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Fibroproliferative Changes on High-Resolution Computed Tomography in the Acute Respiratory Distress Syndrome Predict Mortality and Ventilator Dependency: A Prospective Observational Cohort Study

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Keywords

acute respiratory distress syndrome, high-resolution computed tomography, ventilator-associated lung injury, corticosteroids

1) Article Focus

• Whether the extent of fibroproliferation on high-resolution CT (HRCT) scan at the time diagnosis of ARDS would impact 60-day and 180-day mortality?

• Whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact ventilator dependency and its associated outcomes?

• Whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact multiple-organ failure?

2) Key Messages

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts increased mortality.

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts ventilator dependency and its associated outcomes (barotraumas, ventilator-associated pneumonia).

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS increases susceptibility to multiple organ failure.

3) Strengths and Limitations

• The CT score is based on our previous published studies correlating HRCT findings with pathology and has been evaluated in the other diseases.

• a relatively small number of patients from a single institution

• lack of correlation with either clinical parameters or pathologic findings

Objectives: To examine whether the extent of fibroproliferative changes on high-resolution computed tomography (HRCT) scan influences prognosis, ventilator dependency, and the associated outcomes in patients with early acute respiratory distress syndrome (ARDS).

Design: A prospective observational cohort study

Setting: Intensive care unit in an educational hospital

Participants: Eighty-five patients with ARDS who met American-European Consensus Conference Criteria and eligible criteria.

Interventions: HRCT scans were performed and prospectively evaluated by two independent observers on the day of diagnosis and graded into six findings according to the extent of fibroproliferation. An overall HRCT score was obtained by previously published method.

Primary and secondary outcomes: The primary outcomes were 60-day and 180-day mortality. Secondary outcomes included the number of ventilator-free days, organ failure-free days, the incidence of barotraumas, and the occurrence of ventilator-associated pneumonia.

Results: Higher HRCT scores were associated with significantly decreased number of organ-failure free days as well as with decreased number of ventilator-free days. Multivariate Cox proportional hazards model showed that the HRCT score remained an independent risk factor for mortality (hazard ratio 1.20; 95% confidence interval 1.06,

1.36; p = 0.005). Multivariate analysis also revealed that the CT score had predictive value for ventilator-weaning within 28 days (odds ratio 0.63; 95% CI 0.48, 0.82; p = 0.0006) as well as for an incidence of barotraumas (1.61; 95%CI 1.08, 2.38; p = 0.018) and for an occurrence of ventilator-associated pneumonia (1.46; 95%CI 1.13,1.89; p = 0.004). An HRCT score < 210 enabled prediction of 180 day survival with 71 % sensitivity and 76 % specificity and of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 % specificity.

Conclusions: Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts increased mortality with an increased susceptibility to multiple organ failure, including ventilator dependency and its associated outcomes.

Data sharing statement

There is no additional data available.

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Abbreviation list

ARDS: acute respiratory distress syndrome

HRCT: high-resolution computed tomography

DAD: diffuse alveolar damage

APACHE II: Acute Physiology and Chronic Health Evaluation II score

SOFA score: Sequential Organ Failure Assessment score

MOF: multi-organ failure

DIC: disseminated intravascular coagulation

MDCT: multidetector-row computed tomography

PEEP: positive end-expiratory pressure

VAP: ventilator associated pneumonia

ROC: receiver-operator characteristic

AUC: area under the curve

CI: confidence interval

SD: standard deviation

INTRODUCTION

The acute respiratory distress syndrome (ARDS) is the most severe form of a wide spectrum of pathological conditions designated as acute lung injury [1,2]. ARDS is considered to have an early and a late phase and is pathologically divided into three stages[3] in which an initial inflammatory injury with protein-rich edema and hemorrhage is followed by fibroproliferation, during which fibroblasts proliferate with organization and subsequent collagen deposition, resulting in lung remodeling, ultimately leading to fibrotic lung disease. The histological features of ARDS represent a poorly defined time-dependent stereotypic response to acute lung injury and are pathologically designated as diffuse alveolar damage[3,4]. Although pathologic staging may be conceptually useful, commonly used clinical indicators such as PaO_2/FiO_2 ratio do not correlate well with lung pathology. Although clinicians can use pathophysiology (shunt vs. V/Q mismatch with increasing deadspace) to distinguish the transition from exudative to fibroproliferative ARDS, few features, except probably time, allow them to distinguish these pathological phases without a lung biopsy [5,6].

Data regarding the significance of a fibroproliferative response on mortality risk assessed using bronchoalveolar lavage or tracheal aspirate in ARDS patients is available [7-10]. High-resolution computed tomographic (HRCT) findings correlate with the pathologic phases of diffuse alveolar damage [12-15]. Furthermore, we have previously reported on the prognostic value of HRCT in determining the extent of

fibroproliferation in ARDS patients[15]. Based on HRCT appearance, less fibroproliferation in early ARDS was associated with greater ventilator-free days and less barotraumas[15]. In this prospective study, we evaluated not only what was found in the retrospective study[15] but also the relationship between early fibroproliferation and the progression to multiple organ failure; whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact the susceptibility for ventilator dependency and its associated complications and on the response to treatment.

METHODS

One hundred and fifty two patients with ARDS diagnosed according to the American-European Consensus Conference Criteria[16] were enrolled from October 1, 2004 to July 31, 2008 at our institution. This study was approved by an institutional review board of our hospital, and informed consent was obtained from the participants or their families. On the basis of the survival in our retrospective study of 44 patients[15], we designated the number of patients more than 80 at least.

Patients

Eligible patients were receiving mechanical ventilation by tracheal tube (n = 79) or mask for non-invasive positive pressure ventilation (n = 6). Furthermore, HRCT scan was performed on the day of diagnosis of ARDS by their consent. Exclusion criteria were shown in Figure. 1. Especially, preexisting chronic interstitial lung diseases were strictly excluded by history taking, imaging data available before onset of ARDS, and

the presence of coarse reticulation and honeycombing on HRCT scans suggesting of chronic pulmonary fibrosis. Furthermore, the other preexisting pulmonary disease such as pulmonary emphysema was documented from review of radiological reports. Information about our patients' severity and characteristics is reported in Table 1.

HRCT examination, assessment, and scoring

All patients underwent helical HRCT scanning of the chest on the day of diagnosis of ARDS using multidetector-row CT (MDCT) scan. All MDCT scans were obtained with 2-mm thickness and 15-mm table speed per rotation and were performed at full inspiration from the lung apex to base. Contiguous CT slices were reconstructed using of a high–spatial frequency algorithm. Sections were displayed at 10-mm intervals throughout the chest with the patient in the supine position and without intravenous contrast medium. The process did not negatively affect the patients' condition. In this study, we evaluated single CT scan acquired at day one of the ARDS diagnosis, because sequential CT scans were hard to be performed after high positive end-expiratory pressure ventilation was introduced. HRCT scans were evaluated on the day of ARDS diagnosis by two independent observers who were unaware of patient condition. The presence and extent of areas of ground-glass attenuation, air-space consolidation, traction bronchiectasis, traction bronchiolectasis, and honeycombing were assessed. Ground-glass attenuation was defined as a hazy area with increased opacification without obscuration of underlying vascular markings. Air-space consolidation was

considered present when the vascular markings were obscured. When bronchi were irregular in contour, the dilated bronchus within areas of parenchymal abnormality was recognized as traction bronchiectasis. Traction bronchiolectasis was identified by the presence of dilated bronchioles within areas with parenchymal abnormality. Honeycombing was defined as the presence of cystic airspaces measuring 2-10 mm in diameter with well-defined walls.

HRCT findings were graded on a scale of 1-6 based on the classification system correlating with previously described pathology (Fig. 2) [13,15]: 1, normal attenuation; 2, ground-glass attenuation; 3, consolidation; 4, ground-glass attenuation with traction bronchiolectasis or bronchiectasis; 5, consolidation with traction bronchiolectasis or bronchiectasis; 6, honeycombing. The presence of each of these six abnormalities was assessed independently in three (upper, middle, lower) zones of each lung. The upper zone was defined as the area above the level of the carina, the middle zone as the area between the level of the carina and that of the infrapulmonary vein, and the lower zone as the area below the level of the infrapulmonary vein. The extent of each abnormality was determined by visually estimating the percentage (to the nearest 10%) of the affected lung parenchyma in each zone. The assessments of the two observers were averaged. The abnormality score for each zone was calculated by multiplying the percentage area by the point value (1-6). The six zone scores were averaged to determine the total score for each abnormality in each patient. The overall

CT score for each patient was obtained by adding the six averaged scores. The scoring system is previously reported [13,15] and has been evaluated in the other diseases[17,18].

Treatment Protocol

All patients underwent a common intensive treatment according to the domestic clinical practical guidelines[19-23]. Antibiotic therapy was performed by these guidelines, which were referenced to the American Thoracic Society/Infectious Diseases Society of America Consensus Guidelines on the Management [24,25].

Although the efficacy of steroids in ARDS patients has been controversial[26-28], when this study protocol was made, the efficacy of corticosteroids to the fibroproliferative ARDS had been reported in a small randomized control study[29]. In the current study, we examined the relationship between the efficacy of steroids and the extent of fibroproliferation on HRCT scans. Ventilator management and ventilator weaning was introduced by the evidence-based guidelines[22, 23]with reference to the lower tidal volume (V_T) strategy (6 ml/kg predicted body weight (PBW) < V_T < 10 ml/kg PBW) in the ARDS Clinical Trial[30] and to the guidelines for weaning and discontinuing ventilatory support from the American College of Chest Physicians[31].

Screening of ventilator associated outcomes

For each patient, we recorded the number of ventilator-free days. Barotrauma, defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, was noted as present or absent on routine chest radiographs or chest tube insertions for

known or suspected spontaneous pneumothorax during the first 28 days[32].

Ventilator associated pneumonia (VAP) surveillance was incorporated into the routine examinations of cultures of sputum obtained using a sterile intratracheal suction tube [33]. VAP was defined as pneumonia occurring after more than 48 hours of mechanical ventilation and for up to 72 hours after weaning.

Organ or system failure

Patients were monitored daily for 28 days for signs of the failure of extrapulmonary organs and systems according to the ARDS Clinical Trial[30]. The number of days without organ or system failure was calculated by subtracting the number of days with organ failure from the lesser of 28 days or the number of days to death. The Sequential Organ Failure Assessment (SOFA) score was sequentially monitored at Day 7 and 14, except for patients who died within 7 days or 14 days.

Outcome measurements

The primary outcome was mortality 60 days and180 days after ARDS diagnosis. Patients discharged from the hospital while alive without assistance for 60 days and180 days were defined as survivors. Non-survivors were defined as patients who died in the hospital. Secondary outcome variables included the number of ventilator-free days, organ failure-free days, the incidence of barotraumas, and the occurrence of ventilator-associated pneumonia.

Statistical analysis

Cox proportional hazards regression analysis was used to examine the influence on survival of 10 % change of radiologically fibroproliferation on HRCT while adjusting for other prognostic clinical factors such as age, severity of illness, non-pulmonary organ dysfunctions, that had been reported [34-36]. Multivariate regression analysis was also performed to assess the impact on ventilator-weaning failure within 28 days, an incidence of barotraumas, and ventilator-associated pneumonia. To analyze the CT score as a predictor of survival, or of the failure of ventilator weaning or of the occurrence of barotrauma within 28 days after the onset of ARDS, we used receiver-operator characteristic (ROC) curves and the corresponding area under the curve (AUC) to evaluate how the prediction model preformed on the test data and to determine the cutoff value of the CT score yielding the highest sensitivity and specificity which were determined by the Youden index (i.e., sensitivity + specificity – 1). Statistical analyses were performed by using the SPSS package (version 18.0J; SPSS, Tokyo, Japan). For all statistical analyses, $p < 0.05$ was considered significant.

RESULTS

Baseline clinical characteristics

Non-survivors had more severe lung injury with fibroproliferative changes on HRCT scan as shown by their higher HRCT scores than survivors, although non-survivors tended to have less severe multiorgan failure as expressed by their smaller SOFA scores. No significant differences were seen between survivors and non-survivors in the number of a history of cigarette smoking and a presence of emphysema. No significant differences were also observed in the therapeutic variables as well (Table 1).

HRCT findings for survivors and non-survivors

The area of increased attenuation associated with traction bronchiolectasis or bronchiectasis, indicative of radiologically fibroproliferation, was observed in 40 (47%) of 85 patients at presentation and was significantly smaller in survivors than in non-survivors (Table 2), whereas the area of increased attenuation without traction bronchiolectasis or bronchiectasis was greater in survivors than in non-survivors. Interobserver variability in evaluation of the presence of lung abnormalities was good (kappa, 0.63-0.83), and the assessments of the extent of abnormality by two different observers also correlated well (Spearman rank correlation coefficient, 0.72; $p < 0.01$).

Prognostic value of the HRCT score

The overall HRCT score of survivors (median ± SD, 195.7 ± 53.7; range,

133.4-325.0) was significantly smaller than that of non-survivors (233.1 ± 46.2; 174.8-384.8). Construction of a ROC curve yielded an optimal cut-off value of the HRCT score of 210 which was determined for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval (CI), 0.61-0.82) and for prediction of survival at Day 180 with 71 % sensitivity and 76 % specificity (AUC, 0.73; 95% CI, 0.62-0.84) (Fig. 3). A significant difference was observed in the 60-day mortality rate between patients with CT score < 210 and those with CT score ≥ 210 ($p < 0.0001$) as well as in the ventilator-free days at day 28 ($p < 0.0001$) (Table 3). The difference in the 60-day mortality rate between patients with more or less fibroproliferative changes on HRCT scan persisted regardless of causes of ARDS (Fig. 4). Multivariate Cox proportional hazards model with adjustment for demographic characteristics, severity of illness, non-pulmonary organ dysfunctions, and HRCT score at diagnosis, the HRCT score remained an independent risk factor for mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36; $p = 0.005$) when expressed as mortality change per 10% increase in the area of attenuation with traction bronchiolectasis or bronchiectasis on HRCT scans (Table 4).

Relation between the HRCT score and the number of ventilator-free days, and the number of organ-failure-free days and sequential changes of SOFA score

An ROC curve determined the best cut-off value of the CT score of 210 for prediction of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 %

specificity (AUC, 0.77; 95% CI, 0.67-0.88) (Fig. 5a). Regardless of significantly higher SOFA score (8.0 ± 3.0 versus 5.0 ± 2.0; $p < 0.0001$) and higher DIC score (2.8 ± 1.5 versus 1.9 ± 1.8; $p < 0.002$) at diagnosis, patients with a CT score of < 210 had a significantly higher number of ventilator-free days (14.0 ± 7.8 versus 5.2 ± 8.0 days; $p < 0.0001$). Those patients with a lower CT score were associated with less severe subsequent multiorgan failure as shown by a significantly higher number of organ-failure-free days (Table 3) and by significant decrease of sequential SOFA score than that of patients with a higher CT score (Fig.7). Multivariate regression analysis, with adjustment for demographic characteristics, general severity, and occurrence of barotraumas, showed that the CT score was independently associated with ventilator-weaning within 28 days with an odds ratio of 0.63 when expressed as weaning failure change per 10% increase in the area of attenuation with traction bronchiolectasis or bronchiectasis on HRCT scans ($p = 0.0006$) (Table 5a).

Relation between the HRCT score and the incidence of barotraumas or ventilator-associated pneumonia

All eleven patients with barotrauma had pneumothorax. Barotrauma occurred 3-28 days (mean ± SD, 12.7 ± 9.4 days) after ARDS onset. An ROC curve identified the optimal cutoff value of the CT score of 235 for prediction of barotrauma onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95% CI, 0.59-0.95) (Fig. 6a). Patients with the CT score < 235 had a significantly lower incidence of barotrauma (5.0

versus 32.0 %; p = 0.0019) within 28 days after the onset of ARDS than those with CT score of ≥ 235 (Fig. 5b). The CT score was also independently associated with the occurrence of barotraumas with an odds ratio of 1.61 by multivariate regression analysis (p = 0.018) (Table 6b). Ventilator-associated pneumonia (VAP) was documented in 36 patients (42.3%) after day 5 since ARDS onset. The percentage of patients complicated with VAP in the higher CT score group tended to be higher than those in the lower CT score groups (51.4 and 35.4 percent, respectively; p = 0.14). Multivariate analysis also demonstrated that the CT score was independently associated with the complication of VAP with an odds ratio of 1.46 (p = 0.0041) (Table 5c).

DISCUSSION

Regardless of the cause of ARDS, we found the extent of fibroproliferative changes on HRCT at diagnosis of ARDS was an independent predictive factor for survival and ventilator dependency. Furthermore, patients with extensive fibroproliferative changes on HRCT scan were more susceptible to associated multiorgan failure, barotraumas and ventilator-associated pneumonia than those with less extensive changes. Semi-quantitative determination of fibroproliferation by means of HRCT assessment was informative with regard to the potential not only for response to treatment but also for susceptibility to subsequent ventilator-associated outcomes (ventilator dependency, barotraumas, and ventilator-associated pneumonia).

Biochemical evidence of fibroproliferation is present early in the acute lung injury process. N-terminal procollagen peptide III (N-PCP-III) is a marker of collagen turnover and is elevated in bronchoalveolar lavage (BAL) fluid and tracheal aspirate from ARDS patients within 24 h of diagnosis [7-10] The increased N-PCP-III concentration in BALF at diagnosis was associated with poor prognosis, suggesting that pulmonary early fibroproliferation is an important determinant of outcome [7-10]. In the present study, traction bronchiectasis within areas of increased attenuation, suggesting radiologically fibroproliferation, was already detectable on HRCT scans obtained on the day of ARDS onset in 40 patients (47%). These results supported the previous reports and suggested that a clinically early time point does

not necessarily correspond to a pathologically early phase of ARDS. Given that no significant difference in the cause of ARDS was apparent between the survivors and non-survivors in this study, no correlation between the HRCT score and the clinical duration of ARDS may also be attributable to differences in individual sensitivity to lung injury and in the intensity of the consequent exaggerated inflammation that occurs between the onset of injury and progression to ARDS. The term "fibroproliferative" ARDS may not necessarily apply only to "late phase" ARDS but possibly also to "early phase". Accordingly, extent of fibroproliferative changes on HRCT scan, together with N-PCP-III concentration in BALF, may be a potential clue to differentiate "real" late ARDS from the early one.

Currently, there have been few prospective clinical studies to validate the susceptibility to ventilator-associated outcomes. The ARDS Network low tidal volume study has suggested that excessive large tidal ventilation induces inflammatory cytokines and is associated with a known risk factor for ventilator associated lung injury[27]. In the present study, patients with extensive fibroproliferation shown as higher HRCT score on the day of ARDS onset needed a longer duration of mechanical ventilation with subsequent ventilator-associated pneumonia and had shorter organ-failure free days, and subsequently suffered from multiple organ failure.

Barotraumas occurring in critically ill patients independently affects intensive care

unit mortality [37]. Barotrauma events occur late in the course of ARDS and are related to lung structural changes such as cystic or fibroproliferative lesions that develop over time [38]. In our study, barotrauma occurred more than 10 days (mean ± SD, 12.7 ± 9.4 days) after the onset of ARDS and was more frequent in patients with a higher HRCT score (score ≥ 235) than in those with a lower HRCT score (score < 235) during the first 28 days. Given that a higher HRCT score at diagnosis suggests advanced fibroproliferation, our data support the relationship between pulmonary fibroproliferation and its susceptibility to barotraumas.

Ventilator-associated pneumonia (VAP) has been a causative factor of subsequent systemic inflammatory syndrome resulting in multi-organ failure[32]. The risk of VAP increases with prolonged mechanical ventilation[33]. More extensive fibroproliferative changes on HRCT scan shown as a higher CT score were associated with a longer ventilator dependency that was more susceptible to VAP onset. These results support that pulmonary fibroproliferation of ARDS increases risk for ventilator dependency and its associated complications.

In a previous study of 45 cases of ARDS confirmed at biopsy, patients whose conditions were shown histologically to be in the acute exudative phase had a better prognosis than did those whose condition was shown to be in the fibroproliferative phases [39]. In our study, the group of patients who had less fibroproliferative changes on HRCT scans (HRCT score, < 210) showed lower mortality and more ventilator-free

days than those who had more extensive areas of fibroproliferation (HRCT score, ≥ 210). This suggests a relationship between the pathologic phases of ARDS and responsiveness to treatment. Whether the patients with fibroproliferative predominance have different treatment strategies compared to those with exudative predominance has been a vexing question [4]. Improving our understanding of disease state and evolution of the disease may be key to the development of the optimal therapy and their timing. A method that could be used to evaluate and calibrate the clinical to pathologic stages may help prognosticate, alter supportive or therapeutic approach to ARDS such as ventilator management and define the treatment window for those interventions. Further prospective studies are needed to examine the efficacy of the drugs such as corticosteroids according to the extent of fibroproliferation on HRCT scans.

There were some potential limitations. First, our study included few patients with ARDS caused by major trauma, multiple transfusion and others, although it included approximately 90% of the patients who had ARDS caused by three major etiologies (pneumonia, aspiration, sepsis) of ARDS; thus, our study may not sufficiently reflect all forms of ARDS. However, previous large randomized control studies also included more than 70% of patients with these three etiologies [26, 30]. Therefore, our results may be applicable to most forms of ARDS.

Second, many elderly patients (mean age, 75.0 years) were included. Clinically, elderly ARDS patients show higher morbidity and need longer duration of mechanical

ventilation with subsequent poorer prognosis than the younger patients [2, 35]. The age-related differences in mortality and outcomes have been considered to be due to the greater number of comorbid illness and higher frequency of non-pulmonary organ system failure in older patients [35]. In this study, preexisting pulmonary emphysema was seen in 32 (38 %) of 85 patients. Although no significant differences were seen between survivors and non-survivors in the number of a history of cigarette smoking and a presence of emphysema, we could not evaluate the severity of emphysema before the onset of ARDS. Such a smoking-induced chronic lung disease could potentially affect ventilator-dependency or prognosis. Although it was problematic whether aging increase susceptibility to lung injury and to pulmonary fibroproliferation, further investigation of younger patients with ARDS is needed to confirm the consistency of the results of our study.

Third, no correlation was provided with either clinical parameters or pathologic findings in the present study. Further investigation is necessary to compare HRCT findings with other predictors of mobidity/mortality-i.e. inflammatory biomarkers such as serum IL-6 or BAL PCP III levels. Recent studies of biopsy findings from ARDS patients have reported the pathologic diversity and only half proportion of typical diffuse alveolar damage [5,6]. Regardless of the cause or pathology of ARDS, our study highlighted the extent of lung architectural distortion (areas with traction bronchiectasis) indicating that pulmonary fibroproliferation on HRCT scans. Although

fibroproliferative ARDS does not warrant different treatment strategies up to the present, prospective evaluation of HRCT findings in patients with ARDS would help therapeutic implications in the development of treatment strategies based on the extent of fibroproliferation, as well as its prognostic implications.

On the basis of our results, extensive HRCT abnormalities indicative of fibroproliferative changes on the day of ARDS diagnosis were independently predictive of poor prognosis and prolonged mechanical ventilation, and were also associated with subsequent multiple organ failure. Pulmonary fibroproliferation that occurs early in ARDS patients increases mortality risk by increasing susceptibility to ventilator dependency and its associated complications.

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Dr Ichikado: contributed to designing the study, collecting the data, analyzing the data, and writing the manuscript.

Dr Muranaka: contributed to collecting data, analyzing the data, and revising the manuscript.

Dr Gushima: contributed to collecting data, analyzing the data, and revising the manuscript.

Dr Kotani: contributed to analyzing the data and revising the manuscript.

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Table 1. Clinical characteristics of patients on the day of ARDS onset

Characteristic	Total (n = 85)	60 days Outcomes		p value
		Survivors (n = 54)	Non-survivors (n = 31)	
Age (years)*	75 ± 10	75 ± 11	76 ± 10	0.60
Sex (M/F)	51/34	30/24	21/10	0.38
Cigarette smoking	33	17	16	0.11
Presence of emphysema	32	18	14	0.39
Liver cirrhosis (%)	6 (7.1)	4 (7.4)	2 (6.5)	> 0.99
Direct/indirect injury	59/26	38/16	21/10	0.81
PaO_2:FiO_2	96.2 ± 45.6	96.5 ± 45.0	96.2 ± 47.5	0.90
Causes of lung injury				
Pneumonia (%)	32 (37.6)	20	12	> 0.99
Sepsis (%)	24 (28.2)	13	11	0.38
Pulmonary (%)	11 (12.9)	5	6	0.20
Extrapulmonary (%)	13 (15.2)	8	5	> 0.99
Aspiration (%)	22 (25.9)	16	6	0.44
Others (%)	7 (8.2)	5	2	> 0.99
Lung injury score*	3.2 ± 0.5	3.3 ± 0.5	3.3 ± 0.5	0.88
APACHE II score	21.0 ± 4.7	21.0 ± 4.6	22.0 ± 4.9	0.76
SOFA score	7.0 ± 2.8	7.0 ± 2.8	6.0 ± 2.9	0.15
McCabe score (1/2/3)	78/5/2	49/4/1	29/1/1	> 0.99
DIC score*#	2.4 ± 1.7	2.4 ± 1.7	2.5 ± 1.6	0.68
White blood cell count (per mm^3)	10600 ± 6788	10600 ± 6178	10600 ± 7839	0.63

C-reactive protein (CRP) (mg/dl)	15.4 ± 10.3	15.4 ± 9.6	16.1 ± 11.5	0.69
Albumin (g/dl)	3.0 ± 0.5	3.1 ± 0.5	2.8 ± 0.5	0.11
Lactate dehydrogenase (LDH) (IU/L)	308 ± 185	301 ± 147	339 ± 235	0.29
Platelet count (per mm^3)	20.1 ± 10.7	20.7 ± 11.0	18.9 ± 10.3	0.94
Days of CT scanning from ARDS onset (day)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	> 0.99
HRCT score #	207 ± 53	196 ± 54	233 ± 46	0.001
Initial steroid therapy				
High dose	14	7	7	0.36
Low dose	71	47	24	0.36
Ventilatory variables				
Tidal volume, ml/kg predicted body weight	8.0 ± 0.8	8.0 ± 0.7	8.0 ± 0.9	0.54
Plateau pressure, cmH_2O	21.5 ± 4.2	21.0 ± 3.8	23.0 ± 4.7	0.34
Initial PEEP, cmH_2O	8.0 ± 3.4	8.0 ± 2.5	8.0 ± 4.3	0.18

Data are expressed as median ± standard deviation. *Data are mean ± standard deviation. The p values refer to comparisons between survivors and non-survivors.

Score ≥ 4 defined as disseminated intravascular coagulation from scoring system for The Japanese Association for Acute Medicine.

Table 2. Extent of each high-resolution CT finding in 60-days survivors and non-survivors of ARDS.

CT Finding	Survivors (n = 54)	Non-survivors (n = 31)	p value
Spared area	37.0 ± 19.2	30.3 ± 14.9	0.15
Ground-glass attenuation	33.5 ± 22.9	30.0 ± 16.0	0.70
Air-space consolidation	17.5 ± 13.8	18.3 ± 19.3	0.72
Total area without traction bronchiolectasis or bronchiectasis	88.0 ± 22.0	78.2 ± 22.5	0.01
Ground-glass attenuation plus traction bronchiolectasis or bronchiectasis	9.3 ± 17.8	16.6 ± 21.7	0.08
Air-space consolidation plus traction bronchiolectasis or bronchiectasis	2.4 ± 7.8	5.6 ± 10.3	0.01
Honeycombing	0.0 ± 0.0	0.0 ± 0.0	NS
Total area with traction bronchiolectasis or bronchiectasis	11.8 ± 18.0	22.1 ± 24.3	0.01

Data are mean ± standard deviation of percentage of lung involvement.

NS = not significant

Mann-Whitney U test

Table 3. Comparison of primary and secondary outcomes between the cut-off value showing extent of fibroproliferative changes on high-resoluiton CT at the onset of ARDS

Variable	High-Resolution Computed Tomographic (CT) score		p value
	< 210 (n = 47)	≥ 210 (n = 38)	
60-Day mortality (%)	19.1	57.9	< 0.0001
No. of hospital death	9	22	
Causes of death			
Multiple organ failure	8	18	
Respiratory failure	1	4	
No. of ventilator-free days at day 28	14.3 ± 7.6	5.1 ± 8.0	< 0.0001
No. of organ-failure-free days			
Cardiovascular failure	22.4 ± 8.1	16.1 ± 10.9	0.009
Coagulation abnormalities	23.0 ± 8.9	17.8 ± 10.4	0.017
Hepatic failure	23.3 ± 8.2	19.6 ± 9.5	0.11
Renal failure	21.7 ± 10.9	19.6 ± 9.6	0.29
No. of incidence of barotraumas (%)	3 (6.4)	8 (21.1)	0.056
No. of ventilator-associated pneumonia (%)	16 (34.0)	20 (52.6)	0.13

Plus-minus values are mean ± SD. Continuous variables with non-normal distribution were compared with the use of Mann-Whitney U test and categorical variables with Fisher's exact test.

Table 4a. Univariate Cox regression analysis of variables potentially associated with mortality at day 180 in patients with ARDS.

Variable	P value	Hazard ratio	95% CI
HRCT score	0.0019	1.22*	1.08-1.38
Age	0.5411	0.99	0.96-1.02
Sepsis	0.4020	1.34	0.67-2.67
APACHE II score	0.6578	0.98	0.92-1.06
SOFA score	0.1724	0.92	0.82-1.04
McCabe score	0.9609	0.98	0.41-2.32
PaO_2 / FiO_2 ratio	0.6119	1.00	0.99-1.01
Serum Albumin	0.0982	0.57	0.30-1.11

Table 4b. Multivariate Cox regression analysis of prognostic factors associated with mortality at day 180 in patients with ARDS

Variable	P value	Hazard ratio	95% CI
HRCT score	0.0051	1.20*	1.06-1.36
Serum Albumin	0.2618	0.67	0.33-1.36

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5. Multiple logistic regression analysis of variables potentially associated with ventilator-associated outcomes.

Table 5a. Ventilator-weaning within 28 days in patients with ARDS.

Variable	P value	Odds ratio	95% CI
HRCT score	0.0006	0.63*	0.48-0.82
Serum Albumin	0.1727	2.09	0.72-6.03

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5b. The incidence of the Barotrauma

Variable	P value	Odds ratio	95% CI
HRCT score	0.0183	1.61*	1.08-2.38
APACHE II	0.4724	0.92	0.74-1.15
SOFA score	0.9110	1.02	0.68-1.55
Serum Albumin	0.5156	0.53	0.08-3.65
Serum LDH	0.0158	1.05	1.01-1.09

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5c. The complication of the Ventilator-associated pneumonia

Variable	P value	Odds ratio	95% CI
Liver cirrhosis	0.0286	13.34	1.31-135.60
HRCT score	0.0041	1.46*	1.13-1.89
PaO_2 / FiO_2 ratio	0.0236	0.99	0.98-1.00

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

FIGURE LEGENDS

Figure 1. Outlines of the study.

Figure 2. High-resolution computed tomography (CT) findings correlated with pathology

a.: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation without traction bronchiectasis and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumonia.*

b.: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis (arrows). The patient was a 84-year-old woman with ARDS due to sepsis.

c.: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old woman with ARDS due to *viral pneumonia.* (Sequential changes of HRCT findings were shown in the supplemental figure.)

Figure 3. Receiver operator characteristic (ROC) curve of prognostic value of the high-resolution computed tomography (HRCT) score. ROC identified the optimal cut-off value of 210 determined by the Youden Index for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval, 0.61-0.82) and for prediction of survival at Day 180 with 71% sensitivity and 76 % specificity (AUC, 0.73; 95%CI, 0.62-0.84).

Figure 4a. Day 60-mortality rate of each major cause of ARDS.

Figure 4b. Day 60-mortality rate compared between the optimal cut-off value of high-resolution computed tomography (HRCT) score in each cause. Regardless of the cause, the mortality rate of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

Figure 5. Receiver operator characteristic (ROC) curve of prediction of the ventilator weaning within 28 days from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 210 determined by the Youden Index for prediction of ventilator weaning at day 28 with 75 % sensitivity and 76 % specificity (AUC, 0.77; 95%CI, 0.67-0.88).

Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumas onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95%CI, 0.59-0.95)

Figure 6b. Comparison of the incidence of barotraumas between patients with the optimal cut-off value of CT score identified from ROC curve. The incidence of barotrauma of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

Figure 7. Sequential changes of Sequential Organ Failure Assessment (SOFA) scores. The SOFA score of a patient with a lower CT score (< 210) significantly decreased from day 1 to day 14 ($p = 0.0016$). The SOFA score of a patient of a patient with a higher CT

score (≥ 210) significantly increased from day 1 to day 14 (p = 0.027). Four patients with a lower CT score (< 210) and 9 patients with a higher CT score (≥ 210) who died within 14 days were excluded.

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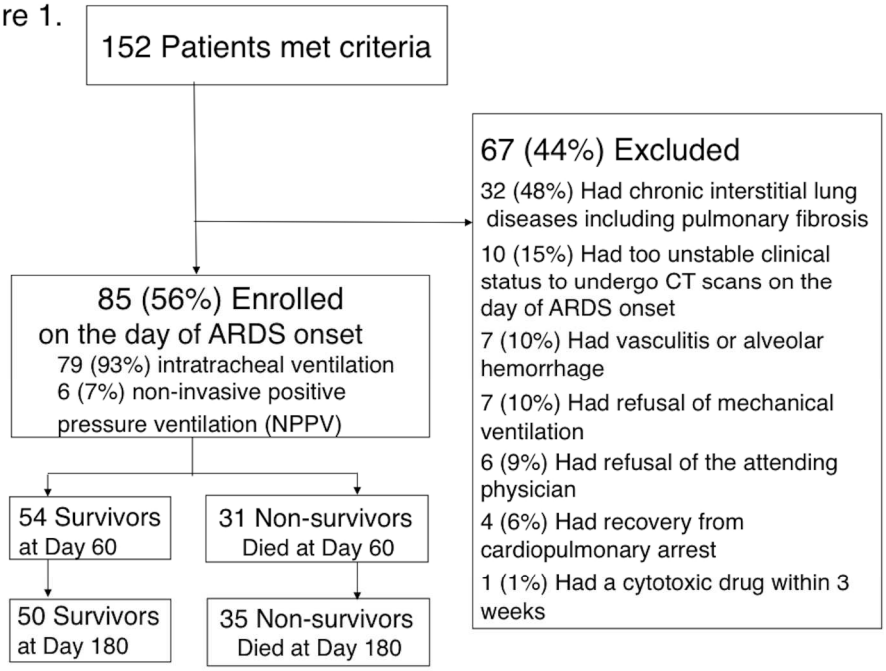
Patient confidentiality

Details has been removed from this case description.

Figure 1.



Outlines of the study.
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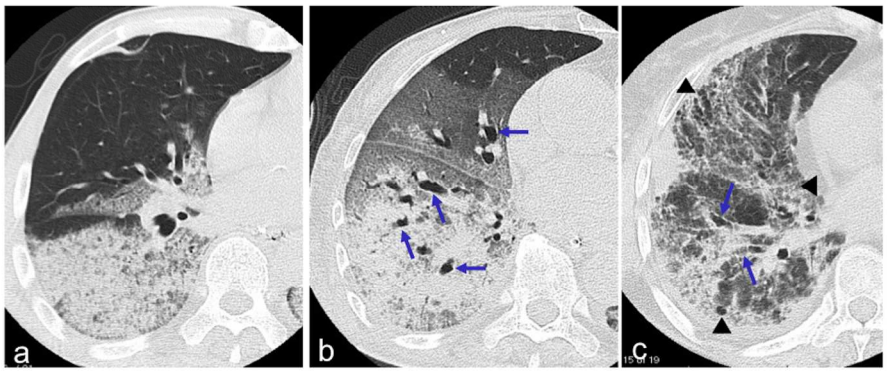

Figure 2a: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumoniae* pneumonia.

Figure 2b: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis(arrows). The patient was a 84-year-old woman with ARDS due to *sepsis*.

Figure 2c: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old woman with ARDS due to *viral pneumonia*. (Sequential changes of HRCT findings were shown in the supplemental figure.)

High-resolution computed tomography (CT) findings correlated with pathology
a.: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation without traction bronchiectasis and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to Streptococcus pneumonia.
b.: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis (arrows). The patient was a 84-year-old woman with ARDS due to sepsis.
c.: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation
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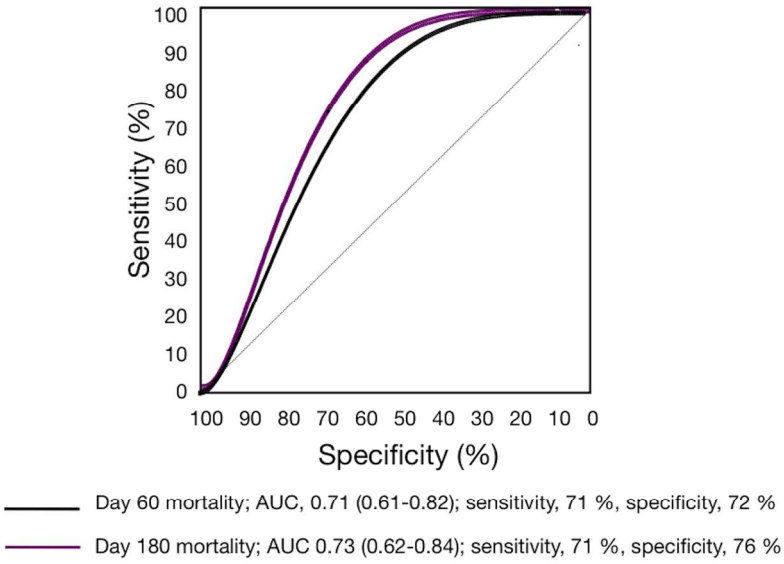
Figure 3 Receiver Operating Characteristic Curve of the prediction of Day 60 and Day 180 mortality



Receiver operator characteristic (ROC) curve of prognostic value of the high-resolution computed tomography (HRCT) score. ROC identified the optimal cut-off value of 210 determined by the Youden Index for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval, 0.61-0.82) and for prediction of survival at Day 180 with 71% sensitivity and 76 % specificity (AUC, 0.73; 95%CI, 0.62-0.84).
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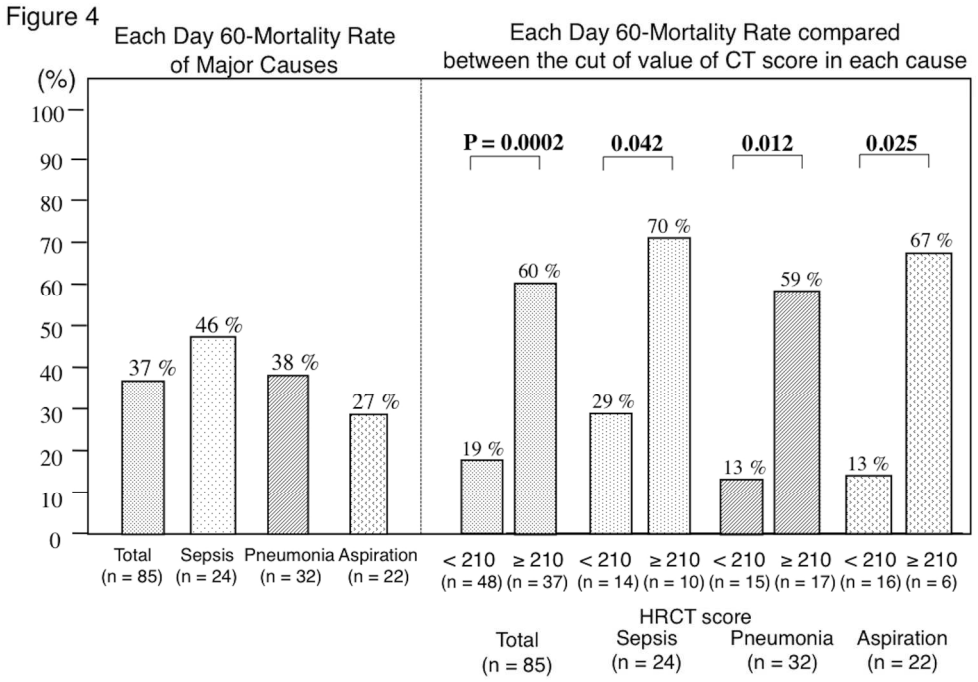

Figure 4a. Day 60-mortality rate of each major cause of ARDS.

Figure 4b. Day 60-mortality rate compared between the optimal cut-off value of high-resolution computed tomography (HRCT) score in each cause. Regardless of the cause, the mortality rate of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

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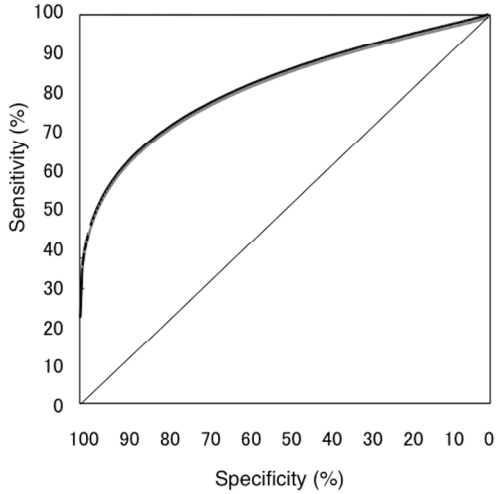
Figure 5
Receiver Operating Characteristic Curve of the prediction of ventilator weaning during 28 days



AUC, 0.77 (0.67-0.88); sensitivity, 75 %, specificity, 76 %

Receiver operator characteristic (ROC) curve of prediction of the ventilator weaning within 28 days from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 210 determined by the Youden Index for prediction of ventilator weaning at day 28 with 75 % sensitivity and 76 % specificity (AUC, 0.77; 95%CI, 0.67-0.88).
180x124mm (300 x 300 DPI)

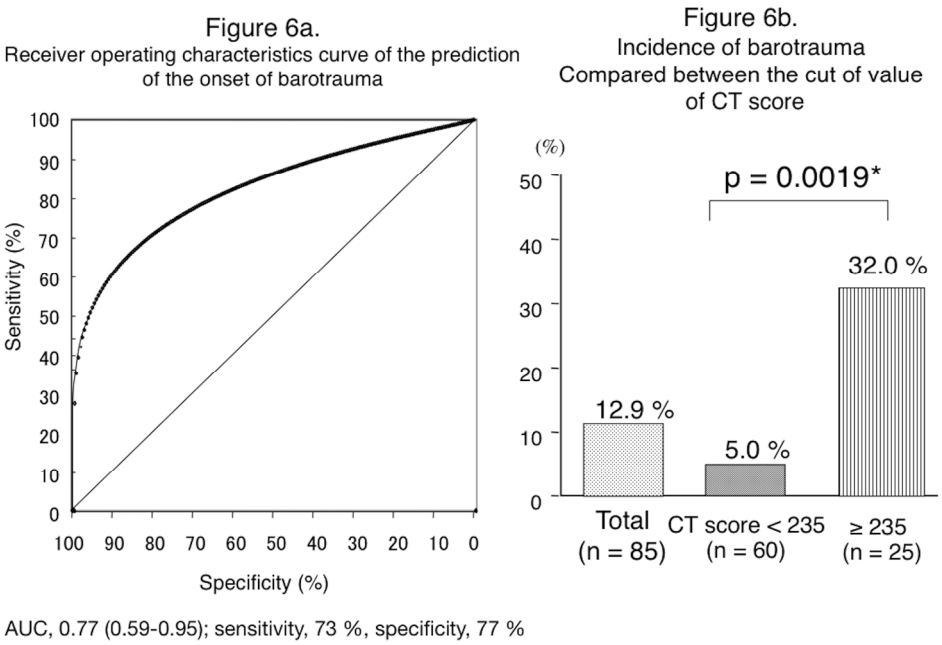


Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumas onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95%CI, 0.59-0.95)

Figure 6b. Comparison of the incidence of barotraumas between patients with the optimal cut-off value of CT score identified from ROC curve. The incidence of barotrauma of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

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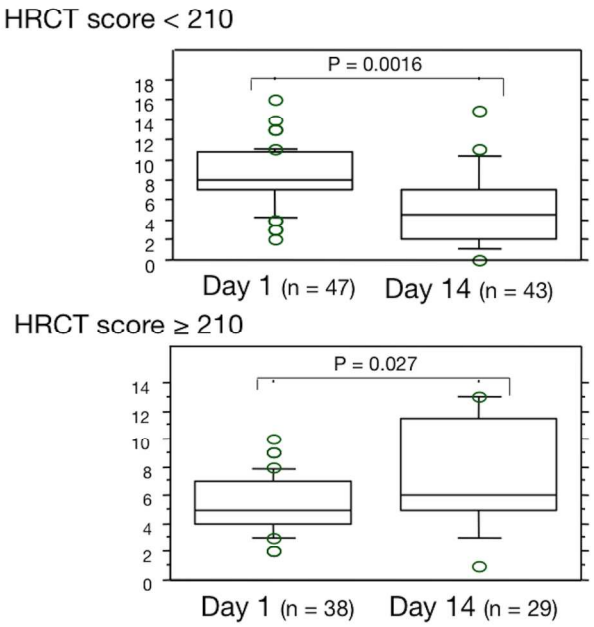
Figure 7. Sequential changes of SOFA score



Sequential changes of Sequential Organ Failure Assessment (SOFA) scores. The SOFA score of a patient with a lower CT score (< 210) significantly decreased from day 1 to day 14 (p = 0.0016). The SOFA score of a patient of a patient with a higher CT score (≥ 210) significantly increased from day 1 to day 14 (p = 0.027). Four patients with a lower CT score (< 210) and 9 patients with a higher CT score (≥ 210) who died within 14 days were excluded.
180x134mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4
Introduction			**Page 7-8**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 8
Methods			**Page 8-13**
Study design	4	Present key elements of study design early in the paper	Page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8, 12
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 26, Table 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8-12
Bias	9	Describe any efforts to address potential sources of bias	Page 8
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 13
		(*b*) Describe any methods used to examine subgroups and interactions	Page 13
		(*c*) Explain how missing data were addressed	Figure 1
		(*d*) If applicable, explain how loss to follow-up was addressed	Figure 1
		(*e*) Describe any sensitivity analyses	Page 13
Results			Page 14-17

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 14, Figure 1
		(b) Give reasons for non-participation at each stage	Page 14, Figure 1
		(c) Consider use of a flow diagram	Page 14, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 26, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 29, Table 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 30-32,Table 4-5
		(*b*) Report category boundaries when continuous variables were categorized	Page 29, Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 30-32, Table 4-5
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 3-7
Discussion			Page 18-23
Key results	18	Summarise key results with reference to study objectives	Page 3
Limitations			Page 21-23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 3
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 21-23
Other information			Page 2, 24-25, 41
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 5

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Fibroproliferative Changes on High-Resolution Computed Tomography in the Acute Respiratory Distress Syndrome Predict Mortality and Ventilator Dependency: A Prospective Observational Cohort Study

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Primary Subject Heading:	Respiratory medicine

Secondary Subject Heading:	Intensive care, Radiology and imaging
Keywords:	Adult intensive & critical care < ANAESTHETICS, Thoracic medicine < INTERNAL MEDICINE, Chest imaging < RADIOLOGY & IMAGING

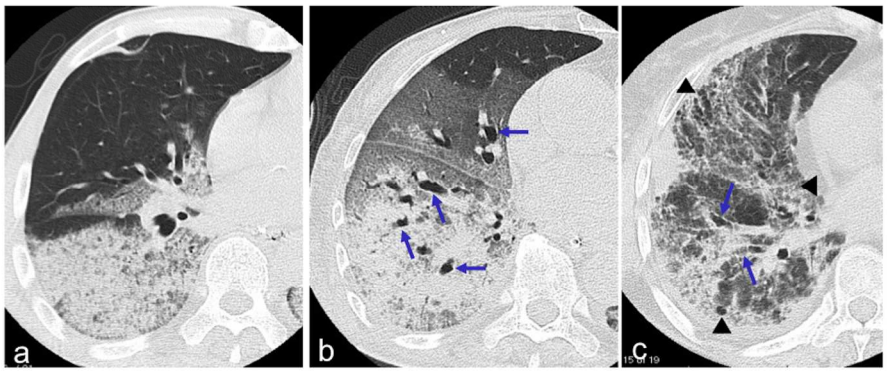

Figure 2a: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumoniae* pneumonia.

Figure 2b: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis(arrows). The patient was a 84-year-old woman with ARDS due to *sepsis*.

Figure 2c: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old woman with ARDS due to *viral pneumonia*. (Sequential changes of HRCT findings were shown in the supplemental figure.)

High-resolution computed tomography (CT) findings correlated with pathology
a.: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation without traction bronchiectasis and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to Streptococcus pneumonia.
b.: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis (arrows). The patient was a 84-year-old woman with ARDS due to sepsis.
c.: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation
associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old woman with ARDS due to viral pneumonia. (Sequential changes of HRCT findings were shown in the supplemental figure.)

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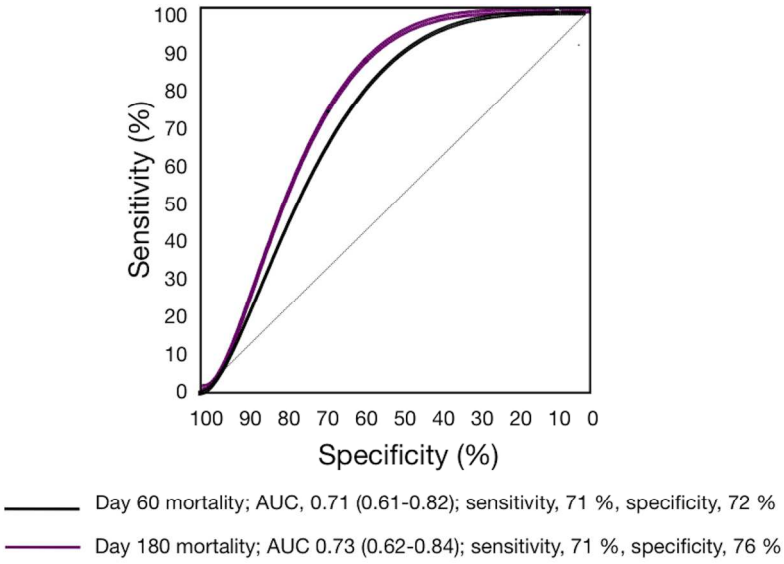
Figure 3 Receiver Operating Characteristic Curve of the prediction of Day 60 and Day 180 mortality



Receiver operator characteristic (ROC) curve of prognostic value of the high-resolution computed tomography (HRCT) score. ROC identified the optimal cut-off value of 210 determined by the Youden Index for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval, 0.61-0.82) and for prediction of survival at Day 180 with 71% sensitivity and 76 % specificity (AUC, 0.73; 95%CI, 0.62-0.84).
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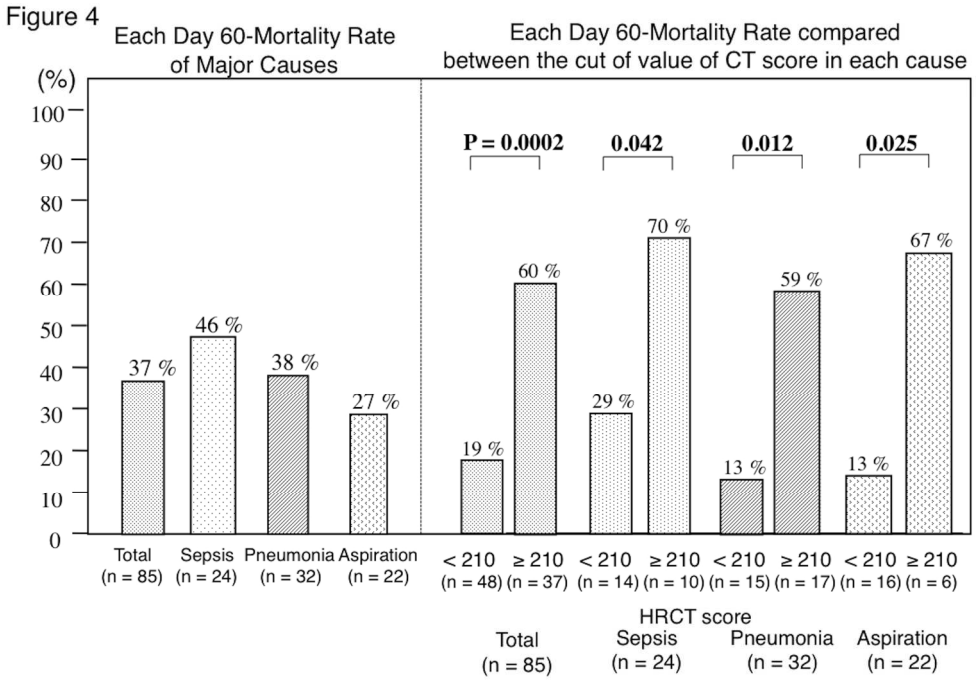

Figure 4a. Day 60-mortality rate of each major cause of ARDS.

Figure 4b. Day 60-mortality rate compared between the optimal cut-off value of high-resolution computed tomography (HRCT) score in each cause. Regardless of the cause, the mortality rate of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

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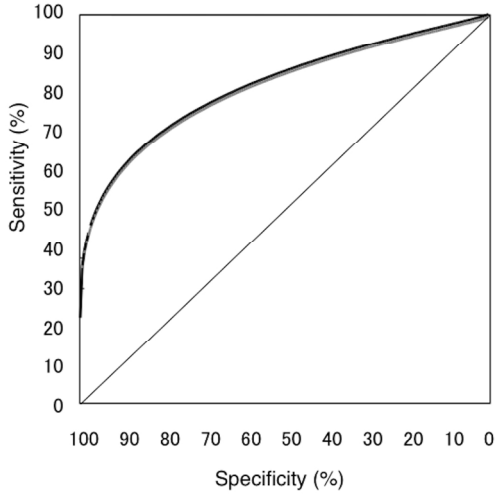
Figure 5
Receiver Operating Characteristic Curve of the prediction of ventilator weaning during 28 days



AUC, 0.77 (0.67-0.88); sensitivity, 75 %, specificity, 76 %

Receiver operator characteristic (ROC) curve of prediction of the ventilator weaning within 28 days from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 210 determined by the Youden Index for prediction of ventilator weaning at day 28 with 75 % sensitivity and 76 % specificity (AUC, 0.77; 95%CI, 0.67-0.88).
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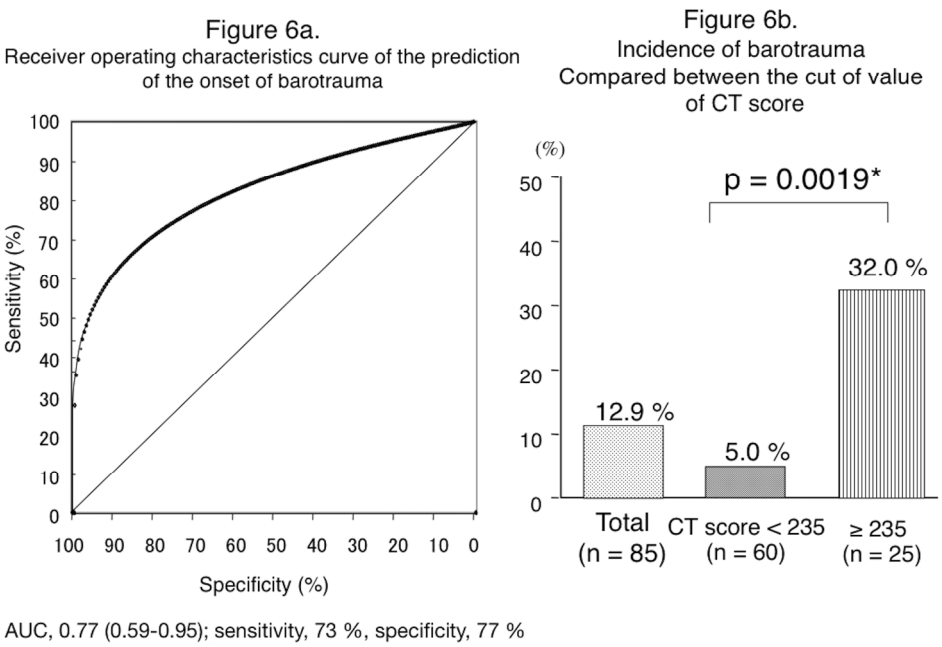

Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumas onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95%CI, 0.59-0.95)

Figure 6b. Comparison of the incidence of barotraumas between patients with the optimal cut-off value of CT score identified from ROC curve. The incidence of barotrauma of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

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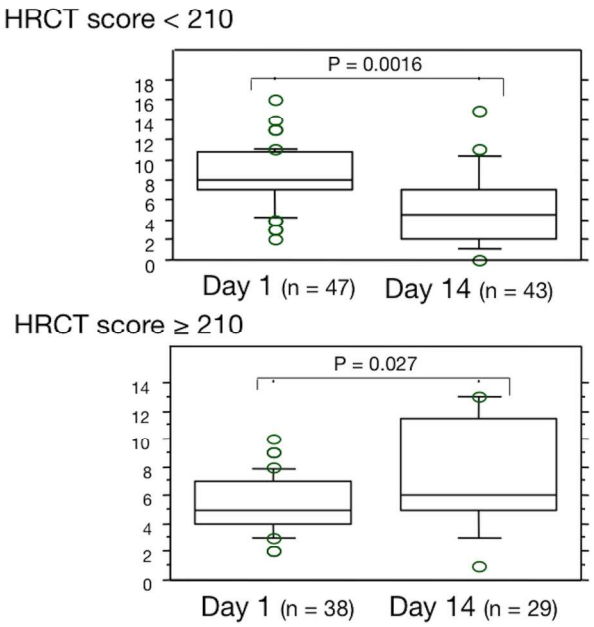
Figure 7. Sequential changes of SOFA score



Sequential changes of Sequential Organ Failure Assessment (SOFA) scores. The SOFA score of a patient with a lower CT score (< 210) significantly decreased from day 1 to day 14 (p = 0.0016). The SOFA score of a patient of a patient with a higher CT score (≥ 210) significantly increased from day 1 to day 14 (p = 0.027). Four patients with a lower CT score (< 210) and 9 patients with a higher CT score (≥ 210) who died within 14 days were excluded.
180x134mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4
Introduction			**Page 7-8**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 8
Methods			**Page 8-13**
Study design	4	Present key elements of study design early in the paper	Page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8, 12
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 26, Table 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8-12
Bias	9	Describe any efforts to address potential sources of bias	Page 8
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 13
		(*b*) Describe any methods used to examine subgroups and interactions	Page 13
		(*c*) Explain how missing data were addressed	Figure 1
		(*d*) If applicable, explain how loss to follow-up was addressed	Figure 1
		(*e*) Describe any sensitivity analyses	Page 13
Results			Page 14-17

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 14, Figure 1
		(b) Give reasons for non-participation at each stage	Page 14, Figure 1
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Fibroproliferative Changes on High-Resolution Computed Tomography in the Acute Respiratory Distress Syndrome Predict Mortality and Ventilator Dependency: A Prospective Observational Cohort Study

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Conflict of interest disclosures: None of the authors has declared any conflict of interest related to this work.

Keywords

acute respiratory distress syndrome, high-resolution computed tomography, ventilator-associated lung injury, corticosteroids

1) Article Focus

• Whether the extent of fibroproliferation on high-resolution CT (HRCT) scan at the time diagnosis of ARDS would impact 60-day and 180-day mortality?

• Whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact ventilator dependency and its associated outcomes?

• Whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact multiple-organ failure?

2) Key Messages

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts increased mortality.

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts ventilator dependency and its associated outcomes (barotraumas, ventilator-associated pneumonia).

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS increases susceptibility to multiple organ failure.

3) Strengths and Limitations

• The CT score is based on our previous published studies correlating HRCT findings with pathology and has been evaluated in the other diseases.

• a relatively small number of patients from a single institution

• lack of correlation with either clinical parameters or pathologic findings

Objectives: To examine whether the extent of fibroproliferative changes on high-resolution computed tomography (HRCT) scan influences prognosis, ventilator dependency, and the associated outcomes in patients with early acute respiratory distress syndrome (ARDS).

Design: A prospective observational cohort study

Setting: Intensive care unit in an educational hospital

Participants: Eighty-five patients with ARDS who met American-European Consensus Conference Criteria and eligible criteria.

Interventions: HRCT scans were performed and prospectively evaluated by two independent observers on the day of diagnosis and graded into six findings according to the extent of fibroproliferation. An overall HRCT score was obtained by previously published method.

Primary and secondary outcomes: The primary outcomes were 60-day and 180-day mortality. Secondary outcomes included the number of ventilator-free days, organ failure-free days, the incidence of barotraumas, and the occurrence of ventilator-associated pneumonia.

Results: Higher HRCT scores were associated with statistically significant decreases in organ-failure free days as well as ventilator-free days. Multivariate Cox proportional hazards model showed that the HRCT score remained an independent risk factor for mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36; p = 0.005).

Multivariate analysis also revealed that the CT score had predictive value for ventilator-weaning within 28 days (odds ratio 0.63; 95% CI 0.48, 0.82; p = 0.0006) as well as for an incidence of barotraumas (1.61; 95%CI 1.08, 2.38; p = 0.018) and for an occurrence of ventilator-associated pneumonia (1.46; 95%CI 1.13,1.89; p = 0.004). An HRCT score < 210 enabled prediction of 180 day survival with 71 % sensitivity and 76 % specificity and of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 % specificity.

Conclusions: Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts increased mortality with an increased susceptibility to multiple organ failure, including ventilator dependency and its associated outcomes.

Data sharing statement

There is no additional data available.

Research grant

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Abbreviation list

ARDS: acute respiratory distress syndrome

HRCT: high-resolution computed tomography

DAD: diffuse alveolar damage

APACHE II: Acute Physiology and Chronic Health Evaluation II score

SOFA score: Sequential Organ Failure Assessment score

MOF: multi-organ failure

DIC: disseminated intravascular coagulation

MDCT: multidetector-row computed tomography

PEEP: positive end-expiratory pressure

VAP: ventilator associated pneumonia

ROC: receiver-operator characteristic

AUC: area under the curve

CI: confidence interval

SD: standard deviation

INTRODUCTION

The acute respiratory distress syndrome (ARDS) is the most severe form of a wide spectrum of pathological conditions designated as acute lung injury [1,2]. ARDS is considered to have an early and a late phase and is **pathologically classified** into three stages[3] in which an initial inflammatory injury with protein-rich edema and hemorrhage is followed by fibroproliferation, during which fibroblasts proliferate with organization and subsequent collagen deposition, resulting in lung remodeling, ultimately leading to fibrotic lung disease. The histological features of ARDS represent a poorly defined time-dependent stereotypic response to acute lung injury and are pathologically designated as diffuse alveolar damage[3,4]. **Although pathologic staging may be conceptually useful, commonly used clinical indicators such as PaO_2/FiO_2 ratio correlate with progression or resolution of ARDS but necessarily reflect the extent of fibroproliferation.** Although clinicians can use pathophysiology (shunt vs. V/Q mismatch with increasing deadspace) to distinguish the transition from exudative to fibroproliferative ARDS, few features, except probably time, allow them to distinguish these pathological phases without a lung biopsy [5,6].

Data regarding the significance of a fibroproliferative response on mortality risk assessed using bronchoalveolar lavage or tracheal aspirate in ARDS patients is available [7-10]. High-resolution computed tomographic (HRCT) findings correlate with the pathologic phases of diffuse alveolar damage [12-15]. Furthermore, we have previously

reported on the prognostic value of HRCT in determining the extent of fibroproliferation in ARDS patients[15]. Based on HRCT appearance, less fibroproliferation in early ARDS was associated with greater ventilator-free days and less barotraumas[15]. In this prospective study, **because of ARDS as a systemic disease with systemic inflammation as core pathogenetic process that affects the lung as well as extra-pulmonary vital organs,** we evaluated not only what was found in the retrospective study[15] but also the relationship between early fibroproliferation and the progression to multiple organ failure; whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact the susceptibility for ventilator dependency and its associated complications and **on the mortality**.

METHODS

One hundred and fifty two patients with ARDS diagnosed according to the American-European Consensus Conference Criteria[16] were enrolled from October 1, 2004 to July 31, 2008 at our institution. This study was approved by an institutional review board of our hospital, and informed consent was obtained from the participants or their families. On the basis of the survival in our retrospective study of 44 patients[15], we designated the number of patients more than 80 at least.

Patients

Eligible patients were receiving mechanical ventilation by tracheal tube (n = 79) or mask for non-invasive positive pressure ventilation (n = 6). Furthermore, HRCT scan

was performed on the day of diagnosis of ARDS by their consent. Exclusion criteria were shown in Figure. 1. Especially, preexisting chronic interstitial lung diseases were strictly excluded by history taking, imaging data available before onset of ARDS, and the presence of coarse reticulation and honeycombing on HRCT scans suggesting of chronic pulmonary fibrosis. Furthermore, the other preexisting pulmonary disease such as pulmonary emphysema was documented from review of radiological reports. Information about our patients' severity and characteristics is reported in Table 1.

HRCT examination, assessment, and scoring

All patients underwent whole lung volumetric HRCT scanning of the chest on the day of diagnosis of ARDS using a multidetector-row CT (MDCT) scan. All MDCT scans were obtained with 2-mm thickness and 15-mm table speed per rotation and were performed at full inspiration from the lung apex to base. Contiguous CT slices were reconstructed using of a high–spatial frequency algorithm. Sections were displayed at 10-mm intervals throughout the chest with the patient in the supine position and without intravenous contrast medium. The process did not negatively affect the patients' condition. In this study, we evaluated single CT scan acquired at day one of the ARDS diagnosis, because sequential CT scans were hard to be performed after high positive end-expiratory pressure ventilation was introduced. HRCT scans were evaluated on the day of ARDS diagnosis by two independent observers **(K.Fujimoto. and T.J.) who were chest radiologists with 23 and 20 years of experience, respectively, and were**

unaware of patient condition. The presence and extent of areas of ground-glass attenuation, air-space consolidation, traction bronchiectasis, traction bronchiolectasis, and honeycombing were assessed. Ground-glass attenuation was defined as a hazy area with increased opacification without obscuration of underlying vascular markings. Air-space consolidation was considered present when the vascular markings were obscured. When bronchi were irregular in contour, the dilated bronchus within areas of parenchymal abnormality was recognized as traction bronchiectasis. Traction bronchiolectasis was identified by the presence of dilated bronchioles within areas with parenchymal abnormality. Honeycombing was defined as the presence of cystic airspaces measuring 2-10 mm in diameter with well-defined walls.

HRCT findings were graded on a scale of 1-6 based on the classification system correlating with previously described pathology (Fig. 2) [13,15]: 1, normal attenuation; 2, ground-glass attenuation; 3, consolidation; 4, ground-glass attenuation with traction bronchiolectasis or bronchiectasis; 5, consolidation with traction bronchiolectasis or bronchiectasis; 6, honeycombing. The presence of each of these six abnormalities was assessed independently in three (upper, middle, lower) zones of each lung. The upper zone was defined as the area above the level of the carina, the middle zone as the area between the level of the carina and that of the infrapulmonary vein, and the lower zone as the area below the level of the infrapulmonary vein. The extent of each abnormality was determined by visually estimating the percentage (to the nearest

10%) of the affected lung parenchyma in each zone. The assessments of the two observers were averaged. The abnormality score for each zone was calculated by multiplying the percentage area by the point value (1-6). The six zone scores were averaged to determine the total score for each abnormality in each patient. The overall CT score for each patient was obtained by adding the six averaged scores. The scoring system is previously reported [13,15] and has been evaluated in the other diseases[17,18].

Treatment Protocol

All patients underwent a common intensive treatment according to the domestic clinical practical guidelines[19-23]. Antibiotic therapy was performed by these guidelines, which were referenced to the American Thoracic Society/Infectious Diseases Society of America Consensus Guidelines **on the management of community-acquired pneumonia in immunocompetent adults.**[24,25].

While there is contracting reports for a survival benefit, all randomized trials have shown a significant reduction in duration of mechanical ventilation[26-29]. When this study protocol was made, the efficacy of prolonged corticosteroids to the fibroproliferative ARDS had been reported in a small randomized control study[30]. In the current study, we examined the relationship between the efficacy of steroids and the extent of fibroproliferation on HRCT scans. **According to our previous study[15], early fibroproliferation on HRCT scans was observed in 64 % of 44 patients with ARDS. Therefore, we started corticosteroid therapy after performing HRCT scans at the**

diagnosis of ARDS. Initial administration of methylprednisolone with a moderate dose (2 mg/kg/day) (n = 71) or high-dose (1000 mg/day for three days followed by a moderate dose) (n = 14) was introduced and was gradually tapered over one month according to the previous study[30]. Ventilator management and ventilator weaning was introduced by the evidence-based guidelines[22, 23]with reference to the lower tidal volume (V_T) strategy (6 ml/kg predicted body weight (PBW) < V_T < 10 ml/kg PBW) in the ARDS Clinical Trial[31] and to the guidelines for weaning and discontinuing ventilatory support from the American College of Chest Physicians[32].

Screening of ventilator associated outcomes

For each patient, we recorded the number of ventilator-free days. Barotrauma, defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, was noted as present or absent on routine chest radiographs or chest tube insertions for known or suspected spontaneous pneumothorax during the first 28 days[33].

Ventilator associated pneumonia (VAP) surveillance was incorporated into the routine examinations of cultures of sputum obtained using a sterile intratracheal suction tube [34]. VAP was defined as pneumonia occurring after more than 48 hours of mechanical ventilation and for up to 72 hours after weaning.

Organ or system failure

Patients were monitored daily for 28 days for signs of the failure of extrapulmonary organs and systems according to the ARDS Clinical Trial[31]. The

number of days without organ or system failure was calculated by subtracting the number of days with organ failure from the lesser of 28 days or the number of days to death. The Sequential Organ Failure Assessment (SOFA) score was sequentially monitored at Day 7 and 14, except for patients who died within 7 days or 14 days.

Outcome measurements

The primary outcome was mortality 60 days and180 days after ARDS diagnosis. Patients discharged from the hospital while alive for 60 days and180 days were defined as survivors. Non-survivors were defined as patients who died in the hospital. Secondary outcome variables included the number of ventilator-free days, organ failure-free days, the incidence of barotraumas, and the occurrence of ventilator-associated pneumonia.

Statistical analysis

Cox proportional hazards regression analysis was used to examine the influence on survival of 10 % change of radiologically fibroproliferation on HRCT while adjusting for other prognostic clinical factors such as age, severity of illness, non-pulmonary organ dysfunctions, that had been reported [35-37]. Multivariate regression analysis was also performed to assess the impact on ventilator-weaning failure within 28 days, an incidence of barotraumas, and ventilator-associated pneumonia. To analyze the CT score as a predictor of survival, or of the failure of ventilator weaning or of the occurrence of barotrauma within 28 days after the onset of ARDS, we used

receiver-operator characteristic (ROC) curves and the corresponding area under the curve (AUC) to evaluate how the prediction model preformed on the test data and to determine the cutoff value of the CT score yielding the highest sensitivity and specificity which were determined by the Youden index (i.e., sensitivity + specificity – 1). Statistical analyses were performed by using the SPSS package (version 18.0J; SPSS, Tokyo, Japan). For all statistical analyses, $p < 0.05$ was considered significant.

RESULTS

Baseline clinical characteristics

Non-survivors had more severe lung injury with fibroproliferative changes on HRCT scan as shown by their higher HRCT scores than survivors, although non-survivors tended to have less severe multiorgan failure as expressed by their **lower SOFA** scores. No significant differences were seen between survivors and non-survivors in the number of a history of cigarette smoking and a presence of emphysema. No significant differences were also observed in **the ventilatory and medicational conditions** as well (Table 1).

HRCT findings for survivors and non-survivors

The area of increased attenuation associated with traction bronchiolectasis or bronchiectasis, indicative of radiologically fibroproliferation, was observed in 40 (47%) of 85 patients at presentation and was significantly smaller in survivors than in non-survivors (Table 2), whereas the area of increased attenuation without traction bronchiolectasis or bronchiectasis was greater in survivors than in non-survivors. Interobserver variability in evaluation of the presence of lung abnormalities was good (kappa, 0.63-0.83), and the assessments of the extent of abnormality by two different observers also correlated well (Spearman rank correlation coefficient, 0.72; $p < 0.01$).

Prognostic value of the HRCT score

The overall HRCT score of survivors (median ± SD, 195.7 ± 53.7; range,

133.4-325.0) was significantly smaller than that of non-survivors (233.1 ± 46.2; 174.8-384.8). Construction of a ROC curve yielded an optimal cut-off value of the HRCT score of 210 which was determined for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval (CI), 0.61-0.82) and for prediction of survival at Day 180 with 71 % sensitivity and 76 % specificity (AUC, 0.73; 95% CI, 0.62-0.84) (Fig. 3). A significant difference was observed in the 60-day mortality rate between patients with CT score < 210 and those with CT score ≥ 210 ($p < 0.0001$) as well as in the ventilator-free days at day 28 ($p < 0.0001$) (Table 3). The difference in the 60-day mortality rate between patients with more or less fibroproliferative changes on HRCT scan persisted regardless of causes of ARDS (Fig. 4). Multivariate Cox proportional hazards model with adjustment for demographic characteristics, severity of illness, non-pulmonary organ dysfunctions, and HRCT score at diagnosis, the HRCT score remained an independent risk factor for mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36; $p = 0.005$) when expressed as mortality change per 10% increase in the area of attenuation with traction bronchiolectasis or bronchiectasis on HRCT scans (Table 4).

Relation between the HRCT score and the number of ventilator-free days, and the number of organ-failure-free days and sequential changes of SOFA score

An ROC curve determined the best cut-off value of the CT score of 210 for prediction of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 %

specificity (AUC, 0.77; 95% CI, 0.67-0.88) (Fig. 5a). Regardless of significantly higher SOFA score (8.0 ± 3.0 versus 5.0 ± 2.0; $p < 0.0001$) and higher DIC score (2.8 ± 1.5 versus 1.9 ± 1.8; $p < 0.002$) at diagnosis, patients with a CT score of < 210 had a significantly higher number of ventilator-free days (14.0 ± 7.8 versus 5.2 ± 8.0 days; $p < 0.0001$). Those patients with a lower CT score were associated with less severe subsequent multiorgan failure as shown by a significantly higher number of organ-failure-free days (Table 3) and by significant decrease of sequential SOFA score than that of patients with a higher CT score (Fig.7). Multivariate regression analysis, with adjustment for demographic characteristics, general severity, and occurrence of barotraumas, showed that the CT score was independently associated with ventilator-weaning within 28 days with an odds ratio of 0.63 when expressed as weaning failure change per 10% increase in the area of attenuation with traction bronchiolectasis or bronchiectasis on HRCT scans ($p = 0.0006$) (Table 5a).

Relation between the HRCT score and the incidence of barotraumas or ventilator-associated pneumonia

All eleven patients with barotrauma had pneumothorax. Barotrauma occurred 3-28 days (mean ± SD, 12.7 ± 9.4 days) after ARDS onset. An ROC curve identified the optimal cutoff value of the CT score of 235 for prediction of barotrauma onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95% CI, 0.59-0.95) (Fig. 6a). Patients with the CT score < 235 had a significantly lower incidence of barotrauma (5.0

versus 32.0 %; p = 0.0019) within 28 days after the onset of ARDS than those with CT score of ≥ 235 (Fig. 5b). The CT score was also independently associated with the occurrence of barotraumas with an odds ratio of 1.61 by multivariate regression analysis (p = 0.018) (Table 6b). Ventilator-associated pneumonia (VAP) was documented in 36 patients (42.3%) after day 5 since ARDS onset. The percentage of patients complicated with VAP in the higher CT score group tended to be higher than those in the lower CT score groups (51.4 and 35.4 percent, respectively; p = 0.14). Multivariate analysis also demonstrated that the CT score was independently associated with the complication of VAP with an odds ratio of 1.46 (p = 0.0041) (Table 5c).

DISCUSSION

Regardless of the cause of ARDS, we found the extent of fibroproliferative changes on HRCT at diagnosis of ARDS was an independent predictive factor for survival and ventilator dependency. Furthermore, patients with extensive fibroproliferative changes on HRCT scan were more susceptible to associated multiorgan failure, barotraumas and ventilator-associated pneumonia than those with less extensive changes. Semi-quantitative determination of fibroproliferation by means of HRCT assessment was informative with regard to the potential not only for response to treatment but also for susceptibility to subsequent ventilator-associated outcomes (ventilator dependency, barotraumas, and ventilator-associated pneumonia).

Biochemical evidence of fibroproliferation is present early in the acute lung injury process. N-terminal procollagen peptide III (N-PCP-III) is a marker of collagen turnover and is elevated in bronchoalveolar lavage (BAL) fluid and tracheal aspirate from ARDS patients within 24 h of diagnosis [7-10] The increased N-PCP-III concentration in BALF at diagnosis was associated with poor prognosis, suggesting that pulmonary early fibroproliferation is an important determinant of outcome [7-10]. In the present study, traction bronchiectasis within areas of increased attenuation, suggesting radiologically fibroproliferation, was already detectable on HRCT scans obtained on the day of ARDS onset in 40 patients (47%). **We also confirmed that HRCT findings of early and late phase of ARDS frequently overlapped.** These results supported the

previous reports and suggested that a clinically early time point does not necessarily correspond to a pathologically early phase of ARDS. Given that no significant difference in the cause of ARDS was apparent between the survivors and non-survivors in this study, no correlation between the HRCT score and the clinical duration of ARDS may also be attributable to differences in individual sensitivity to lung injury and in the intensity of the consequent exaggerated inflammation that occurs between the onset of injury and progression to ARDS. The term "fibroproliferative" ARDS may not necessarily apply only to "late phase" ARDS but possibly also to "early phase". Accordingly, extent of fibroproliferative changes on HRCT scan, together with N-PCP-III concentration in BALF, may be a potential clue to differentiate "real" late ARDS from the early one.

Currently, there have been few prospective clinical studies to validate the susceptibility to ventilator-associated outcomes. The ARDS Network low tidal volume study has suggested that excessive large tidal ventilation induces inflammatory cytokines and is associated with a known risk factor for ventilator associated lung injury[27]. In the present study, patients with extensive fibroproliferation shown as higher HRCT score on the day of ARDS onset needed a longer duration of mechanical ventilation with subsequent ventilator-associated pneumonia and had shorter organ-failure free days, and subsequently suffered from multiple organ failure.

Barotraumas occurring in critically ill patients independently affects intensive care unit mortality [38]. Barotrauma events occur late in the course of ARDS and are related to lung structural changes such as cystic or fibroproliferative lesions that develop over time [39]. In our study, barotrauma occurred more than 10 days (mean ± SD, 12.7 ± 9.4 days) after the onset of ARDS and was more frequent in patients with a higher HRCT score (score ≥ 235) than in those with a lower HRCT score (score < 235) during the first 28 days. Given that a higher HRCT score at diagnosis suggests advanced fibroproliferation, our data support the relationship between pulmonary fibroproliferation and its susceptibility to barotraumas.

Ventilator-associated pneumonia (VAP) has been a causative factor of subsequent systemic inflammatory syndrome resulting in multi-organ failure[33]. The risk of VAP increases with prolonged mechanical ventilation[34]. **Furthermore, sustained and intense inflammatory responses in unresolving ARDS increase the bi-directional effects on bacterial growth[40]**. More extensive fibroproliferative changes on HRCT scan shown as a higher CT score were associated with a longer ventilator dependency that was more susceptible to VAP onset. These results support that pulmonary fibroproliferation of ARDS increases risk for ventilator dependency and its associated complications.

In a previous study of 45 cases of ARDS confirmed at biopsy, patients whose conditions were shown histologically to be in the acute exudative phase had a better

prognosis than did those whose condition was shown to be in the fibroproliferative phases [41]. **Persistent dysregulated systemic inflammation leading to maladaptive lung repair results in pulmonary fibroproliferation and progression of extrapulmonary organ dysfunction[29]. Prolonged corticosteroid therapy attenuates systemic inflammation and reduced duration of mechanical ventilation[29].** In our study, the group of patients who had less fibroproliferative changes on HRCT scans (HRCT score, < 210) showed lower mortality and more ventilator-free days than those who had more extensive areas of fibroproliferation (HRCT score, ≥ 210). This may suggest a relationship between the pathologic phases of ARDS and responsiveness to treatment. **More extensive and rapidly progressive pulmonary fibroproliferation resulting from intense exaggerated systemic inflammation at presentation occurs, less effective even prolonged corticosteroid therapy may be.** Whether the patients with fibroproliferative predominance have different treatment strategies compared to those with exudative predominance has been a vexing question [4]. Improving our understanding of disease state and evolution of the disease may be key to the development of the optimal therapy and their timing. A method that could be used to evaluate and calibrate the clinical to pathologic stages may help prognosticate, alter supportive or therapeutic approach to ARDS such as ventilator management and define the treatment window for those interventions. Further prospective studies are needed to examine the efficacy of the drugs such as corticosteroids according to the extent of

fibroproliferation on HRCT scans.

There were some potential limitations. First, our study included few patients with ARDS caused by major trauma, multiple transfusion and others, although it included approximately 90% of the patients who had ARDS caused by three major etiologies (pneumonia, aspiration, sepsis) of ARDS; thus, our study may not sufficiently reflect all forms of ARDS. However, previous large randomized control studies also included more than 70% of patients with these three etiologies [26, 31]. Therefore, our results may be applicable to most forms of ARDS.

Second, many elderly patients (mean age, 75.0 years) were included. Clinically, elderly ARDS patients show higher morbidity and need longer duration of mechanical ventilation with subsequent poorer prognosis than the younger patients [2, 37]. The age-related differences in mortality and outcomes have been considered to be due to the greater number of comorbid illness and higher frequency of non-pulmonary organ system failure in older patients [37]. In this study, preexisting pulmonary emphysema was seen in 32 (38 %) of 85 patients. Although no significant differences were seen between survivors and non-survivors in the number of a history of cigarette smoking and a presence of emphysema, we could not evaluate the severity of emphysema before the onset of ARDS. Such a smoking-induced chronic lung disease could potentially affect ventilator-dependency or prognosis. Although it was problematic whether aging increase susceptibility to lung injury and to pulmonary fibroproliferation, further

investigation of younger patients with ARDS is needed to confirm the consistency of the results of our study.

Third, no correlation was provided with either clinical parameters or pathologic findings in the present study. Further investigation is necessary to compare HRCT findings with other predictors of mobidity/mortality-i.e. inflammatory biomarkers such as serum IL-6 or BAL PCP III levels. Recent studies of biopsy findings from ARDS patients have reported the pathologic diversity and only half proportion of typical diffuse alveolar damage [5,6]. Regardless of the cause or pathology of ARDS, our study highlighted the extent of lung architectural distortion (areas with traction bronchiectasis) indicating that pulmonary fibroproliferation on HRCT scans. Although fibroproliferative ARDS does not warrant different treatment strategies up to the present, prospective evaluation of HRCT findings in patients with ARDS would help therapeutic implications in the development of treatment strategies based on the extent of fibroproliferation, as well as its prognostic implications.

Fourth, when using our cutoff values of HRCT scores, there were approximately 25 % of our patients who did not fit for prediction of poor prognosis or ventilator dependency. Recently, multiple organ failure in ARDS patients is considered to be either as the predisposing condition or as a consequence of ARDS[42]. If ARDS occurs as one of multiple organ failure, even though pulmonary fibroproliferation was mild, extra-pulmonary dysfunction

could be the determinant of the outcome.

On the basis of our results, extensive HRCT abnormalities indicative of fibroproliferative changes on the day of ARDS diagnosis were independently predictive of poor prognosis and prolonged mechanical ventilation, and were also associated with subsequent multiple organ failure. Pulmonary fibroproliferation that occurs early in ARDS patients increases mortality risk by increasing susceptibility to ventilator dependency and its associated complications.

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Table 1. Clinical characteristics of patients on the day of ARDS onset

Characteristic	Total (n = 85)	60 days Outcomes		p value
		Survivors (n = 54)	Non-survivors (n = 31)	
Age (years)*	75 ± 10	75 ± 11	76 ± 10	0.60
Sex (M/F)	51/34	30/24	21/10	0.38
Cigarette smoking	33	17	16	0.11
Presence of emphysema	32	18	14	0.39
Liver cirrhosis (%)	6 (7.1)	4 (7.4)	2 (6.5)	> 0.99
Direct/indirect injury	59/26	38/16	21/10	0.81
PaO_2:FiO_2	96.2 ± 45.6	96.5 ± 45.0	96.2 ± 47.5	0.90
Causes of lung injury				
Pneumonia (%)	32 (37.6)	20	12	> 0.99
Sepsis (%)	24 (28.2)	13	11	0.38
Pulmonary (%)	11 (12.9)	5	6	0.20
Extrapulmonary (%)	13 (15.2)	8	5	> 0.99
Aspiration (%)	22 (25.9)	16	6	0.44
Others (%)	7 (8.2)	5	2	> 0.99
Lung injury score*	3.2 ± 0.5	3.3 ± 0.5	3.3 ± 0.5	0.88
APACHE II score	21.0 ± 4.7	21.0 ± 4.6	22.0 ± 4.9	0.76
SOFA score	7.0 ± 2.8	7.0 ± 2.8	6.0 ± 2.9	0.15
McCabe score (1/2/3)	78/5/2	49/4/1	29/1/1	> 0.99
DIC score*#	2.4 ± 1.7	2.4 ± 1.7	2.5 ± 1.6	0.68
White blood cell count (per mm^3)	10600 ± 6788	10600 ± 6178	10600 ± 7839	0.63

C-reactive protein (CRP) (mg/dl)	15.4 ± 10.3	15.4 ± 9.6	16.1 ± 11.5	0.69
Albumin (g/dl)	3.0 ± 0.5	3.1 ± 0.5	2.8 ± 0.5	0.11
Lactate dehydrogenase (LDH) (IU/L)	308 ± 185	301 ± 147	339 ± 235	0.29
Platelet count (per mm^3)	20.1 ± 10.7	20.7 ± 11.0	18.9 ± 10.3	0.94
Days of CT scanning from ARDS onset (day)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	> 0.99
HRCT score #	207 ± 53	196 ± 54	233 ± 46	0.001
Initial steroid therapy				
High dose	14	7	7	0.36
Low dose	71	47	24	0.36
Ventilatory variables				
Tidal volume, ml/kg predicted body weight	8.0 ± 0.8	8.0 ± 0.7	8.0 ± 0.9	0.54
Plateau pressure, cmH_2O	21.5 ± 4.2	21.0 ± 3.8	23.0 ± 4.7	0.34
Initial PEEP, cmH_2O	8.0 ± 3.4	8.0 ± 2.5	8.0 ± 4.3	0.18

Data are expressed as median ± standard deviation. *Data are mean ± standard deviation. The p values refer to comparisons between survivors and non-survivors.

Score ≥ 4 defined as disseminated intravascular coagulation from scoring system for The Japanese Association for Acute Medicine.

Table 2. Extent of each high-resolution CT finding in 60-days survivors and non-survivors of ARDS.

CT Finding	Survivors (n = 54)	Non-survivors (n = 31)	p value
Spared area	37.0 ± 19.2	30.3 ± 14.9	0.15
Ground-glass attenuation	33.5 ± 22.9	30.0 ± 16.0	0.70
Air-space consolidation	17.5 ± 13.8	18.3 ± 19.3	0.72
Total area without traction bronchiolectasis or bronchiectasis	88.0 ± 22.0	78.2 ± 22.5	0.01
Ground-glass attenuation plus traction bronchiolectasis or bronchiectasis	9.3 ± 17.8	16.6 ± 21.7	0.08
Air-space consolidation plus traction bronchiolectasis or bronchiectasis	2.4 ± 7.8	5.6 ± 10.3	0.01
Honeycombing	0.0 ± 0.0	0.0 ± 0.0	NS
Total area with traction bronchiolectasis or bronchiectasis	11.8 ± 18.0	22.1 ± 24.3	0.01

Data are mean ± standard deviation of percentage of lung involvement.

NS = not significant

Mann-Whitney U test

Table 3. Comparison of primary and secondary outcomes between the cut-off value showing extent of fibroproliferative changes on high-resoluiton CT at the onset of ARDS

Variable	High-Resolution Computed Tomographic (CT) score		p value
	< 210 (n = 47)	≥ 210 (n = 38)	
60-Day mortality (%)	19.1	57.9	< 0.0001
No. of hospital death	9	22	
Causes of death			
Multiple organ failure	8	18	
Respiratory failure	1	4	
No. of ventilator-free days at day 28	14.3 ± 7.6	5.1 ± 8.0	< 0.0001
No. of organ-failure-free days			
Cardiovascular failure	22.4 ± 8.1	16.1 ± 10.9	0.009
Coagulation abnormalities	23.0 ± 8.9	17.8 ± 10.4	0.017
Hepatic failure	23.3 ± 8.2	19.6 ± 9.5	0.11
Renal failure	21.7 ± 10.9	19.6 ± 9.6	0.29
No. of incidence of barotraumas (%)	3 (6.4)	8 (21.1)	0.056
No. of ventilator-associated pneumonia (%)	16 (34.0)	20 (52.6)	0.13

Plus-minus values are mean ± SD. Continuous variables with non-normal distribution were compared with the use of Mann-Whitney U test and categorical variables with Fisher's exact test.

Table 4a. Univariate Cox regression analysis of variables potentially associated with mortality at day 180 in patients with ARDS.

Variable	P value	Hazard ratio	95% CI
HRCT score	0.0019	1.22*	1.08-1.38
Age	0.5411	0.99	0.96-1.02
Sepsis	0.4020	1.34	0.67-2.67
APACHE II score	0.6578	0.98	0.92-1.06
SOFA score	0.1724	0.92	0.82-1.04
McCabe score	0.9609	0.98	0.41-2.32
PaO_2 / FiO_2 ratio	0.6119	1.00	0.99-1.01
Serum Albumin	0.0982	0.57	0.30-1.11

Table 4b. Multivariate Cox regression analysis of prognostic factors associated with mortality at day 180 in patients with ARDS

Variable	P value	Hazard ratio	95% CI
HRCT score	0.0051	1.20*	1.06-1.36
Serum Albumin	0.2618	0.67	0.33-1.36

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5. Multiple logistic regression analysis of variables potentially associated with ventilator-associated outcomes.

Table 5a. Ventilator-weaning within 28 days in patients with ARDS.

Variable	P value	Odds ratio	95% CI
HRCT score	0.0006	0.63*	0.48-0.82
Serum Albumin	0.1727	2.09	0.72-6.03

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5b. The incidence of the Barotrauma

Variable	P value	Odds ratio	95% CI
HRCT score	0.0183	1.61*	1.08-2.38
APACHE II	0.4724	0.92	0.74-1.15
SOFA score	0.9110	1.02	0.68-1.55
Serum Albumin	0.5156	0.53	0.08-3.65
Serum LDH	0.0158	1.05	1.01-1.09

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5c. The complication of the Ventilator-associated pneumonia

Variable	P value	Odds ratio	95% CI
Liver cirrhosis	0.0286	13.34	1.31-135.60
HRCT score	0.0041	1.46*	1.13-1.89
PaO_2 / FiO_2 ratio	0.0236	0.99	0.98-1.00

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

FIGURE LEGENDS

Figure 1. Outlines of the study.

Figure 2. High-resolution computed tomography (CT) findings correlated with pathology

a.: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation without traction bronchiectasis and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumonia.*

b.: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis (arrows). The patient was a 84-year-old woman with ARDS due to sepsis.

c.: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old woman with ARDS due to *viral pneumonia.* (Sequential changes of HRCT findings were shown in the supplemental figure.)

Figure 3. Receiver operator characteristic (ROC) curve of prognostic value of the high-resolution computed tomography (HRCT) score. ROC identified the optimal cut-off value of 210 determined by the Youden Index for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval, 0.61-0.82) and for prediction of survival at Day 180 with 71% sensitivity and 76 % specificity (AUC, 0.73; 95%CI, 0.62-0.84).

Figure 4a. Day 60-mortality rate of each major cause of ARDS.

Figure 4b. Day 60-mortality rate compared between the optimal cut-off value of high-resolution computed tomography (HRCT) score in each cause. Regardless of the cause, the mortality rate of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

Figure 5. Receiver operator characteristic (ROC) curve of prediction of the ventilator weaning within 28 days from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 210 determined by the Youden Index for prediction of ventilator weaning at day 28 with 75 % sensitivity and 76 % specificity (AUC, 0.77; 95%CI, 0.67-0.88).

Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumas onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95%CI, 0.59-0.95)

Figure 6b. Comparison of the incidence of barotraumas between patients with the optimal cut-off value of CT score identified from ROC curve. The incidence of barotrauma of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

Figure 7. Sequential changes of Sequential Organ Failure Assessment (SOFA) scores. The SOFA score of a patient with a lower CT score (< 210) significantly decreased from day 1 to day 14 ($p = 0.0016$). The SOFA score of a patient of a patient with a higher CT

score (≥ 210) significantly increased from day 1 to day 14 (p = 0.027). Four patients with a lower CT score (< 210) and 9 patients with a higher CT score (≥ 210) who died within 14 days were excluded.

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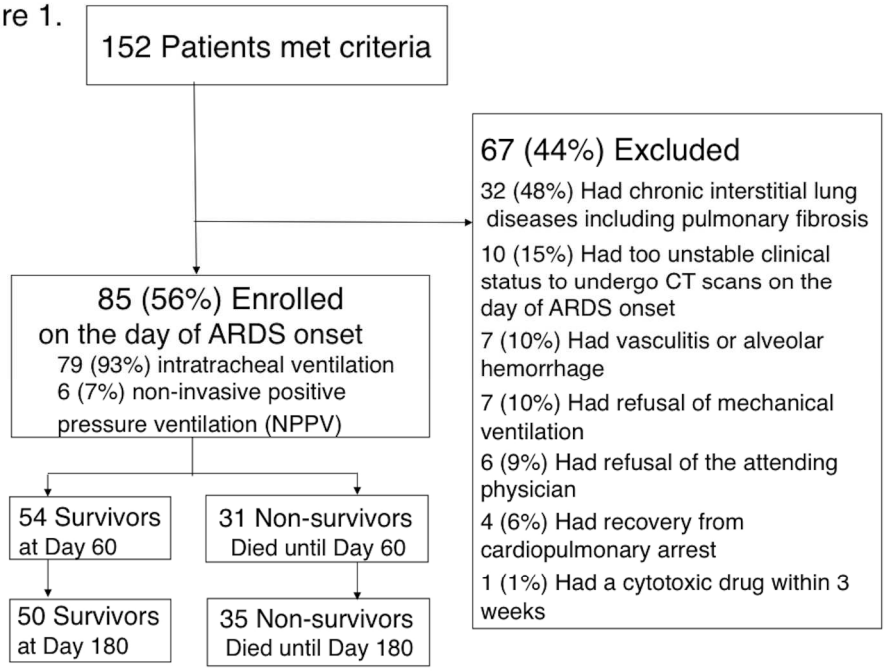
Patient confidentiality

Details has been removed from this case description.

Figure 1.



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Fibroproliferative Changes on High-Resolution Computed Tomography in the Acute Respiratory Distress Syndrome Predict Mortality and Ventilator Dependency: A Prospective Observational Cohort Study

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Primary Subject Heading:	Respiratory medicine

Secondary Subject Heading:	Intensive care, Radiology and imaging
Keywords:	Adult intensive & critical care < ANAESTHETICS, Thoracic medicine < INTERNAL MEDICINE, Chest imaging < RADIOLOGY & IMAGING

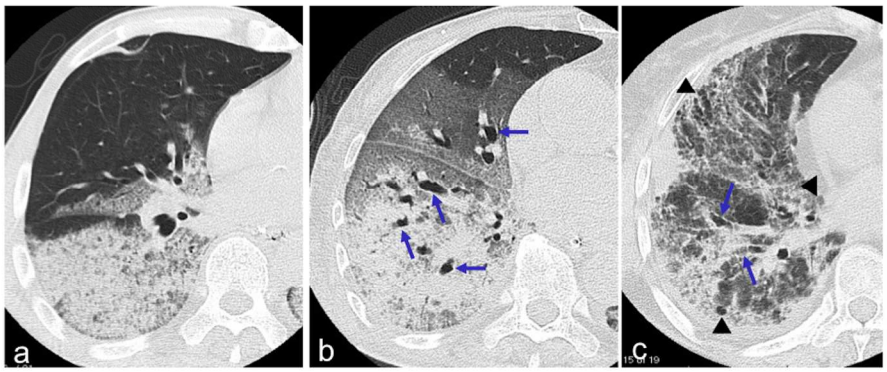

Figure 2a: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumoniae* pneumonia.

Figure 2b: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis(arrows). The patient was a 84-year-old woman with ARDS due to *sepsis*.

Figure 2c: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old woman with ARDS due to *viral pneumonia*. (Sequential changes of HRCT findings were shown in the supplemental figure.)

High-resolution computed tomography (CT) findings correlated with pathology
a.: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation without traction bronchiectasis and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to Streptococcus pneumonia.
b.: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis (arrows). The patient was a 84-year-old woman with ARDS due to sepsis.
c.: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation
associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old woman with ARDS due to viral pneumonia. (Sequential changes of HRCT findings were shown in the supplemental figure.)

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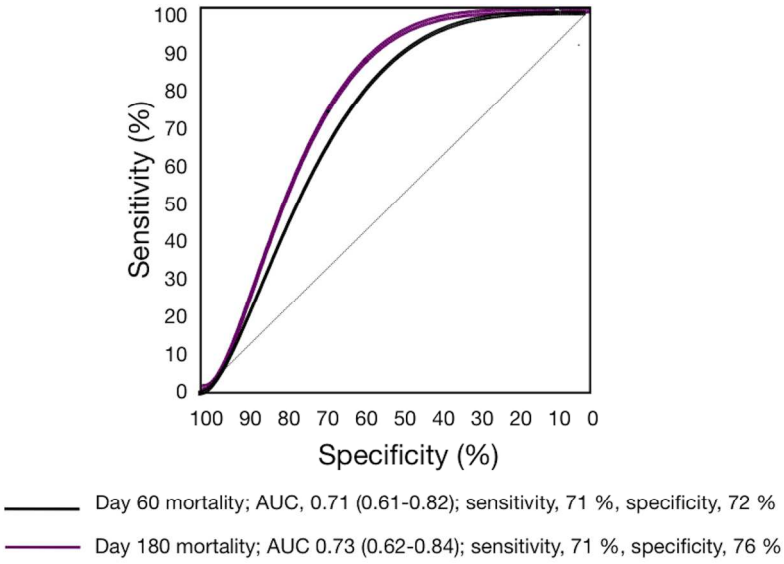
Figure 3 Receiver Operating Characteristic Curve of the prediction of Day 60 and Day 180 mortality



Receiver operator characteristic (ROC) curve of prognostic value of the high-resolution computed tomography (HRCT) score. ROC identified the optimal cut-off value of 210 determined by the Youden Index for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval, 0.61-0.82) and for prediction of survival at Day 180 with 71% sensitivity and 76 % specificity (AUC, 0.73; 95%CI, 0.62-0.84).
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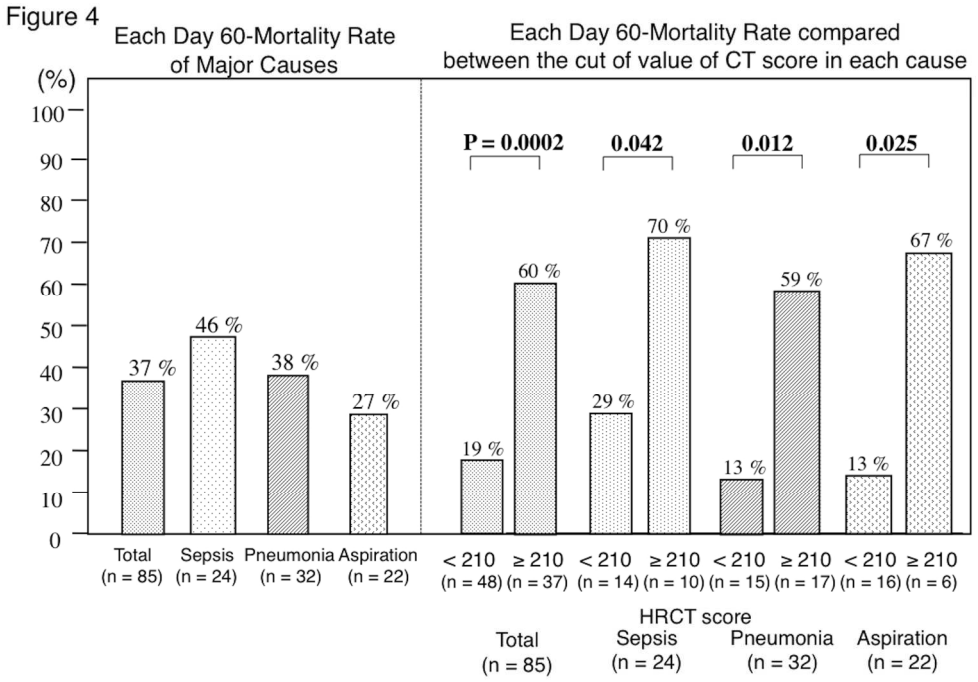

Figure 4a. Day 60-mortality rate of each major cause of ARDS.

Figure 4b. Day 60-mortality rate compared between the optimal cut-off value of high-resolution computed tomography (HRCT) score in each cause. Regardless of the cause, the mortality rate of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

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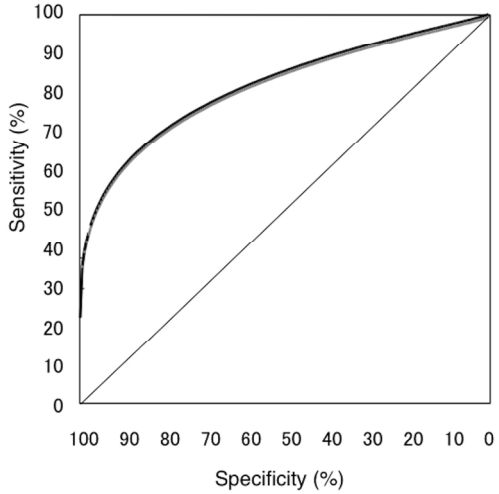
Figure 5
Receiver Operating Characteristic Curve of the prediction of ventilator weaning during 28 days



AUC, 0.77 (0.67-0.88); sensitivity, 75 %, specificity, 76 %

Receiver operator characteristic (ROC) curve of prediction of the ventilator weaning within 28 days from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 210 determined by the Youden Index for prediction of ventilator weaning at day 28 with 75 % sensitivity and 76 % specificity (AUC, 0.77; 95%CI, 0.67-0.88).
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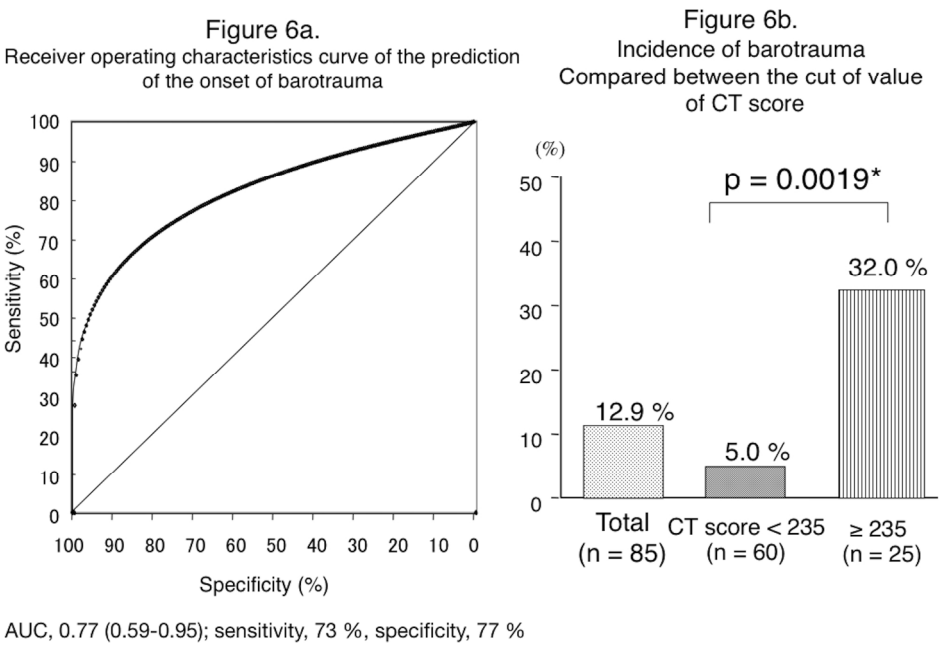

Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumas onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95%CI, 0.59-0.95)

Figure 6b. Comparison of the incidence of barotraumas between patients with the optimal cut-off value of CT score identified from ROC curve. The incidence of barotrauma of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

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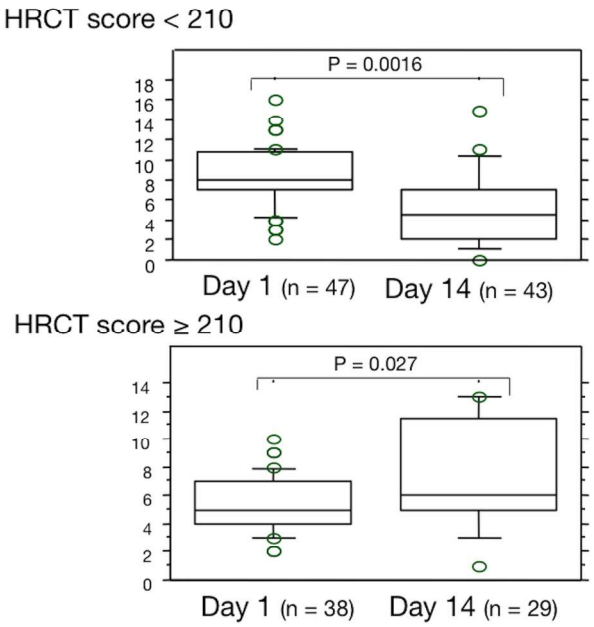
Figure 7. Sequential changes of SOFA score



Sequential changes of Sequential Organ Failure Assessment (SOFA) scores. The SOFA score of a patient with a lower CT score (< 210) significantly decreased from day 1 to day 14 (p = 0.0016). The SOFA score of a patient of a patient with a higher CT score (≥ 210) significantly increased from day 1 to day 14 (p = 0.027). Four patients with a lower CT score (< 210) and 9 patients with a higher CT score (≥ 210) who died within 14 days were excluded.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

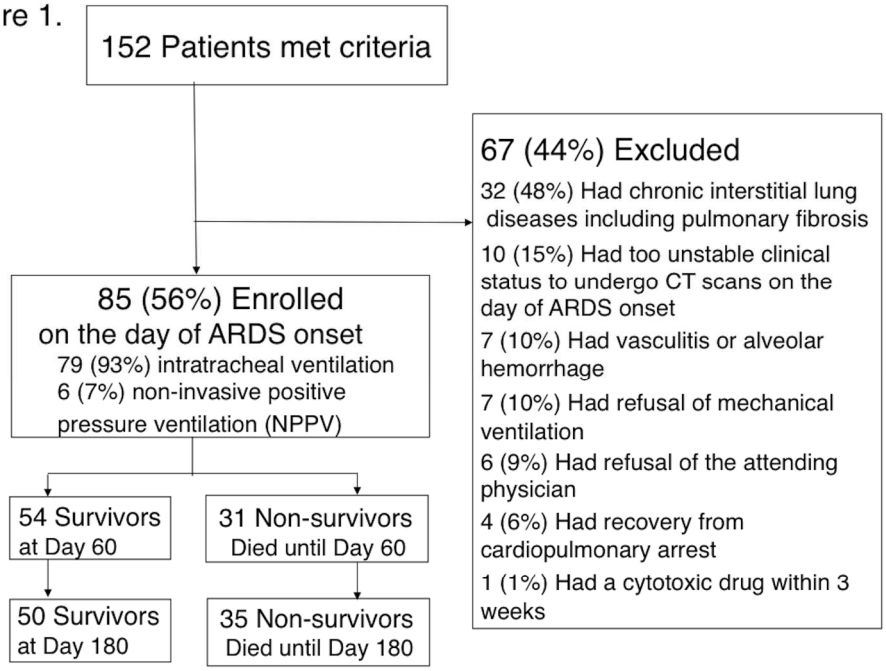
Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 4
Introduction			**Page 7-8**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 8
Methods			**Page 8-13**
Study design	4	Present key elements of study design early in the paper	Page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 8, 12
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 26, Table 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 8-12
Bias	9	Describe any efforts to address potential sources of bias	Page 8
Study size	10	Explain how the study size was arrived at	Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 8-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 13
		(*b*) Describe any methods used to examine subgroups and interactions	Page 13
		(*c*) Explain how missing data were addressed	Figure 1
		(*d*) If applicable, explain how loss to follow-up was addressed	Figure 1
		(*e*) Describe any sensitivity analyses	Page 13
Results			Page 14-17

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 14, Figure 1
		(b) Give reasons for non-participation at each stage	Page 14, Figure 1
		(c) Consider use of a flow diagram	Page 14, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 26, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 29, Table 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 30-32,Table 4-5
		(*b*) Report category boundaries when continuous variables were categorized	Page 29, Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 30-32, Table 4-5
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 3-7
Discussion			Page 18-23
Key results	18	Summarise key results with reference to study objectives	Page 3
Limitations			Page 21-23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 3
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 21-23
Other information			Page 2, 24-25, 41
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 5

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Figure 1.



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Fibroproliferative Changes on High-Resolution Computed Tomography in the Acute Respiratory Distress Syndrome Predict Mortality and Ventilator Dependency: A Prospective Observational Cohort Study

Kazuya Ichikado, MD, PhD[1], Hiroyuki Muranaka, MD, PhD[1], Yasuhiro Gushima, MD, PhD[1], Toru Kotani, MD[2], Habashi M. Nader, MD[3], Kiminori Fujimoto, MD, PhD[4], Takeshi Johkoh, MD, PhD[5], Norihiro Iwamoto, MD, PhD[1], Kodai Kawamura, MD, PhD[1], , Junji Nagano, MD, PhD[6], Kohichiro Fukuda, MD, PhD [6], Naomi Hirata, MD, PhD[7], Takeshi Yoshinaga, MD, PhD[7], Hidenori Ichiyasu, MD, PhD[8], Shinsuke Tsumura, MD[8], Hirotsugu Kohrogi, MD, PhD[8], Atsushi Kawaguchi, PhD[9], Masakazu Yoshioka, MD[1], Tsutomu Sakuma, MD, PhD[10], Moritaka Suga, MD, PhD[1]

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Conflict of interest disclosures: None of the authors has declared any conflict of interest related to this work.

Keywords

acute respiratory distress syndrome, high-resolution computed tomography, ventilator-associated lung injury, corticosteroids

1) Article Focus

• Whether the extent of fibroproliferation on high-resolution CT (HRCT) scan at the time diagnosis of ARDS would impact 60-day and 180-day mortality?

• Whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact ventilator dependency and its associated outcomes?

• Whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact multiple-organ failure?

2) Key Messages

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts increased mortality.

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts ventilator dependency and its associated outcomes (barotraumas, ventilator-associated pneumonia).

• Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS increases susceptibility to multiple organ failure.

3) Strengths and Limitations

• The CT score is based on our previous published studies correlating HRCT findings with pathology and has been evaluated in the other diseases.

• a relatively small number of patients from a single institution

• lack of correlation with either clinical parameters or pathologic findings

Objectives: To examine whether the extent of fibroproliferative changes on high-resolution computed tomography (HRCT) scan influences prognosis, ventilator dependency, and the associated outcomes in patients with early acute respiratory distress syndrome (ARDS).

Design: A prospective observational cohort study

Setting: Intensive care unit in a teaching hospital

Participants: Eighty-five patients with ARDS who met American-European Consensus Conference Criteria and eligible criteria.

Interventions: HRCT scans were performed and prospectively evaluated by two independent observers on the day of diagnosis and graded into six findings according to the extent of fibroproliferation. An overall HRCT score was obtained by previously published method.

Primary and secondary outcomes: The primary outcome was 60-day mortality. Secondary outcomes included the number of ventilator-free days, organ failure-free days, the incidence of barotraumas, and the occurrence of ventilator-associated pneumonia.

Results: Higher HRCT scores were associated with statistically significant decreases in organ-failure free days as well as ventilator-free days. Multivariate Cox proportional hazards model showed that the HRCT score remained an independent risk factor for mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36; p = 0.005).

Multivariate analysis also revealed that the CT score had predictive value for ventilator-weaning within 28 days (odds ratio 0.63; 95% CI 0.48, 0.82; p = 0.0006) as well as for an incidence of barotraumas (1.61; 95%CI 1.08, 2.38; p = 0.018) and for an occurrence of ventilator-associated pneumonia (1.46; 95%CI 1.13,1.89; p = 0.004). **An HRCT score < 210 enabled prediction of 60 day survival with 71 % sensitivity and 72 % specificity** and of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 % specificity.

Conclusions: Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts increased mortality with an increased susceptibility to multiple organ failure, including ventilator dependency and its associated outcomes.

Data sharing statement

There is no additional data available.

Research grant

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Abbreviation list

ARDS: acute respiratory distress syndrome

HRCT: high-resolution computed tomography

DAD: diffuse alveolar damage

APACHE II: Acute Physiology and Chronic Health Evaluation II score

SOFA score: Sequential Organ Failure Assessment score

MOF: multi-organ failure

DIC: disseminated intravascular coagulation

MDCT: multidetector-row computed tomography

PEEP: positive end-expiratory pressure

VAP: ventilator associated pneumonia

ROC: receiver-operator characteristic

AUC: area under the curve

CI: confidence interval

SD: standard deviation

INTRODUCTION

The acute respiratory distress syndrome (ARDS) is the most severe form of a wide spectrum of pathological conditions designated as acute lung injury [1,2]. ARDS is considered to have an early and a late phase and is pathologically classified into three stages[3] in which an initial inflammatory injury with protein-rich edema and hemorrhage is followed by fibroproliferation, during which fibroblasts proliferate with organization and subsequent collagen deposition, resulting in lung remodeling, ultimately leading to fibrotic lung disease. The histological features of ARDS represent a poorly defined time-dependent stereotypic response to acute lung injury and are pathologically designated as diffuse alveolar damage[3,4]. **Fibroproliferation is part of the tissue host defense response – a tissue-protective reaction that consists of an integrated network of three simultaneously activated pathways [inflammation, coagulation, and tissue repair (finbroproliferation is one component of tissue repair)], which account for the histologic and physiologic changes observed with progression (maladaptive response) or resolution (adaptive response) of ARDS and multiple organ failure syndrome[5]. Although pathologic staging may be conceptually useful, improvement vs. worsening in physiological parameters (i.e., PaO_2/FiO_2 ratio, etc) over time correlates with adaptive vs. maladaptive lung repair and outcome.** Clinicians can use pathophysiology (shunt vs. V/Q mismatch with increasing deadspace) to distinguish the transition from exudative to fibroproliferative ARDS,

however, few features, except probably time, allow them to distinguish these pathological phases without a lung biopsy [6,7].

Data regarding the significance of a fibroproliferative response on mortality risk assessed using bronchoalveolar lavage or tracheal aspirate in ARDS patients is available [8-11]. High-resolution computed tomographic (HRCT) findings correlate with the pathologic phases of diffuse alveolar damage [12-15]. Furthermore, we have previously reported on the prognostic value of HRCT in determining the extent of fibroproliferation in ARDS patients[16]. Based on HRCT appearance, less fibroproliferation in early ARDS was associated with greater ventilator-free days and less barotraumas[16]. **Because ARDS is a systemic disease with systemic inflammation, core pathogenetic process affects the lung as well as extra-pulmonary vital organs. In this prospective study, we evaluated not only what was found in the retrospective study[16] but also the relationship between early fibroproliferation and the progression to multiple organ failure**; whether the extent of fibroproliferation on HRCT scan at the time diagnosis of ARDS would impact the susceptibility for ventilator dependency and its associated complications and on the mortality.

METHODS

One hundred and fifty two patients with ARDS diagnosed according to the American-European Consensus Conference Criteria[17] were enrolled from October 1, 2004 to July 31, 2008 at our institution. This study was approved by an institutional

review board of our hospital, and informed consent was obtained from the participants or their families. On the basis of the survival in our retrospective study of 44 patients[16], we designated the number of patients more than 80 at least.

Patients

Eligible patients were receiving mechanical ventilation by tracheal tube (n = 79) or mask for non-invasive positive pressure ventilation (n = 6). Furthermore, HRCT scan was performed on the day of diagnosis of ARDS by their consent. Exclusion criteria were shown in Figure. 1. Especially, preexisting chronic interstitial lung diseases were strictly excluded by history taking, imaging data available before onset of ARDS, and the presence of coarse reticulation and honeycombing on HRCT scans suggesting of chronic pulmonary fibrosis. Furthermore, the other preexisting pulmonary disease such as pulmonary emphysema was documented from review of radiological reports. Information about our patients' severity and characteristics is reported in Table 1.

HRCT examination, assessment, and scoring

All patients underwent whole lung volumetric HRCT scanning of the chest on the day of diagnosis of ARDS using a multidetector-row CT (MDCT) scan. All MDCT scans were obtained with 2-mm thickness and 15-mm table speed per rotation and were performed at full inspiration from the lung apex to base. Contiguous CT slices were reconstructed using of a high–spatial frequency algorithm. Sections were displayed at 10-mm intervals throughout the chest with the patient in the supine position and without

intravenous contrast medium. The process did not negatively affect the patients' condition. In this study, we evaluated single CT scan acquired at day one of the ARDS diagnosis, because sequential CT scans were hard to be performed after high positive end-expiratory pressure ventilation was introduced. HRCT scans were evaluated on the day of ARDS diagnosis by two independent observers (K.Fujimoto. and T.J.) who were chest radiologists with 23 and 20 years of experience, respectively, and were unaware of patient condition. The presence and extent of areas of ground-glass attenuation, air-space consolidation, traction bronchiectasis, traction bronchiolectasis, and honeycombing were assessed. Ground-glass attenuation was defined as a hazy area with increased opacification without obscuration of underlying vascular markings. Air-space consolidation was considered present when the vascular markings were obscured. When bronchi were irregular in contour, the dilated bronchus within areas of parenchymal abnormality was recognized as traction bronchiectasis. Traction bronchiolectasis was identified by the presence of dilated bronchioles within areas with parenchymal abnormality. Honeycombing was defined as the presence of cystic airspaces measuring 2-10 mm in diameter with well-defined walls.

HRCT findings were graded on a scale of 1-6 based on the classification system correlating with previously described pathology (Fig. 2) [14,16]: 1, normal attenuation; 2, ground-glass attenuation; 3, consolidation; 4, ground-glass attenuation with traction bronchiolectasis or bronchiectasis; 5, consolidation with traction

bronchiolectasis or bronchiectasis; 6, honeycombing. The presence of each of these six abnormalities was assessed independently in three (upper, middle, lower) zones of each lung. The upper zone was defined as the area above the level of the carina, the middle zone as the area between the level of the carina and that of the infrapulmonary vein, and the lower zone as the area below the level of the infrapulmonary vein. The extent of each abnormality was determined by visually estimating the percentage (to the nearest 10%) of the affected lung parenchyma in each zone. The assessments of the two observers were averaged. The abnormality score for each zone was calculated by multiplying the percentage area by the point value (1-6). The six zone scores were averaged to determine the total score for each abnormality in each patient. The overall CT score for each patient was obtained by adding the six averaged scores. The scoring system is previously reported [14,16] and has been evaluated in the other diseases[18,19].

Treatment Protocol

All patients underwent a common intensive treatment according to the domestic clinical practical guidelines[20-24]. Antibiotic therapy was performed by these guidelines, which were referenced to the American Thoracic Society/Infectious Diseases Society of America Consensus Guidelines on the management of community-acquired pneumonia in immunocompetent adults.[25,26].

While there is contradicting reports for a survival benefit, all randomized trials have shown a significant reduction in duration of mechanical ventilation[27-30].

When this study protocol was made, the efficacy of prolonged corticosteroids to the fibroproliferative ARDS had been reported in a small randomized control study[30]. In the current study, we examined the relationship between the efficacy of steroids and the extent of fibroproliferation on HRCT scans. According to our previous study[16], early fibroproliferation on HRCT scans was observed in 64 % of 44 patients with ARDS. Therefore, we started corticosteroid therapy after performing HRCT scans at the diagnosis of ARDS. Initial administration of methylprednisolone with a moderate dose (2 mg/kg/day) (n = 71) or high-dose (1000 mg/day for three days followed by a moderate dose) (n = 14) was introduced and was gradually tapered over one month according to the previous study[30]. Ventilator management and ventilator weaning was introduced by the evidence-based guidelines[23, 24] with reference to the lower tidal volume (V_T) strategy (6 ml/kg predicted body weight (PBW) < V_T < 10 ml/kg PBW) in the ARDS Clinical Trial[31] and to the guidelines for weaning and discontinuing ventilatory support from the American College of Chest Physicians[32].

Screening of ventilator associated outcomes

For each patient, we recorded the number of ventilator-free days. Barotrauma, defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, was noted as present or absent on routine chest radiographs or chest tube insertions for known or suspected spontaneous pneumothorax during the first 28 days[33].

Ventilator associated pneumonia (VAP) surveillance was incorporated into the

routine examinations of cultures of sputum obtained using a sterile intratracheal suction tube [34]. VAP was defined as pneumonia occurring after more than 48 hours of mechanical ventilation and for up to 72 hours after weaning.

Organ or system failure

Patients were monitored daily for 28 days for signs of the failure of extrapulmonary organs and systems according to the ARDS Clinical Trial[31]. The number of days without organ or system failure was calculated by subtracting the number of days with organ failure from the lesser of 28 days or the number of days to death. The Sequential Organ Failure Assessment (SOFA) score was sequentially monitored at Day 7 and 14, except for patients who died within 7 days or 14 days.

Outcome measurements

The primary outcome was mortality 60 days after ARDS diagnosis. Patients discharged from the hospital while alive for 60 days were defined as survivors. Their prognoses were eventually followed until 180 days. Non-survivors were defined as patients who died in the hospital. Secondary outcome variables included the number of ventilator-free days, organ failure-free days, the incidence of barotraumas, and the occurrence of ventilator-associated pneumonia.

Statistical analysis

Cox proportional hazards regression analysis was used to examine the influence on survival of 10 % change of radiologically fibroproliferation on HRCT while adjusting

for other prognostic clinical factors such as age, severity of illness, non-pulmonary organ dysfunctions, that had been reported [35-37]. Multivariate regression analysis was also performed to assess the impact on ventilator-weaning failure within 28 days, an incidence of barotraumas, and ventilator-associated pneumonia. To analyze the CT score as a predictor of survival, or of the failure of ventilator weaning or of the occurrence of barotrauma within 28 days after the onset of ARDS, we used receiver-operator characteristic (ROC) curves and the corresponding area under the curve (AUC) to evaluate how the prediction model preformed on the test data and to determine the cutoff value of the CT score yielding the highest sensitivity and specificity which were determined by the Youden index (i.e., sensitivity + specificity – 1). Statistical analyses were performed by using the SPSS package (version 18.0J; SPSS, Tokyo, Japan). For all statistical analyses, $p < 0.05$ was considered significant.

RESULTS

Baseline clinical characteristics

Non-survivors had more severe lung injury with fibroproliferative changes on HRCT scan as shown by their higher HRCT scores than survivors, although non-survivors tended to have less severe multiorgan failure as expressed by their lower SOFA scores. No significant differences were seen between survivors and non-survivors in the number of a history of cigarette smoking and a presence of emphysema. No significant differences were also observed in the ventilatory and medicational conditions as well (Table 1).

HRCT findings for survivors and non-survivors

The area of increased attenuation associated with traction bronchiolectasis or bronchiectasis, indicative of radiologically fibroproliferation, was observed in 40 (47%) of 85 patients at presentation and was significantly smaller in survivors than in non-survivors (Table 2), whereas the area of increased attenuation without traction bronchiolectasis or bronchiectasis was greater in survivors than in non-survivors. Interobserver variability in evaluation of the presence of lung abnormalities was good (kappa, 0.63-0.83), and the assessments of the extent of abnormality by two different observers also correlated well (Spearman rank correlation coefficient, 0.72; $p < 0.01$).

Prognostic value of the HRCT score

The overall HRCT score of survivors (median ± SD, 195.7 ± 53.7; range,

133.4-325.0) was significantly smaller than that of non-survivors (233.1 ± 46.2; 174.8-384.8). Construction of a ROC curve yielded an optimal cut-off value of the HRCT score of 210 which was determined for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval (CI), 0.61-0.82) and for prediction of survival at Day 180 with 71 % sensitivity and 76 % specificity (AUC, 0.73; 95% CI, 0.62-0.84) (Fig. 3). A significant difference was observed in the 60-day mortality rate between patients with CT score < 210 and those with CT score ≥ 210 ($p < 0.0001$) as well as in the ventilator-free days at day 28 ($p < 0.0001$) (Table 3). The difference in the 60-day mortality rate between patients with more or less fibroproliferative changes on HRCT scan persisted regardless of causes of ARDS (Fig. 4). Multivariate Cox proportional hazards model with adjustment for demographic characteristics, severity of illness, non-pulmonary organ dysfunctions, and HRCT score at diagnosis, the HRCT score remained an independent risk factor for mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36; $p = 0.005$) when expressed as mortality change per 10% increase in the area of attenuation with traction bronchiolectasis or bronchiectasis on HRCT scans (Table 4).

Relation between the HRCT score and the number of ventilator-free days, and the number of organ-failure-free days and sequential changes of SOFA score

An ROC curve determined the best cut-off value of the CT score of 210 for prediction of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 %

specificity (AUC, 0.77; 95% CI, 0.67-0.88) (Fig. 5a). Regardless of significantly higher SOFA score (8.0 ± 3.0 versus 5.0 ± 2.0; $p < 0.0001$) and higher DIC score (2.8 ± 1.5 versus 1.9 ± 1.8; $p < 0.002$) at diagnosis, patients with a CT score of < 210 had a significantly higher number of ventilator-free days (14.0 ± 7.8 versus 5.2 ± 8.0 days; $p < 0.0001$). Those patients with a lower CT score were associated with less severe subsequent multiorgan failure as shown by a significantly higher number of organ-failure-free days (Table 3) and by significant decrease of sequential SOFA score than that of patients with a higher CT score (Fig.7). Multivariate regression analysis, with adjustment for demographic characteristics, general severity, and occurrence of barotraumas, showed that the CT score was independently associated with ventilator-weaning within 28 days with an odds ratio of 0.63 when expressed as weaning failure change per 10% increase in the area of attenuation with traction bronchiolectasis or bronchiectasis on HRCT scans ($p = 0.0006$) (Table 5a).

Relation between the HRCT score and the incidence of barotraumas or ventilator-associated pneumonia

All eleven patients with barotrauma had pneumothorax. Barotrauma occurred 3-28 days (mean ± SD, 12.7 ± 9.4 days) after ARDS onset. An ROC curve identified the optimal cutoff value of the CT score of 235 for prediction of barotrauma onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95% CI, 0.59-0.95) (Fig. 6a). Patients with the CT score < 235 had a significantly lower incidence of barotrauma (5.0

versus 32.0 %; p = 0.0019) within 28 days after the onset of ARDS than those with CT score of ≥ 235 (Fig. 5b). The CT score was also independently associated with the occurrence of barotraumas with an odds ratio of 1.61 by multivariate regression analysis (p = 0.018) (Table 6b). Ventilator-associated pneumonia (VAP) was documented in 36 patients (42.3%) after day 5 since ARDS onset. The percentage of patients complicated with VAP in the higher CT score group tended to be higher than those in the lower CT score groups (51.4 and 35.4 percent, respectively; p = 0.14). Multivariate analysis also demonstrated that the CT score was independently associated with the complication of VAP with an odds ratio of 1.46 (p = 0.0041) (Table 5c).

DISCUSSION

Regardless of the cause of ARDS, we found the extent of fibroproliferative changes on HRCT at diagnosis of ARDS was an independent predictive factor for survival and ventilator dependency. Furthermore, patients with extensive fibroproliferative changes on HRCT scan were more susceptible to associated multiorgan failure, barotraumas and ventilator-associated pneumonia than those with less extensive changes. Semi-quantitative determination of fibroproliferation by means of HRCT assessment was informative with regard to the potential not only for response to treatment but also for susceptibility to subsequent ventilator-associated outcomes (ventilator dependency, barotraumas, and ventilator-associated pneumonia).

Biochemical evidence of fibroproliferation is present early in the acute lung injury process. N-terminal procollagen peptide III (N-PCP-III) is a marker of collagen turnover and is elevated in bronchoalveolar lavage (BAL) fluid and tracheal aspirate from ARDS patients within 24 h of diagnosis [8-11] The increased N-PCP-III concentration in BALF at diagnosis was associated with poor prognosis, suggesting that pulmonary early fibroproliferation is an important determinant of outcome [8-11]. In the present study, traction bronchiectasis within areas of increased attenuation, suggesting radiologically fibroproliferation, was already detectable on HRCT scans obtained on the day of ARDS onset in 40 patients (47%). We also confirmed that HRCT findings of early and late phase of ARDS frequently overlapped. These results supported the

previous reports and suggested that a clinically early time point does not necessarily correspond to a pathologically early phase of ARDS. Given that no significant difference in the cause of ARDS was apparent between the survivors and non-survivors in this study, no correlation between the HRCT score and the clinical duration of ARDS may also be attributable to differences in individual sensitivity to lung injury and in the intensity of the consequent exaggerated inflammation that occurs between the onset of injury and progression to ARDS. The term "fibroproliferative" ARDS may not necessarily apply only to "late phase" ARDS but possibly also to "early phase". Accordingly, extent of fibroproliferative changes on HRCT scan, together with N-PCP-III concentration in BALF, may be a potential clue to differentiate "real" late ARDS from the early one.

Currently, there have been few prospective clinical studies to validate the susceptibility to ventilator-associated outcomes. The ARDS Network low tidal volume study has suggested that excessive large tidal ventilation induces inflammatory cytokines and is associated with a known risk factor for ventilator associated lung injury[31]. In the present study, patients with extensive fibroproliferation shown as higher HRCT score on the day of ARDS onset needed a longer duration of mechanical ventilation with subsequent ventilator-associated pneumonia and had shorter organ-failure free days, and subsequently suffered from multiple organ failure.

Barotraumas occurring in critically ill patients independently affects intensive care unit mortality [38]. Barotrauma events occur late in the course of ARDS and are related to lung structural changes such as cystic or fibroproliferative lesions that develop over time [39]. In our study, barotrauma occurred more than 10 days (mean ± SD, 12.7 ± 9.4 days) after the onset of ARDS and was more frequent in patients with a higher HRCT score (score ≥ 235) than in those with a lower HRCT score (score < 235) during the first 28 days. Given that a higher HRCT score at diagnosis suggests advanced fibroproliferation, our data support the relationship between pulmonary fibroproliferation and its susceptibility to barotraumas.

Ventilator-associated pneumonia (VAP) has been a causative factor of subsequent systemic inflammatory syndrome resulting in multi-organ failure[33]. The risk of VAP increases with prolonged mechanical ventilation[34]. **Furthermore, sustained and intense inflammatory responses in unresolving ARDS increase intracellular and extra-cellular growth of nosocomial pathogens and increase the risk for nosocomial infections** [40]. More extensive fibroproliferative changes on HRCT scan shown as a higher CT score were associated with a longer ventilator dependency that was more susceptible to VAP onset. These results support that pulmonary fibroproliferation of ARDS increases risk for ventilator dependency and its associated complications.

In a previous study of 45 cases of ARDS confirmed at biopsy, patients whose conditions were shown histologically to be in the acute exudative phase had a better

prognosis than did those whose condition was shown to be in the fibroproliferative phases [41]. Persistent dysregulated systemic inflammation leading to maladaptive lung repair results in pulmonary fibroproliferation and progression of extrapulmonary organ dysfunction[5]. Prolonged corticosteroid therapy attenuates systemic inflammation and reduced duration of mechanical ventilation[5]**.** In our study, the group of patients who had less fibroproliferative changes on HRCT scans (HRCT score, < 210) showed lower mortality and more ventilator-free days than those who had more extensive areas of fibroproliferation (HRCT score, ≥ 210). This may suggest a relationship between the pathologic phases of ARDS and responsiveness to treatment. **When more extensive and rapidly progressive pulmonary fibroproliferation resulting from intense exaggerated systemic inflammation at presentation occurs, even prolonged corticosteroid therapy may not be effective.** Whether the patients with fibroproliferative predominance have different treatment strategies compared to those with exudative predominance has been a vexing question [4]. Improving our understanding of disease state and evolution of the disease may be key to the development of the optimal therapy and their timing. A method that could be used to evaluate and calibrate the clinical to pathologic stages may help prognosticate, alter supportive or therapeutic approach to ARDS such as ventilator management and define the treatment window for those interventions. Further prospective studies are needed to examine the efficacy of the drugs such as corticosteroids according to the extent of

fibroproliferation on HRCT scans.

There were some potential limitations. First, our study included few patients with ARDS caused by major trauma, multiple transfusion and others, although it included approximately 90% of the patients who had ARDS caused by three major etiologies (pneumonia, aspiration, sepsis) of ARDS; thus, our study may not sufficiently reflect all forms of ARDS. However, previous large randomized control studies also included more than 70% of patients with these three etiologies [27, 31]. Therefore, our results may be applicable to most forms of ARDS.

Second, many elderly patients (mean age, 75.0 years) were included. Clinically, elderly ARDS patients show higher morbidity and need longer duration of mechanical ventilation with subsequent poorer prognosis than the younger patients [2, 37]. The age-related differences in mortality and outcomes have been considered to be due to the greater number of comorbid illness and higher frequency of non-pulmonary organ system failure in older patients [37]. In this study, preexisting pulmonary emphysema was seen in 32 (38 %) of 85 patients. Although no significant differences were seen between survivors and non-survivors in the number of a history of cigarette smoking and a presence of emphysema, we could not evaluate the severity of emphysema before the onset of ARDS. Such a smoking-induced chronic lung disease could potentially affect ventilator-dependency or prognosis. Although it was problematic whether aging increase susceptibility to lung injury and to pulmonary fibroproliferation, further

investigation of younger patients with ARDS is needed to confirm the consistency of the results of our study.

Third, no correlation was provided with either clinical parameters or pathologic findings in the present study. Further investigation is necessary to compare HRCT findings with other predictors of mobidity/mortality-i.e. inflammatory biomarkers such as serum IL-6 or BAL PCP III levels. Recent studies of biopsy findings from ARDS patients have reported the pathologic diversity and only half proportion of typical diffuse alveolar damage [6,7]. Regardless of the cause or pathology of ARDS, our study highlighted the extent of lung architectural distortion (areas with traction bronchiectasis) indicating that pulmonary fibroproliferation on HRCT scans. Although fibroproliferative ARDS does not warrant different treatment strategies up to the present, prospective evaluation of HRCT findings in patients with ARDS would help therapeutic implications in the development of treatment strategies based on the extent of fibroproliferation, as well as its prognostic implications.

Fourth, when using our cutoff values of HRCT scores, there were approximately 30 % of our patients who did not fit for prediction of poor prognosis or ventilator dependency. Recently, multiple organ failure in ARDS patients is considered to be either as the predisposing condition or as a consequence of ARDS[42]. If ARDS occurs as one of multiple organ failure, even though pulmonary fibroproliferation was mild, extra-pulmonary dysfunction could be the determinant of the outcome.

On the basis of our results, extensive HRCT abnormalities indicative of fibroproliferative changes on the day of ARDS diagnosis were independently predictive of poor prognosis and prolonged mechanical ventilation, and were also associated with subsequent multiple organ failure. Pulmonary fibroproliferation that occurs early in ARDS patients increases mortality risk by increasing susceptibility to ventilator dependency and its associated complications.

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Table 1. Clinical characteristics of patients on the day of ARDS onset

Characteristic	Total (n = 85)	60 days Outcomes		p value
		Survivors (n = 54)	Non-survivors (n = 31)	
Age (years)*	75 ± 10	75 ± 11	76 ± 10	0.60
Sex (M/F)	51/34	30/24	21/10	0.38
Cigarette smoking	33	17	16	0.11
Presence of emphysema	32	18	14	0.39
Liver cirrhosis (%)	6 (7.1)	4 (7.4)	2 (6.5)	> 0.99
Direct/indirect injury	59/26	38/16	21/10	0.81
PaO_2:FiO_2	96.2 ± 45.6	96.5 ± 45.0	96.2 ± 47.5	0.90
Causes of lung injury				
Pneumonia (%)	32 (37.6)	20	12	> 0.99
Sepsis (%)	24 (28.2)	13	11	0.38
Pulmonary (%)	11 (12.9)	5	6	0.20
Extrapulmonary (%)	13 (15.2)	8	5	> 0.99
Aspiration (%)	22 (25.9)	16	6	0.44
Others (%)	7 (8.2)	5	2	> 0.99
Lung injury score*	3.2 ± 0.5	3.3 ± 0.5	3.3 ± 0.5	0.88
APACHE II score	21.0 ± 4.7	21.0 ± 4.6	22.0 ± 4.9	0.76
SOFA score	7.0 ± 2.8	7.0 ± 2.8	6.0 ± 2.9	0.15
McCabe score (1/2/3)	78/5/2	49/4/1	29/1/1	> 0.99
DIC score*#	2.4 ± 1.7	2.4 ± 1.7	2.5 ± 1.6	0.68
White blood cell count (per mm^3)	10600 ± 6788	10600 ± 6178	10600 ± 7839	0.63

C-reactive protein (CRP) (mg/dl)	15.4 ± 10.3	15.4 ± 9.6	16.1 ± 11.5	0.69
Albumin (g/dl)	3.0 ± 0.5	3.1 ± 0.5	2.8 ± 0.5	0.11
Lactate dehydrogenase (LDH) (IU/L)	308 ± 185	301 ± 147	339 ± 235	0.29
Platelet count (per mm^3)	20.1 ± 10.7	20.7 ± 11.0	18.9 ± 10.3	0.94
Days of CT scanning from ARDS onset (day)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	> 0.99
HRCT score #	207 ± 53	196 ± 54	233 ± 46	0.001
Initial steroid therapy				
High dose	14	7	7	0.36
Low dose	71	47	24	0.36
Ventilatory variables				
Tidal volume, ml/kg predicted body weight	8.0 ± 0.8	8.0 ± 0.7	8.0 ± 0.9	0.54
Plateau pressure, cmH_2O	21.5 ± 4.2	21.0 ± 3.8	23.0 ± 4.7	0.34
Initial PEEP, cmH_2O	8.0 ± 3.4	8.0 ± 2.5	8.0 ± 4.3	0.18

Data are expressed as median ± standard deviation. *Data are mean ± standard deviation. The p values refer to comparisons between survivors and non-survivors.

Score ≥ 4 defined as disseminated intravascular coagulation from scoring system for The Japanese Association for Acute Medicine.

Table 2. Extent of each high-resolution CT finding in 60-days survivors and non-survivors of ARDS.

CT Finding	Survivors (n = 54)	Non-survivors (n = 31)	p value
Spared area	37.0 ± 19.2	30.3 ± 14.9	0.15
Ground-glass attenuation	33.5 ± 22.9	30.0 ± 16.0	0.70
Air-space consolidation	17.5 ± 13.8	18.3 ± 19.3	0.72
Total area without traction bronchiolectasis or bronchiectasis	88.0 ± 22.0	78.2 ± 22.5	0.01
Ground-glass attenuation plus traction bronchiolectasis or bronchiectasis	9.3 ± 17.8	16.6 ± 21.7	0.08
Air-space consolidation plus traction bronchiolectasis or bronchiectasis	2.4 ± 7.8	5.6 ± 10.3	0.01
Honeycombing	0.0 ± 0.0	0.0 ± 0.0	NS
Total area with traction bronchiolectasis or bronchiectasis	11.8 ± 18.0	22.1 ± 24.3	0.01

Data are mean ± standard deviation of percentage of lung involvement.

NS = not significant

Mann-Whitney U test

Table 3. Comparison of primary and secondary outcomes between the cut-off value showing extent of fibroproliferative changes on high-resoluiton CT at the onset of ARDS

Variable	High-Resolution Computed Tomographic (CT) score		p value
	< 210 (n = 47)	≥ 210 (n = 38)	
60-Day mortality (%)	19.1	57.9	< 0.0001
No. of hospital death	9	22	
Causes of death			
Multiple organ failure	8	18	
Respiratory failure	1	4	
No. of ventilator-free days at day 28	14.3 ± 7.6	5.1 ± 8.0	< 0.0001
No. of organ-failure-free days			
Cardiovascular failure	22.4 ± 8.1	16.1 ± 10.9	0.009
Coagulation abnormalities	23.0 ± 8.9	17.8 ± 10.4	0.017
Hepatic failure	23.3 ± 8.2	19.6 ± 9.5	0.11
Renal failure	21.7 ± 10.9	19.6 ± 9.6	0.29
No. of incidence of barotraumas (%)	3 (6.4)	8 (21.1)	0.056
No. of ventilator-associated pneumonia (%)	16 (34.0)	20 (52.6)	0.13

Plus-minus values are mean ± SD. Continuous variables with non-normal distribution were compared with the use of Mann-Whitney U test and categorical variables with Fisher's exact test.

Table 4a. Univariate Cox regression analysis of variables potentially associated with mortality at day 180 in patients with ARDS.

Variable	P value	Hazard ratio	95% CI
HRCT score	0.0019	1.22*	1.08-1.38
Age	0.5411	0.99	0.96-1.02
Sepsis	0.4020	1.34	0.67-2.67
APACHE II score	0.6578	0.98	0.92-1.06
SOFA score	0.1724	0.92	0.82-1.04
McCabe score	0.9609	0.98	0.41-2.32
PaO_2 / FiO_2 ratio	0.6119	1.00	0.99-1.01
Serum Albumin	0.0982	0.57	0.30-1.11

Table 4b. Multivariate Cox regression analysis of prognostic factors associated with mortality at day 180 in patients with ARDS

Variable	P value	Hazard ratio	95% CI
HRCT score	0.0051	1.20*	1.06-1.36
Serum Albumin	0.2618	0.67	0.33-1.36

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5. Multiple logistic regression analysis of variables potentially associated with ventilator-associated outcomes.

Table 5a. Ventilator-weaning within 28 days in patients with ARDS.

Variable	P value	Odds ratio	95% CI
HRCT score	0.0006	0.63*	0.48-0.82
Serum Albumin	0.1727	2.09	0.72-6.03

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5b. The incidence of the Barotrauma

Variable	P value	Odds ratio	95% CI
HRCT score	0.0183	1.61*	1.08-2.38
APACHE II	0.4724	0.92	0.74-1.15
SOFA score	0.9110	1.02	0.68-1.55
Serum Albumin	0.5156	0.53	0.08-3.65
Serum LDH	0.0158	1.05	1.01-1.09

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

Table 5c. The complication of the Ventilator-associated pneumonia

Variable	P value	Odds ratio	95% CI
Liver cirrhosis	0.0286	13.34	1.31-135.60
HRCT score	0.0041	1.46*	1.13-1.89
PaO_2 / FiO_2 ratio	0.0236	0.99	0.98-1.00

Abbreviation: HRCT: high-resolution computed tomography

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on high-resolution CT.

FIGURE LEGENDS

Figure 1. Outlines of the study.

Figure 2. High-resolution computed tomography (CT) findings correlated with pathology

a.: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation without traction bronchiectasis and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumonia.*

b.: High-resolution CT findings corresponding to fibroproliferative phase of ARDS. HRCT scan at the level of right lower lobe shows extensive airspace consolidation and ground-glass attenuation associated with traction bronchiectasis (arrows). The patient was a 84-year-old woman with ARDS due to sepsis.

c.: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old woman with ARDS due to *viral pneumonia.* (Sequential changes of HRCT findings were shown in the supplemental figure.)

Figure 3. Receiver operator characteristic (ROC) curve of prognostic value of the high-resolution computed tomography (HRCT) score. ROC identified the optimal cut-off value of 210 determined by the Youden Index for prediction of survival at Day 60 with 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval, 0.61-0.82) and for prediction of survival at Day 180 with 71% sensitivity and 76 % specificity (AUC, 0.73; 95%CI, 0.62-0.84).

Figure 4a. Day 60-mortality rate of each major cause of ARDS.

Figure 4b. Day 60-mortality rate compared between the optimal cut-off value of high-resolution computed tomography (HRCT) score in each cause. Regardless of the cause, the mortality rate of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

Figure 5. Receiver operator characteristic (ROC) curve of prediction of the ventilator weaning within 28 days from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 210 determined by the Youden Index for prediction of ventilator weaning at day 28 with 75 % sensitivity and 76 % specificity (AUC, 0.77; 95%CI, 0.67-0.88).

Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumas onset with 73 % sensitivity and 77 % specificity (AUC, 0.77; 95%CI, 0.59-0.95)

Figure 6b. Comparison of the incidence of barotraumas between patients with the optimal cut-off value of CT score identified from ROC curve. The incidence of barotrauma of a patient with a lower CT score was significantly lower than that of a patient with a higher CT score.

Figure 7. Sequential changes of Sequential Organ Failure Assessment (SOFA) scores. The SOFA score of a patient with a lower CT score (< 210) significantly decreased from day 1 to day 14 ($p = 0.0016$). The SOFA score of a patient of a patient with a higher CT

score (≥ 210) significantly increased from day 1 to day 14 (p = 0.027). Four patients with a lower CT score (< 210) and 9 patients with a higher CT score (≥ 210) who died within 14 days were excluded.

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Patient confidentiality

Details have been removed from this case description.