             | 0.94               | 22.53       | 0.059   | 4.19                 | 0.70               | 24.96       | 0.116   |
| **Consciousness disturbance**       | 48                 | 12                     | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **Lumbar pain**                     | 5                  | 3                      | 2.40             | 0.50               | 11.48       | 0.273   | 9.25                 | 0.82               | 104.24      | 0.072   |
| **Lymphocyte count**                | 47                 | 14                     | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **CRP**                             | 6                  | 1                      | 0.56             | 0.06               | 5.05        | 0.605   | 2.32                 | 0.15               | 35.66       | 0.545   |
| **Platelet count**                  | 13                 | 8                      | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **Alb**                             | 17                 | 10                     | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **BUN**                             | 13                 | 0                      | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **Cr**                              | 13                 | 2                      | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **LDH**                             | 17                 | 2                      | 1.00 Reference   |                    |             |         |                      |                    |             |         |
| **Non-survivors**                   |                    |                        |                  |                    |             |         |                      |                    |             |         |
| **Crude odds ratio**                |                    |                        |                  |                    |             |         |                      |                    |             |         |
| **95% CI Lower limit**              |                    |                        |                  |                    |             |         |                      |                    |             |         |
| **Upper limit**                     |                    |                        |                  |                    |             |         |                      |                    |             |         |
| **p-value**                         |                    |                        |                  |                    |             |         |                      |                    |             |         |
| **Adjusted* odds ratio**            |                    |                        |                  |                    |             |         |                      |                    |             |         |
| **95% CI Lower limit**              |                    |                        |                  |                    |             |         |                      |                    |             |         |
| **Upper limit**                     |                    |                        |                  |                    |             |         |                      |                    |             |         |
| **p-value**                         |                    |                        |                  |                    |             |         |                      |                    |             |         |

*: 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 |
|-----------------------------------|-------------------|------------------------|----------------------|-------------------------|-----------|
| 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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