



**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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| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID:                  | bmjopen-2011-000545  |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 01-Nov-2011  |
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| <b>Primary Subject Heading</b>: | Respiratory medicine   |

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| Secondary Subject Heading: | Intensive care, Radiology and imaging  |
| Keywords:                  | Adult intensive & critical care < ANAESTHETICS, Thoracic medicine < INTERNAL MEDICINE, Chest imaging < RADIOLOGY & IMAGING |
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6 Fibroproliferative Changes on High-Resolution Computed  
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8 Tomography in the Acute Respiratory Distress Syndrome  
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11 Predict Mortality and Ventilator Dependency: A Prospective  
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14 Observational Cohort Study  
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6 **Conflict of interest disclosures:** None of the authors has declared any conflict of interest  
7  
8 related to this work.  
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13 **Keywords**

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

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6 **Objectives:** To examine whether the extent of fibroproliferative changes on

7  
8 high-resolution computed tomography (HRCT) scan influences prognosis, ventilator

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10 dependency, and the associated outcomes in patients with early acute respiratory

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12 distress syndrome (ARDS).

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15 **Design:** A prospective observational cohort study

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18 **Setting:** Intensive care unit in an educational hospital

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21 **Participants:** Eighty-five patients with ARDS who met American-European Consensus

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24 Conference Criteria and eligible criteria.

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27 **Interventions:** HRCT scans were performed and prospectively evaluated by two

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29 independent observers on the day of diagnosis and graded into six findings according to

30  
31 the extent of fibroproliferation. An overall HRCT score was obtained by previously

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33 published method.

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37 **Primary and secondary outcomes:** The primary outcomes were 60-day and 180-day

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39 mortality. Secondary outcomes included the number of ventilator-free days, organ

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41 failure-free days, the incidence of barotraumas, and the occurrence of

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43 ventilator-associated pneumonia.

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47 **Results:** Higher HRCT scores were associated with significantly decreased number of

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49 organ-failure free days as well as with decreased number of ventilator-free days.

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52 Multivariate Cox proportional hazards model showed that the HRCT score remained an

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54 independent risk factor for mortality (hazard ratio 1.20; 95% confidence interval 1.06,

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6 1.36;  $p = 0.005$ ). Multivariate analysis also revealed that the CT score had predictive  
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8 value for ventilator-weaning within 28 days (odds ratio 0.63; 95% CI 0.48, 0.82;  $p =$   
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10 0.0006) as well as for an incidence of barotraumas (1.61; 95%CI 1.08, 2.38;  $p = 0.018$ )  
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12 and for an occurrence of ventilator-associated pneumonia (1.46; 95%CI 1.13,1.89;  $p =$   
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14 0.004). An HRCT score  $< 210$  enabled prediction of 180 day survival with 71 %  
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16 sensitivity and 76 % specificity and of ventilator-weaning failure within 28 days with  
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18 75 % sensitivity and 76 % specificity.  
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24 **Conclusions:** Pulmonary fibroproliferation assessed by HRCT in patients with early  
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26 ARDS predicts increased mortality with an increased susceptibility to multiple organ  
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28 failure, including ventilator dependency and its associated outcomes.  
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#### 35 **Data sharing statement**

36  
37 There is no additional data available.  
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#### 40 **Research grant**

41  
42 This research received no specific grant from any funding agency in the public,  
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44 commercial or not-for-profit sectors.  
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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<sup>1,2</sup>. ARDS is considered to have an early and a late phase and is pathologically divided into three stages<sup>3</sup> 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<sup>3,4</sup>. Although pathologic staging may be conceptually useful, commonly used clinical indicators such as PaO<sub>2</sub>/FiO<sub>2</sub> 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<sup>5,6</sup>.

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

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6 fibroproliferation in ARDS patients<sup>15</sup>. Based on HRCT appearance, less  
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8 fibroproliferation in early ARDS was associated with greater ventilator-free days and  
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10 less barotraumas<sup>15</sup>. In this prospective study, we evaluated not only what was found in  
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12 the retrospective study<sup>15</sup> but also the relationship between early fibroproliferation and  
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14 the progression to multiple organ failure; whether the extent of fibroproliferation on  
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16 HRCT scan at the time diagnosis of ARDS would impact the susceptibility for ventilator  
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18 dependency and its associated complications and on the response to treatment.  
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## 24 **METHODS**

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

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

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19 All patients underwent helical HRCT scanning of the chest on the day of diagnosis of  
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21 ARDS using multidetector-row CT (MDCT) scan. All MDCT scans were obtained with  
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23 2-mm thickness and 15-mm table speed per rotation and were performed at full  
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25 inspiration from the lung apex to base. Contiguous CT slices were reconstructed using  
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27 of a high-spatial frequency algorithm. Sections were displayed at 10-mm intervals  
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29 throughout the chest with the patient in the supine position and without intravenous  
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31 contrast medium. The process did not negatively affect the patients' condition. In this  
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33 study, we evaluated single CT scan acquired at day one of the ARDS diagnosis, because  
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35 sequential CT scans were hard to be performed after high positive end-expiratory  
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37 pressure ventilation was introduced. HRCT scans were evaluated on the day of ARDS  
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39 diagnosis by two independent observers who were unaware of patient condition. The  
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41 presence and extent of areas of ground-glass attenuation, air-space consolidation,  
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43 traction bronchiectasis, traction bronchiolectasis, and honeycombing were assessed.  
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51 Ground-glass attenuation was defined as a hazy area with increased opacification  
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53 without obscuration of underlying vascular markings. Air-space consolidation was  
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6 considered present when the vascular markings were obscured. When bronchi were  
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8 irregular in contour, the dilated bronchus within areas of parenchymal abnormality was  
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10 recognized as traction bronchiectasis. Traction bronchiolectasis was identified by the  
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12 presence of dilated bronchioles within areas with parenchymal abnormality.  
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15 Honeycombing was defined as the presence of cystic airspaces measuring 2-10 mm in  
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17 diameter with well-defined walls.  
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22 HRCT findings were graded on a scale of 1-6 based on the classification  
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24 system correlating with previously described pathology (Fig. 2)<sup>13,15</sup>: 1, normal  
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26 attenuation; 2, ground-glass attenuation; 3, consolidation; 4, ground-glass attenuation  
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28 with traction bronchiolectasis or bronchiectasis; 5, consolidation with traction  
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30 bronchiolectasis or bronchiectasis; 6, honeycombing. The presence of each of these six  
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32 abnormalities was assessed independently in three (upper, middle, lower) zones of each  
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34 lung. The upper zone was defined as the area above the level of the carina, the middle  
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36 zone as the area between the level of the carina and that of the infrapulmonary vein, and  
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38 the lower zone as the area below the level of the infrapulmonary vein. The extent of  
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40 each abnormality was determined by visually estimating the percentage (to the nearest  
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42 10%) of the affected lung parenchyma in each zone. The assessments of the two  
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44 observers were averaged. The abnormality score for each zone was calculated by  
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46 multiplying the percentage area by the point value (1-6). The six zone scores were  
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48 averaged to determine the total score for each abnormality in each patient. The overall  
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6 CT score for each patient was obtained by adding the six averaged scores. The scoring  
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8 system is previously reported<sup>13,15</sup> and has been evaluated in the other diseases<sup>17,18</sup>.

### 11 **Treatment Protocol**

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

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

### 48 **Screening of ventilator associated outcomes**

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51 For each patient, we recorded the number of ventilator-free days. Barotrauma,  
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53 defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema,  
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55 was noted as present or absent on routine chest radiographs or chest tube insertions for  
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6 known or suspected spontaneous pneumothorax during the first 28 days<sup>32</sup>.  
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9 Ventilator associated pneumonia (VAP) surveillance was incorporated into the  
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11 routine examinations of cultures of sputum obtained using a sterile intratracheal suction  
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13 tube<sup>33</sup>. VAP was defined as pneumonia occurring after more than 48 hours of  
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15 mechanical ventilation and for up to 72 hours after weaning.  
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### 18 19 **Organ or system failure**

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21 Patients were monitored daily for 28 days for signs of the failure of  
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23 extrapulmonary organs and systems according to the ARDS Clinical Trial<sup>30</sup>. The  
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25 number of days without organ or system failure was calculated by subtracting the  
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27 number of days with organ failure from the lesser of 28 days or the number of days to  
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29 number of days with organ failure from the lesser of 28 days or the number of days to  
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31 death. The Sequential Organ Failure Assessment (SOFA) score was sequentially  
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33 monitored at Day 7 and 14, except for patients who died within 7 days or 14 days.  
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### 37 38 **Outcome measurements**

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40 The primary outcome was mortality 60 days and 180 days after ARDS diagnosis.  
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42 Patients discharged from the hospital while alive without assistance for 60 days and 180  
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44 days were defined as survivors. Non-survivors were defined as patients who died in the  
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46 hospital. Secondary outcome variables included the number of ventilator-free days,  
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48 organ failure-free days, the incidence of barotraumas, and the occurrence of  
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50 ventilator-associated pneumonia.  
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### 55 56 **Statistical analysis**

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6 Cox proportional hazards regression analysis was used to examine the influence on  
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8 survival of 10 % change of radiologically fibroproliferation on HRCT while adjusting  
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10 for other prognostic clinical factors such as age, severity of illness, non-pulmonary  
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12 organ dysfunctions, that had been reported<sup>34-36</sup>. Multivariate regression analysis was  
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14 also performed to assess the impact on ventilator-weaning failure within 28 days, an  
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16 incidence of barotraumas, and ventilator-associated pneumonia. To analyze the CT  
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18 score as a predictor of survival, or of the failure of ventilator weaning or of the  
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20 occurrence of barotrauma within 28 days after the onset of ARDS, we used  
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22 receiver-operator characteristic (ROC) curves and the corresponding area under the  
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24 curve (AUC) to evaluate how the prediction model performed on the test data and to  
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26 determine the cutoff value of the CT score yielding the highest sensitivity and  
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28 specificity which were determined by the Youden index (i.e., sensitivity + specificity –  
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30 1). Statistical analyses were performed by using the SPSS package (version 18.0J; SPSS,  
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32 Tokyo, Japan). For all statistical analyses,  $p < 0.05$  was considered significant.  
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## 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  $\pm$  SD, 195.7  $\pm$  53.7; range,



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6 133.4-325.0) was significantly smaller than that of non-survivors ( $233.1 \pm 46.2$ ;  
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9 174.8-384.8). Construction of a ROC curve yielded an optimal cut-off value of the  
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11 HRCT score of 210 which was determined for prediction of survival at Day 60 with  
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13 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval (CI),  
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15 0.61-0.82) and for prediction of survival at Day 180 with 71 % sensitivity and 76 %  
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17 specificity (AUC, 0.73; 95% CI, 0.62-0.84) (Fig. 3). A significant difference was  
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19 observed in the 60-day mortality rate between patients with CT score < 210 and those  
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21 with CT score  $\geq$  210 ( $p < 0.0001$ ) as well as in the ventilator-free days at day 28 ( $p <$   
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23 0.0001) (Table 3). The difference in the 60-day mortality rate between patients with  
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25 more or less fibroproliferative changes on HRCT scan persisted regardless of causes of  
26  
27 ARDS (Fig. 4). Multivariate Cox proportional hazards model with adjustment for  
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29 demographic characteristics, severity of illness, non-pulmonary organ dysfunctions, and  
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31 HRCT score at diagnosis, the HRCT score remained an independent risk factor for  
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33 mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36;  $p = 0.005$ ) when  
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35 expressed as mortality change per 10% increase in the area of attenuation with traction  
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37 bronchiolectasis or bronchiectasis on HRCT scans (Table 4).  
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48 **Relation between the HRCT score and the number of ventilator-free days, and the**  
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50 **number of organ-failure-free days and sequential changes of SOFA score**  
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52  
53 An ROC curve determined the best cut-off value of the CT score of 210 for  
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55 prediction of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 %  
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6 specificity (AUC, 0.77; 95% CI, 0.67-0.88) (Fig. 5a). Regardless of significantly higher  
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8 SOFA score ( $8.0 \pm 3.0$  versus  $5.0 \pm 2.0$ ;  $p < 0.0001$ ) and higher DIC score ( $2.8 \pm 1.5$   
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10 versus  $1.9 \pm 1.8$ ;  $p < 0.002$ ) at diagnosis, patients with a CT score of  $< 210$  had a  
11  
12 significantly higher number of ventilator-free days ( $14.0 \pm 7.8$  versus  $5.2 \pm 8.0$  days;  $p <$   
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14  $0.0001$ ). Those patients with a lower CT score were associated with less severe  
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16 subsequent multiorgan failure as shown by a significantly higher number of  
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18 organ-failure-free days (Table 3) and by significant decrease of sequential SOFA score  
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20 than that of patients with a higher CT score (Fig.7). Multivariate regression analysis,  
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22 with adjustment for demographic characteristics, general severity, and occurrence of  
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24 barotraumas, showed that the CT score was independently associated with  
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26 ventilator-weaning within 28 days with an odds ratio of 0.63 when expressed as  
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28 weaning failure change per 10% increase in the area of attenuation with traction  
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30 bronchiolectasis or bronchiectasis on HRCT scans ( $p = 0.0006$ ) (Table 5a).  
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#### 40 **Relation between the HRCT score and the incidence of barotraumas or** 41 42 **ventilator-associated pneumonia** 43 44

45 All eleven patients with barotrauma had pneumothorax. Barotrauma occurred  
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47 3-28 days (mean  $\pm$  SD,  $12.7 \pm 9.4$  days) after ARDS onset. An ROC curve identified the  
48  
49 optimal cutoff value of the CT score of 235 for prediction of barotrauma onset with  
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51 73 % sensitivity and 77 % specificity (AUC, 0.77; 95% CI, 0.59-0.95) (Fig. 6a).  
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56 Patients with the CT score  $< 235$  had a significantly lower incidence of barotrauma (5.0  
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6 versus 32.0 %;  $p = 0.0019$ ) within 28 days after the onset of ARDS than those with CT  
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8 score of  $\geq 235$  (Fig. 5b). The CT score was also independently associated with the  
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10 occurrence of barotraumas with an odds ratio of 1.61 by multivariate regression analysis  
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12 ( $p = 0.018$ ) (Table 6b). Ventilator-associated pneumonia (VAP) was documented in 36  
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14 patients (42.3%) after day 5 since ARDS onset. The percentage of patients complicated  
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16 with VAP in the higher CT score group tended to be higher than those in the lower CT  
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18 score groups (51.4 and 35.4 percent, respectively;  $p = 0.14$ ). Multivariate analysis also  
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20 demonstrated that the CT score was independently associated with the complication of  
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22 VAP with an odds ratio of 1.46 ( $p = 0.0041$ ) (Table 5c).  
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## 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<sup>7-10</sup>. 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<sup>7-10</sup>. 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

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6 not necessarily correspond to a pathologically early phase of ARDS. Given that no  
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9 significant difference in the cause of ARDS was apparent between the survivors and  
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11 non-survivors in this study, no correlation between the HRCT score and the clinical  
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13 duration of ARDS may also be attributable to differences in individual sensitivity to  
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15 lung injury and in the intensity of the consequent exaggerated inflammation that  
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17 occurs between the onset of injury and progression to ARDS. The term  
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21 “fibroproliferative” ARDS may not necessarily apply only to “late phase” ARDS but  
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23 possibly also to “early phase”. Accordingly, extent of fibroproliferative changes on  
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25 HRCT scan, together with N-PCP-III concentration in BALF, may be a potential  
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30 clue to differentiate “real” late ARDS from the early one.  
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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<sup>27</sup>. 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

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6 unit mortality<sup>37</sup>. Barotrauma events occur late in the course of ARDS and are related to  
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8 lung structural changes such as cystic or fibroproliferative lesions that develop over  
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10 time<sup>38</sup>. In our study, barotrauma occurred more than 10 days (mean  $\pm$  SD, 12.7  $\pm$  9.4  
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12 days) after the onset of ARDS and was more frequent in patients with a higher HRCT  
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14 score (score  $\geq$  235) than in those with a lower HRCT score (score  $<$  235) during the first  
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16 28 days. Given that a higher HRCT score at diagnosis suggests advanced  
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18 fibroproliferation, our data support the relationship between pulmonary  
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20 fibroproliferation and its susceptibility to barotraumas.  
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27 Ventilator-associated pneumonia (VAP) has been a causative factor of subsequent  
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29 systemic inflammatory syndrome resulting in multi-organ failure<sup>32</sup>. The risk of VAP  
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31 increases with prolonged mechanical ventilation<sup>33</sup>. More extensive fibroproliferative  
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33 changes on HRCT scan shown as a higher CT score were associated with a longer  
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35 ventilator dependency that was more susceptible to VAP onset. These results support  
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37 that pulmonary fibroproliferation of ARDS increases risk for ventilator dependency and  
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39 its associated complications.  
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46 In a previous study of 45 cases of ARDS confirmed at biopsy, patients whose  
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48 conditions were shown histologically to be in the acute exudative phase had a better  
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50 prognosis than did those whose condition was shown to be in the fibroproliferative  
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52 phases<sup>39</sup>. In our study, the group of patients who had less fibroproliferative changes on  
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54 HRCT scans (HRCT score,  $<$  210) showed lower mortality and more ventilator-free  
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6 days than those who had more extensive areas of fibroproliferation (HRCT score,  $\geq$   
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8 210). This suggests a relationship between the pathologic phases of ARDS and  
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10 responsiveness to treatment. Whether the patients with fibroproliferative predominance  
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12 have different treatment strategies compared to those with exudative predominance has  
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14 been a vexing question<sup>4</sup>. Improving our understanding of disease state and evolution of  
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16 the disease may be key to the development of the optimal therapy and their timing. A  
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18 method that could be used to evaluate and calibrate the clinical to pathologic stages may  
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20 help prognosticate, alter supportive or therapeutic approach to ARDS such as ventilator  
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22 management and define the treatment window for those interventions. Further  
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24 prospective studies are needed to examine the efficacy of the drugs such as  
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26 corticosteroids according to the extent of fibroproliferation on HRCT scans.  
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35 There were some potential limitations. First, our study included few patients with  
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37 ARDS caused by major trauma, multiple transfusion and others, although it included  
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39 approximately 90% of the patients who had ARDS caused by three major etiologies  
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41 (pneumonia, aspiration, sepsis) of ARDS; thus, our study may not sufficiently reflect all  
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43 forms of ARDS. However, previous large randomized control studies also included  
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45 more than 70% of patients with these three etiologies<sup>26,30</sup>. Therefore, our results may  
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47 be applicable to most forms of ARDS.  
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53 Second, many elderly patients (mean age, 75.0 years) were included. Clinically,  
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55 elderly ARDS patients show higher morbidity and need longer duration of mechanical  
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6 ventilation with subsequent poorer prognosis than the younger patients<sup>2, 35</sup>. The  
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8 age-related differences in mortality and outcomes have been considered to be due to the  
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10 greater number of comorbid illness and higher frequency of non-pulmonary organ  
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12 system failure in older patients<sup>35</sup>. In this study, preexisting pulmonary emphysema was  
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14 seen in 32 (38 %) of 85 patients. Although no significant differences were seen between  
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16 survivors and non-survivors in the number of a history of cigarette smoking and a  
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18 presence of emphysema, we could not evaluate the severity of emphysema before the  
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20 onset of ARDS. Such a smoking-induced chronic lung disease could potentially affect  
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22 ventilator-dependency or prognosis. Although it was problematic whether aging  
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24 increase susceptibility to lung injury and to pulmonary fibroproliferation, further  
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26 investigation of younger patients with ARDS is needed to confirm the consistency of  
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28 the results of our study.  
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38 Third, no correlation was provided with either clinical parameters or pathologic  
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40 findings in the present study. Further investigation is necessary to compare HRCT  
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42 findings with other predictors of morbidity/mortality-i.e. inflammatory biomarkers such  
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44 as serum IL-6 or BAL PCP III levels. Recent studies of biopsy findings from ARDS  
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46 patients have reported the pathologic diversity and only half proportion of typical  
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48 diffuse alveolar damage<sup>5,6</sup>. Regardless of the cause or pathology of ARDS, our study  
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50 highlighted the extent of lung architectural distortion (areas with traction  
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52 bronchiectasis) indicating that pulmonary fibroproliferation on HRCT scans. Although  
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6 fibroproliferative ARDS does not warrant different treatment strategies up to the present,  
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9 prospective evaluation of HRCT findings in patients with ARDS would help therapeutic  
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11 implications in the development of treatment strategies based on the extent of  
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14 fibroproliferation, as well as its prognostic implications.

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

**Author contributions:** Dr Suga takes full responsibility for the integrity of all the data and the accuracy of the data analysis.

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.

Dr Habashi: contributed to reanalyzing the data and revising the manuscript.

Dr Fujimoto: contributed to reanalyzing the data and revising the manuscript.

Dr Johkoh: contributed to reanalyzing the data and revising the manuscript.

Dr Iwamoto: contributed to collecting the data and revising the manuscript.

Dr Kawamura: contributed to collecting the data and revising the manuscript.

Dr Nagano: contributed to collecting the data and revising the manuscript.

Dr Fukuda: contributed to collecting the data and revising the manuscript.

Dr Hirata: contributed to collecting the data and revising the manuscript.

Dr Yoshinaga: contributed to reanalyzing the data and revising the manuscript.

Dr Ichiyasu: contributed to collecting the data and revising the manuscript.

Dr Tsumura: contributed to collecting the data and revising the manuscript.

Dr Kohrogi: contributed to reanalyzing the data and revising the manuscript.

Dr Kawaguchi: contributed to reanalyzing the data and revising the manuscript.

Dr Yoshioka: contributed to reanalyzing the data and revising the manuscript.

Dr Sakuma: contributed to reanalyzing the data and revising the manuscript.

**Other persons contributing to this study:** We appreciate Michael A. Matthay, MD<sup>1</sup>, and

Hiroshi Kubo, MD, PhD<sup>2</sup> for their editorial assistance and also thank Isamu Cho, MD, PhD<sup>3</sup>,

Tomoki Tanaka, MD<sup>3</sup>, Junichi Maehara, MD<sup>4</sup>, Shigeo Hiroshige, MD<sup>5</sup>, Makoto Takaki, MD<sup>5</sup>,

Mitsuko Honda, MD<sup>5</sup>, Naoko Arakawa, MD<sup>5</sup>, Yuko Yasuda, MD<sup>5</sup>, Makiko Takeguchi, MD<sup>5</sup>,

Aoi Teruya, MD<sup>5</sup>, Yoshitomo Eguchi, MD<sup>5</sup>, Naoki Shingu, MD<sup>5</sup>, and Yoshihiko Sakata, MD<sup>5</sup>

for their clinical assistance.

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For peer review only

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

| Characteristic                                   | Total<br>(n = 85) | 60 days               |                                       | p value |
|--|-------------------|-----------------------|---------------------------------------|---------|
|  |                   | Survivors<br>(n = 54) | Outcomes<br>Non-survivors<br>(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 <sub>2</sub> :FiO <sub>2</sub>               | 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<br>(per mm <sup>3</sup> ) | 10600 ± 6788      | 10600 ± 6178          | 10600 ± 7839                          | 0.63    |

|  |             |             |             |        |
|--|-------------|-------------|-------------|--------|
| C-reactive protein (CRP)<br>(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<br>(LDH) (IU/L)        | 308 ± 185   | 301 ± 147   | 339 ± 235   | 0.29   |
| Platelet count (per mm <sup>3</sup> )        | 20.1 ± 10.7 | 20.7 ± 11.0 | 18.9 ± 10.3 | 0.94   |
| Days of CT scanning<br>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<br>predicted body weight | 8.0 ± 0.8   | 8.0 ± 0.7   | 8.0 ± 0.9   | 0.54   |
| Plateau pressure, cmH <sub>2</sub> O         | 21.5 ± 4.2  | 21.0 ± 3.8  | 23.0 ± 4.7  | 0.34   |
| Initial PEEP, cmH <sub>2</sub> O             | 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<br>(n = 54) | Non-survivors<br>(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<br>or bronchiectasis            | 88.0 ± 22.0           | 78.2 ± 22.5               | 0.01    |
| Ground-glass attenuation plus traction<br>bronchiolectasis or bronchiectasis | 9.3 ± 17.8            | 16.6 ± 21.7               | 0.08    |
| Air-space consolidation plus traction<br>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<br>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-resolution CT at the onset of**

**ARDS**

| Variable                                   | High-Resolution Computed Tomographic<br>(CT) score |                   | p value  |
|--|--|-------------------|----------|
|  | < 210<br>(n = 47)                                  | ≥ 210<br>(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 <sub>2</sub> / FiO <sub>2</sub> 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 <sub>2</sub> / FiO <sub>2</sub> 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 pneumoniae*.

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 pneumoniae*. (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).

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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.

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

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6 score ( $\geq 210$ ) significantly increased from day 1 to day 14 ( $p = 0.027$ ). Four patients  
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8 with a lower CT score ( $< 210$ ) and 9 patients with a higher CT score ( $\geq 210$ ) who died  
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10 within 14 days were excluded.  
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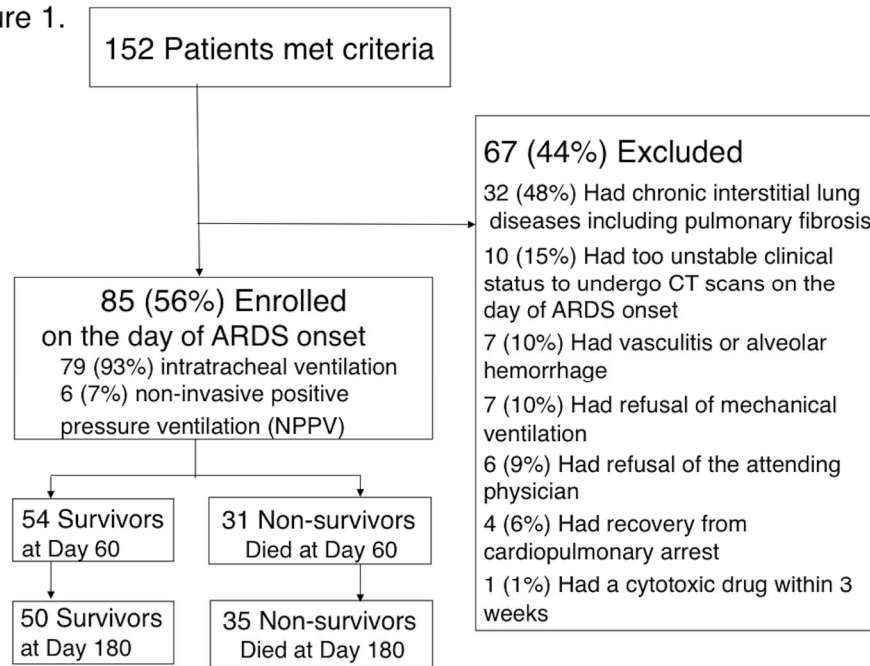
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Figure 1.



Outlines of the study.  
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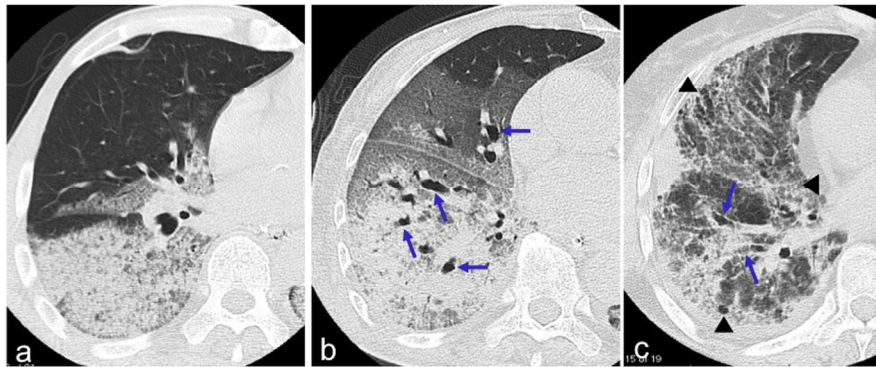


Figure 2a: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumoniae* pneumonia.

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.

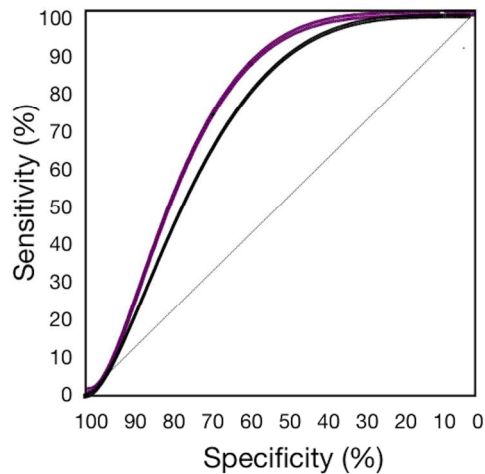
Figure 2c: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old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



— Day 60 mortality; AUC, 0.71 (0.61-0.82); sensitivity, 71 %, specificity, 72 %  
— Day 180 mortality; AUC 0.73 (0.62-0.84); sensitivity, 71 %, specificity, 76 %

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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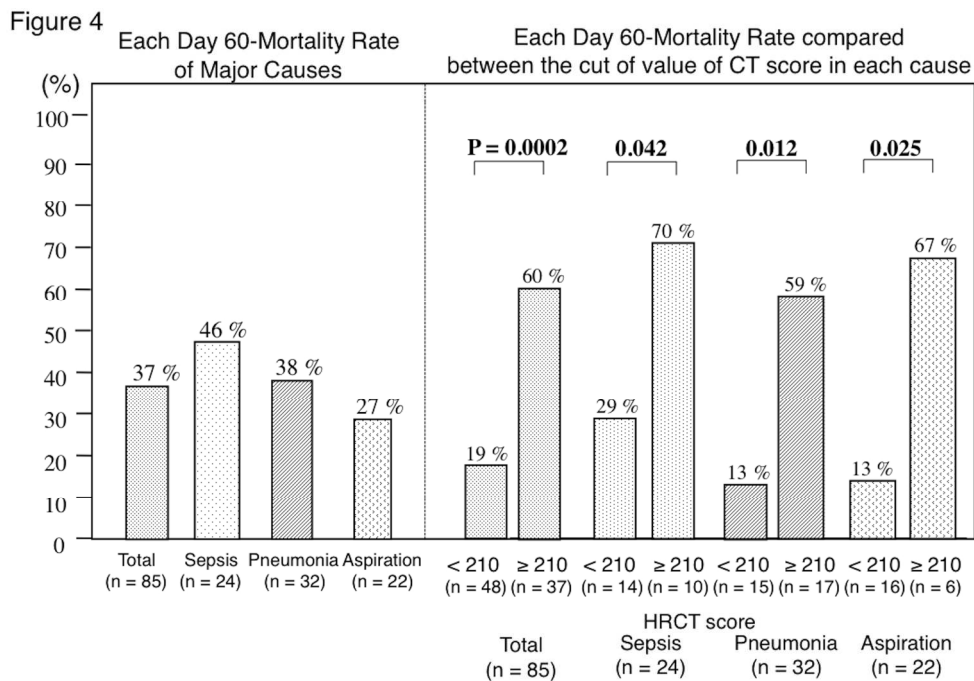
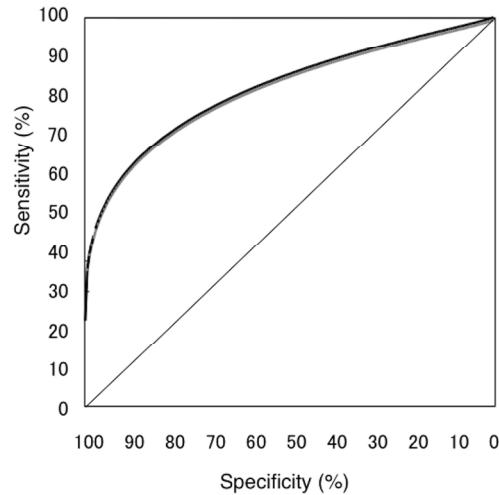


Figure 4a. Day 60-mortality rate of each major cause of ARDS.

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



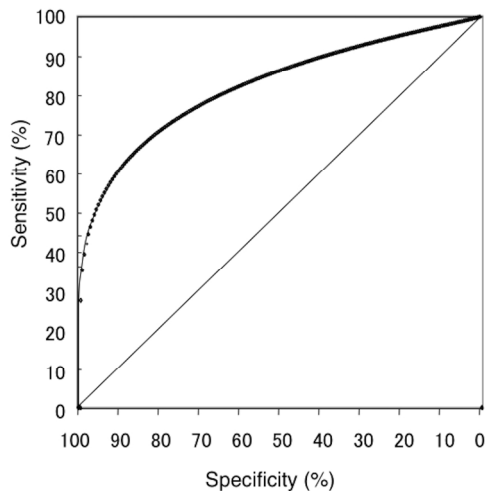
AUC, 0.77 (0.67-0.88); sensitivity, 75 %, specificity, 76 %

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 operating characteristics curve of the prediction  
of the onset of barotrauma



AUC, 0.77 (0.59-0.95); sensitivity, 73 %, specificity, 77 %

Figure 6b.  
Incidence of barotrauma  
Compared between the cut of value  
of CT score

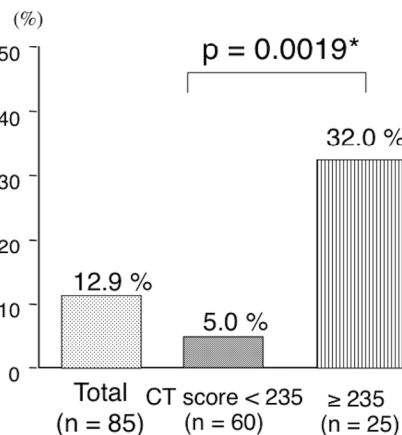
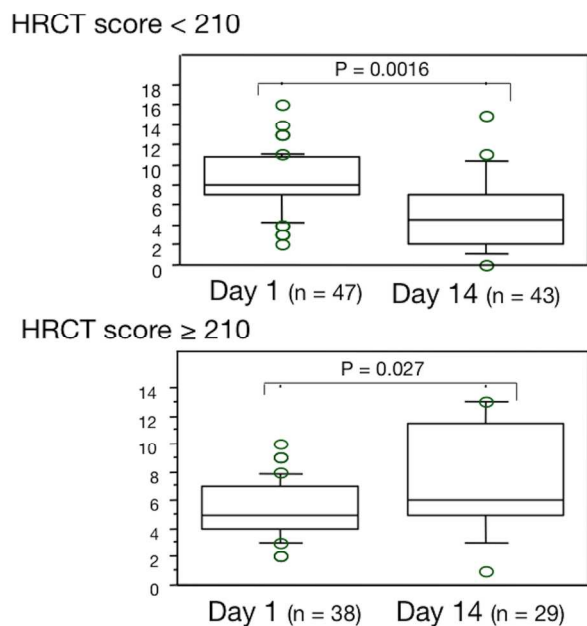


Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumias onset with 73 % sensitivity and 77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

Figure 6b. Comparison of the incidence of barotraumias 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 ( $\geq 210$ ) 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 ( $\geq 210$ ) 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             |
| <b>Introduction</b>          |        |  | <b>Page 7-8</b>    |
| 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             |
| <b>Methods</b>               |        |  | <b>Page 8-13</b>   |
| 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/<br>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            |
| <b>Results</b>               |        |  | <b>Page 14-17</b>  |

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| 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<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram   | Page 14, Figure 1<br>Page 14, Figure 1<br>Page 14, Figure 1        |
| Descriptive data         | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) Summarise follow-up time (eg, average and total amount)  | Page 26, Table 1<br>Figure 1<br>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<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Page 30-32, Table 4-5<br>Page 29, Table 3<br>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   |
| <b>Discussion</b>        |     |   | Page 18-23   |
| Key results              | 18  | Summarise key results with reference to study objectives  | Page 3   |
| <b>Limitations</b>       |     |   | 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   |
| <b>Other information</b> |     |   | 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](http://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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|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID:                  | bmjopen-2011-000545.R1   |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 24-Dec-2011  |
| Complete List of Authors:       | <p>Ichikado, Kazuya; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Muranaka, Hiroyuki; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Gushima, Yasuhiro; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Kotani, Toru; Tokyo Women's Medical University, Department of Anesthesiology and Intensive Care<br/> Nader, Habashi; R Adams Cowley Shock Trauma Center, Multi-trauma Intensive Care Unit<br/> Fujimoto, Kiminori; Kurume University School of Medicine, Department of Radiology; Kurume University Hospital, Center for Diagnostic Imaging<br/> Johkoh, Takeshi; Kinki Central Hospital of Mutual Aid Association of Public Teachers, Department of Radiology<br/> Iwamoto, Norihiro; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Kawamura, Kodai; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Nagano, Junji; Kumamoto City Hospital, Pulmonary Division<br/> Fukuda, Kohichiro; Kumamoto City Hospital, Pulmonary Division<br/> Hirata, Naomi; Kumamoto Chu-oh Hospital, Pulmonary Division<br/> Yoshinaga, Takeshi; Kumamoto Chu-oh Hospital, Pulmonary Division<br/> Ichiyasu, Hidenori; Kumamoto University Graduate School of Medical Sciences, Department of Respiratory Medicine<br/> Tsumura, Shinsuke; Kumamoto University Graduate School of Medical Sciences, Department of Respiratory Medicine<br/> Kohrogi, Hirotsugu; Kumamoto University Graduate School of Medical Sciences, Department of Respiratory Medicine<br/> Kawaguchi, Atsushi; Biostatistics Center, Kurume University School of Medicine<br/> Yoshioka, Masakazu; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Sakuma, Tsutomu; Kanazawa Medical University, Thoracic Surgery<br/> Suga, Moritaka; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine</p> |
| <b>Primary Subject Heading</b>: | Respiratory medicine   |

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

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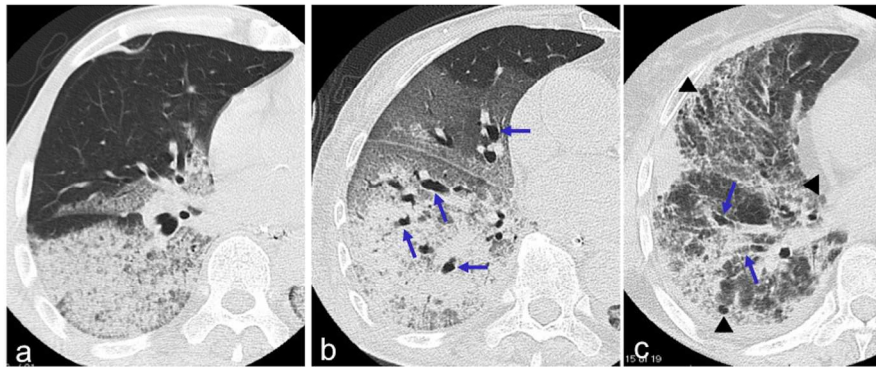


Figure 2a: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumoniae* pneumonia.

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*.

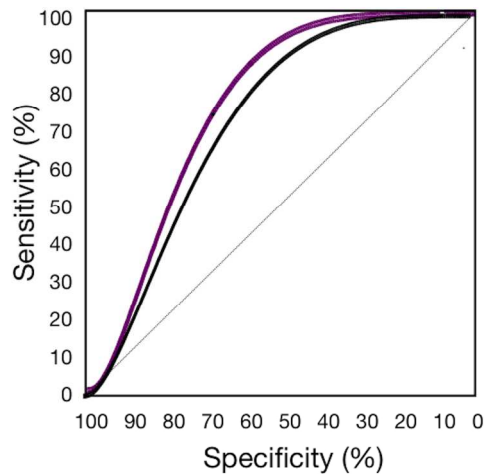
Figure 2c: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old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



— Day 60 mortality; AUC, 0.71 (0.61-0.82); sensitivity, 71 %, specificity, 72 %  
— Day 180 mortality; AUC 0.73 (0.62-0.84); sensitivity, 71 %, specificity, 76 %

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).  
180x124mm (300 x 300 DPI)



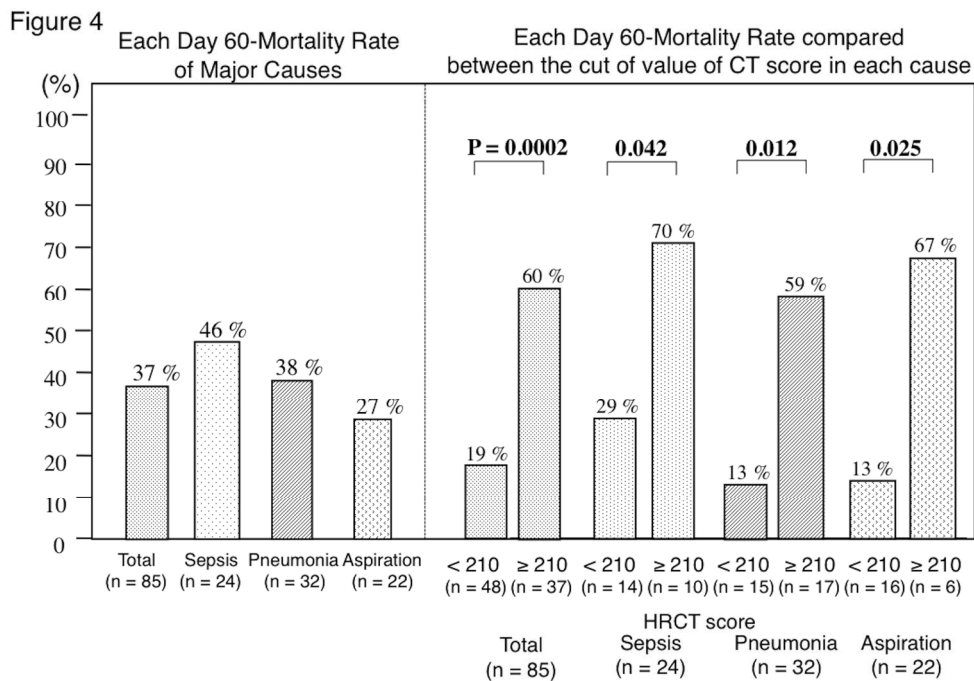
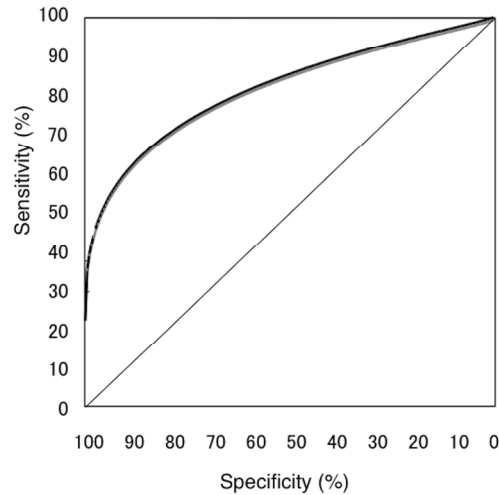


Figure 4a. Day 60-mortality rate of each major cause of ARDS.

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

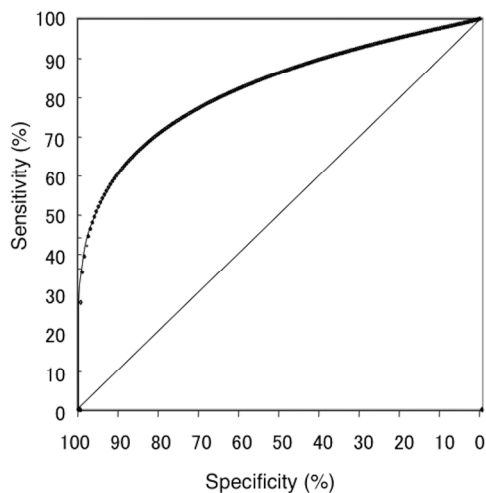


AUC, 0.77 (0.67-0.88); sensitivity, 75 %, specificity, 76 %

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 operating characteristics curve of the prediction  
of the onset of barotrauma



AUC, 0.77 (0.59-0.95); sensitivity, 73 %, specificity, 77 %

Figure 6b.  
Incidence of barotrauma  
Compared between the cut of value  
of CT score

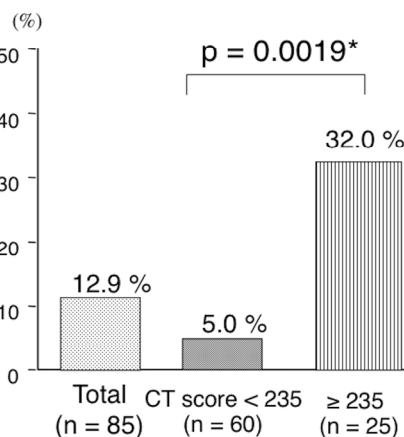
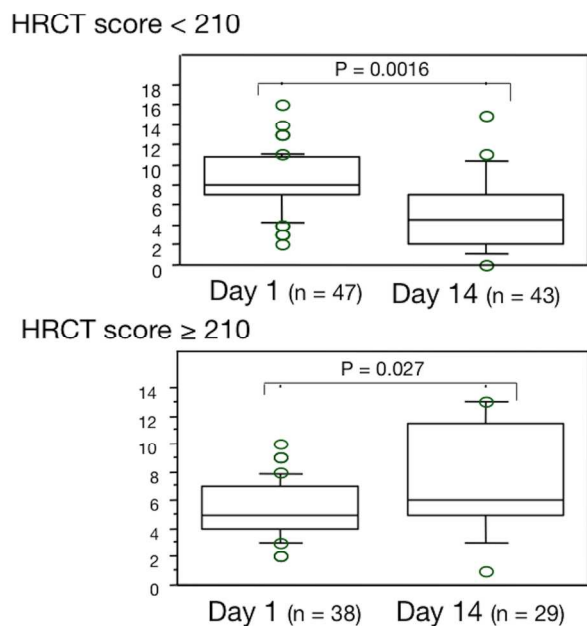


Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumias onset with 73 % sensitivity and 77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

Figure 6b. Comparison of the incidence of barotraumias 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 ( $\geq 210$ ) 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 ( $\geq 210$ ) 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             |
| <b>Introduction</b>          |        |  | <b>Page 7-8</b>    |
| 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             |
| <b>Methods</b>               |        |  | <b>Page 8-13</b>   |
| 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/<br>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            |
| <b>Results</b>               |        |  | <b>Page 14-17</b>  |

|                          |     |  |                       |
|--------------------------|-----|--|-----------------------|
| 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            |
| <b>Discussion</b>        |     |  | Page 18-23            |
| Key results              | 18  | Summarise key results with reference to study objectives   | Page 3                |
| <b>Limitations</b>       |     |  | Page 21-23            |
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\*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.

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6 Fibroproliferative Changes on High-Resolution Computed  
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8 Tomography in the Acute Respiratory Distress Syndrome  
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11 Predict Mortality and Ventilator Dependency: A Prospective  
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48 [ichikado-k-991017@lib.bbiq.jp](mailto:ichikado-k-991017@lib.bbiq.jp) or [kazuya-ichikado@saiseikaikumamoto.jp](mailto:kazuya-ichikado@saiseikaikumamoto.jp)  
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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

For peer review only



### 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

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6 **Objectives:** To examine whether the extent of fibroproliferative changes on  
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8 high-resolution computed tomography (HRCT) scan influences prognosis, ventilator  
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10 dependency, and the associated outcomes in patients with early acute respiratory  
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12 distress syndrome (ARDS).  
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16 **Design:** A prospective observational cohort study  
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19 **Setting:** Intensive care unit in an educational hospital  
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22 **Participants:** Eighty-five patients with ARDS who met American-European Consensus  
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24 Conference Criteria and eligible criteria.  
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27 **Interventions:** HRCT scans were performed and prospectively evaluated by two  
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29 independent observers on the day of diagnosis and graded into six findings according to  
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31 the extent of fibroproliferation. An overall HRCT score was obtained by previously  
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33 published method.  
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37 **Primary and secondary outcomes:** The primary outcomes were 60-day and 180-day  
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39 mortality. Secondary outcomes included the number of ventilator-free days, organ  
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41 failure-free days, the incidence of barotraumas, and the occurrence of  
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43 ventilator-associated pneumonia.  
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48 **Results:** Higher HRCT scores were associated with statistically significant  
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50 decreases in organ-failure free days as well as ventilator-free days. Multivariate Cox  
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52 proportional hazards model showed that the HRCT score remained an independent risk  
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54 factor for mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36; p = 0.005).  
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6 Multivariate analysis also revealed that the CT score had predictive value for  
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8 ventilator-weaning within 28 days (odds ratio 0.63; 95% CI 0.48, 0.82; p = 0.0006) as  
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10 well as for an incidence of barotraumas (1.61; 95%CI 1.08, 2.38; p = 0.018) and for an  
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12 occurrence of ventilator-associated pneumonia (1.46; 95%CI 1.13,1.89; p = 0.004). An  
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14 HRCT score < 210 enabled prediction of 180 day survival with 71 % sensitivity and  
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16 76 % specificity and of ventilator-weaning failure within 28 days with 75 % sensitivity  
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18 and 76 % specificity.  
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24 **Conclusions:** Pulmonary fibroproliferation assessed by HRCT in patients with early  
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26 ARDS predicts increased mortality with an increased susceptibility to multiple organ  
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28 failure, including ventilator dependency and its associated outcomes.  
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#### 34 **Data sharing statement**

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37 There is no additional data available.  
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#### 40 **Research grant**

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43 This research received no specific grant from any funding agency in the public,  
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45 commercial or not-for-profit sectors.  
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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<sup>1,2</sup>. ARDS is considered to have an early and a late phase and is **pathologically classified** into three stages<sup>3</sup> 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<sup>3,4</sup>. **Although pathologic staging may be conceptually useful, commonly used clinical indicators such as PaO<sub>2</sub>/FiO<sub>2</sub> 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<sup>5,6</sup>.

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

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

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35 One hundred and fifty two patients with ARDS diagnosed according to the  
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37 American-European Consensus Conference Criteria<sup>16</sup> were enrolled from October 1,  
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39 2004 to July 31, 2008 at our institution. This study was approved by an institutional  
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41 review board of our hospital, and informed consent was obtained from the participants  
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43 or their families. On the basis of the survival in our retrospective study of 44 patients<sup>15</sup>,  
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46 we designated the number of patients more than 80 at least.  
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## 50 Patients

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53 Eligible patients were receiving mechanical ventilation by tracheal tube (n = 79)  
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55 or mask for non-invasive positive pressure ventilation (n = 6). Furthermore, HRCT scan  
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6 was performed on the day of diagnosis of ARDS by their consent. Exclusion criteria  
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8 were shown in Figure. 1. Especially, preexisting chronic interstitial lung diseases were  
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10 strictly excluded by history taking, imaging data available before onset of ARDS, and  
11  
12 the presence of coarse reticulation and honeycombing on HRCT scans suggesting of  
13  
14 chronic pulmonary fibrosis. Furthermore, the other preexisting pulmonary disease such  
15  
16 as pulmonary emphysema was documented from review of radiological reports.  
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21 Information about our patients' severity and characteristics is reported in Table 1.  
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#### 24 **HRCT examination, assessment, and scoring**

25  
26 All patients underwent whole lung volumetric HRCT scanning of the chest on the day  
27  
28 of diagnosis of ARDS using a multidetector-row CT (MDCT) scan. All MDCT scans  
29  
30 were obtained with 2-mm thickness and 15-mm table speed per rotation and were  
31  
32 performed at full inspiration from the lung apex to base. Contiguous CT slices were  
33  
34 reconstructed using of a high-spatial frequency algorithm. Sections were displayed at  
35  
36 10-mm intervals throughout the chest with the patient in the supine position and without  
37  
38 intravenous contrast medium. The process did not negatively affect the patients'  
39  
40 condition. In this study, we evaluated single CT scan acquired at day one of the ARDS  
41  
42 diagnosis, because sequential CT scans were hard to be performed after high positive  
43  
44 end-expiratory pressure ventilation was introduced. HRCT scans were evaluated on the  
45  
46 day of ARDS diagnosis by two independent observers (**K.Fujimoto. and T.J.**) who  
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60 **were chest radiologists with 23 and 20 years of experience, respectively, and were**

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6 **unaware of patient condition.** The presence and extent of areas of ground-glass  
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8 attenuation, air-space consolidation, traction bronchiectasis, traction bronchiolectasis,  
9  
10 and honeycombing were assessed. Ground-glass attenuation was defined as a hazy area  
11  
12 with increased opacification without obscuration of underlying vascular markings.  
13  
14 Air-space consolidation was considered present when the vascular markings were  
15  
16 obscured. When bronchi were irregular in contour, the dilated bronchus within areas of  
17  
18 parenchymal abnormality was recognized as traction bronchiectasis. Traction  
19  
20 bronchiolectasis was identified by the presence of dilated bronchioles within areas with  
21  
22 parenchymal abnormality. Honeycombing was defined as the presence of cystic  
23  
24 airspaces measuring 2-10 mm in diameter with well-defined walls.  
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32 HRCT findings were graded on a scale of 1-6 based on the classification  
33  
34 system correlating with previously described pathology (Fig. 2)<sup>13,15</sup>: 1, normal  
35  
36 attenuation; 2, ground-glass attenuation; 3, consolidation; 4, ground-glass attenuation  
37  
38 with traction bronchiolectasis or bronchiectasis; 5, consolidation with traction  
39  
40 bronchiolectasis or bronchiectasis; 6, honeycombing. The presence of each of these six  
41  
42 abnormalities was assessed independently in three (upper, middle, lower) zones of each  
43  
44 lung. The upper zone was defined as the area above the level of the carina, the middle  
45  
46 zone as the area between the level of the carina and that of the infrapulmonary vein, and  
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48 the lower zone as the area below the level of the infrapulmonary vein. The extent of  
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50 each abnormality was determined by visually estimating the percentage (to the nearest  
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6 10%) of the affected lung parenchyma in each zone. The assessments of the two  
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8  
9 observers were averaged. The abnormality score for each zone was calculated by  
10  
11 multiplying the percentage area by the point value (1-6). The six zone scores were  
12  
13 averaged to determine the total score for each abnormality in each patient. The overall  
14  
15 CT score for each patient was obtained by adding the six averaged scores. The scoring  
16  
17 system is previously reported<sup>13,15</sup> and has been evaluated in the other diseases<sup>17,18</sup>.

### 21 **Treatment Protocol**

22  
23 All patients underwent a common intensive treatment according to the  
24  
25 domestic clinical practical guidelines<sup>19-23</sup>. Antibiotic therapy was performed by these  
26  
27 guidelines, which were referenced to the American Thoracic Society/Infectious  
28  
29 Diseases Society of America Consensus Guidelines **on the management of**  
30  
31 **community-acquired pneumonia in immunocompetent adults.**<sup>24,25</sup>

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33 **While there is contracting reports for a survival benefit, all randomized**  
34  
35 **trials have shown a significant reduction in duration of mechanical ventilation**<sup>26-29</sup>.  
36  
37 When this study protocol was made, the efficacy of prolonged corticosteroids to the  
38  
39 fibroproliferative ARDS had been reported in a small randomized control study<sup>30</sup>. In the  
40  
41 current study, we examined the relationship between the efficacy of steroids and the  
42  
43 extent of fibroproliferation on HRCT scans. **According to our previous study**<sup>15</sup>, **early**  
44  
45 **fibroproliferation on HRCT scans was observed in 64 % of 44 patients with ARDS.**  
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47 **Therefore, we started corticosteroid therapy after performing HRCT scans at the**  
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6 **diagnosis of ARDS. Initial administration of methylprednisolone with a moderate**  
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8 **dose (2 mg/kg/day) (n = 71) or high-dose (1000 mg/day for three days followed by a**  
9  
10 **moderate dose) (n = 14) was introduced and was gradually tapered over one month**  
11  
12 **according to the previous study<sup>30</sup>. Ventilator management and ventilator weaning was**  
13  
14 introduced by the evidence-based guidelines<sup>22, 23</sup> with reference to the lower tidal  
15  
16 volume ( $V_T$ ) strategy (6 ml/kg predicted body weight (PBW)  $< V_T < 10$  ml/kg PBW) in  
17  
18 the ARDS Clinical Trial<sup>31</sup> and to the guidelines for weaning and discontinuing  
19  
20 ventilatory support from the American College of Chest Physicians<sup>32</sup>.  
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### 26 27 **Screening of ventilator associated outcomes**

28  
29 For each patient, we recorded the number of ventilator-free days. Barotrauma,  
30  
31 defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema,  
32  
33 was noted as present or absent on routine chest radiographs or chest tube insertions for  
34  
35 known or suspected spontaneous pneumothorax during the first 28 days<sup>33</sup>.  
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40 Ventilator associated pneumonia (VAP) surveillance was incorporated into the  
41  
42 routine examinations of cultures of sputum obtained using a sterile intratracheal suction  
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44 tube<sup>34</sup>. VAP was defined as pneumonia occurring after more than 48 hours of  
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46 mechanical ventilation and for up to 72 hours after weaning.  
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### 50 51 **Organ or system failure**

52  
53 Patients were monitored daily for 28 days for signs of the failure of  
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55 extrapulmonary organs and systems according to the ARDS Clinical Trial<sup>31</sup>. The  
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6 number of days without organ or system failure was calculated by subtracting the  
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8 number of days with organ failure from the lesser of 28 days or the number of days to  
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10 death. The Sequential Organ Failure Assessment (SOFA) score was sequentially  
11  
12 monitored at Day 7 and 14, except for patients who died within 7 days or 14 days.  
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### 15 16 **Outcome measurements**

17  
18 The primary outcome was mortality 60 days and 180 days after ARDS diagnosis.  
19  
20 Patients discharged from the hospital while alive for 60 days and 180 days were defined  
21  
22 as survivors. Non-survivors were defined as patients who died in the hospital.  
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24 Secondary outcome variables included the number of ventilator-free days, organ  
25  
26 failure-free days, the incidence of barotraumas, and the occurrence of  
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28 ventilator-associated pneumonia.  
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### 35 36 **Statistical analysis**

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38 Cox proportional hazards regression analysis was used to examine the influence on  
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40 survival of 10 % change of radiologically fibroproliferation on HRCT while adjusting  
41  
42 for other prognostic clinical factors such as age, severity of illness, non-pulmonary  
43  
44 organ dysfunctions, that had been reported<sup>35-37</sup>. Multivariate regression analysis was  
45  
46 also performed to assess the impact on ventilator-weaning failure within 28 days, an  
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48 incidence of barotraumas, and ventilator-associated pneumonia. To analyze the CT  
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50 score as a predictor of survival, or of the failure of ventilator weaning or of the  
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52 occurrence of barotrauma within 28 days after the onset of ARDS, we used  
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6 receiver-operator characteristic (ROC) curves and the corresponding area under the  
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9 curve (AUC) to evaluate how the prediction model performed on the test data and to  
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11 determine the cutoff value of the CT score yielding the highest sensitivity and  
12  
13 specificity which were determined by the Youden index (i.e., sensitivity + specificity –  
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15 1). Statistical analyses were performed by using the SPSS package (version 18.0J; SPSS,  
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17 Tokyo, Japan). For all statistical analyses,  $p < 0.05$  was considered significant.  
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## 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  $\pm$  SD, 195.7  $\pm$  53.7; range,

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6 133.4-325.0) was significantly smaller than that of non-survivors ( $233.1 \pm 46.2$ ;  
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8 174.8-384.8). Construction of a ROC curve yielded an optimal cut-off value of the  
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10 HRCT score of 210 which was determined for prediction of survival at Day 60 with  
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12 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval (CI),  
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14 0.61-0.82) and for prediction of survival at Day 180 with 71 % sensitivity and 76 %  
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16 specificity (AUC, 0.73; 95% CI, 0.62-0.84) (Fig. 3). A significant difference was  
17  
18 observed in the 60-day mortality rate between patients with CT score < 210 and those  
19  
20 with CT score  $\geq$  210 ( $p < 0.0001$ ) as well as in the ventilator-free days at day 28 ( $p <$   
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22 0.0001) (Table 3). The difference in the 60-day mortality rate between patients with  
23  
24 more or less fibroproliferative changes on HRCT scan persisted regardless of causes of  
25  
26 ARDS (Fig. 4). Multivariate Cox proportional hazards model with adjustment for  
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28 demographic characteristics, severity of illness, non-pulmonary organ dysfunctions, and  
29  
30 HRCT score at diagnosis, the HRCT score remained an independent risk factor for  
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32 mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36;  $p = 0.005$ ) when  
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34 expressed as mortality change per 10% increase in the area of attenuation with traction  
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36 bronchiolectasis or bronchiectasis on HRCT scans (Table 4).  
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48 **Relation between the HRCT score and the number of ventilator-free days, and the**  
49 **number of organ-failure-free days and sequential changes of SOFA score**  
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51 An ROC curve determined the best cut-off value of the CT score of 210 for  
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53 prediction of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 %  
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6 specificity (AUC, 0.77; 95% CI, 0.67-0.88) (Fig. 5a). Regardless of significantly higher  
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8 SOFA score ( $8.0 \pm 3.0$  versus  $5.0 \pm 2.0$ ;  $p < 0.0001$ ) and higher DIC score ( $2.8 \pm 1.5$   
9  
10 versus  $1.9 \pm 1.8$ ;  $p < 0.002$ ) at diagnosis, patients with a CT score of  $< 210$  had a  
11  
12 significantly higher number of ventilator-free days ( $14.0 \pm 7.8$  versus  $5.2 \pm 8.0$  days;  $p <$   
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14  $0.0001$ ). Those patients with a lower CT score were associated with less severe  
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16 subsequent multiorgan failure as shown by a significantly higher number of  
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18 organ-failure-free days (Table 3) and by significant decrease of sequential SOFA score  
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20 than that of patients with a higher CT score (Fig.7). Multivariate regression analysis,  
21  
22 with adjustment for demographic characteristics, general severity, and occurrence of  
23  
24 barotraumas, showed that the CT score was independently associated with  
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26 ventilator-weaning within 28 days with an odds ratio of 0.63 when expressed as  
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28 weaning failure change per 10% increase in the area of attenuation with traction  
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30 bronchiolectasis or bronchiectasis on HRCT scans ( $p = 0.0006$ ) (Table 5a).  
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#### 40 **Relation between the HRCT score and the incidence of barotraumas or** 41 42 **ventilator-associated pneumonia** 43 44

45 All eleven patients with barotrauma had pneumothorax. Barotrauma occurred  
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47 3-28 days (mean  $\pm$  SD,  $12.7 \pm 9.4$  days) after ARDS onset. An ROC curve identified the  
48  
49 optimal cutoff value of the CT score of 235 for prediction of barotrauma onset with  
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51 73 % sensitivity and 77 % specificity (AUC, 0.77; 95% CI, 0.59-0.95) (Fig. 6a).  
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56 Patients with the CT score  $< 235$  had a significantly lower incidence of barotrauma (5.0  
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6 versus 32.0 %;  $p = 0.0019$ ) within 28 days after the onset of ARDS than those with CT  
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8 score of  $\geq 235$  (Fig. 5b). The CT score was also independently associated with the  
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10 occurrence of barotraumas with an odds ratio of 1.61 by multivariate regression analysis  
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12 ( $p = 0.018$ ) (Table 6b). Ventilator-associated pneumonia (VAP) was documented in 36  
13  
14 patients (42.3%) after day 5 since ARDS onset. The percentage of patients complicated  
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16 with VAP in the higher CT score group tended to be higher than those in the lower CT  
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18 score groups (51.4 and 35.4 percent, respectively;  $p = 0.14$ ). Multivariate analysis also  
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20 demonstrated that the CT score was independently associated with the complication of  
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22 VAP with an odds ratio of 1.46 ( $p = 0.0041$ ) (Table 5c).  
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## 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<sup>7-10</sup>. 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<sup>7-10</sup>. 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

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6 previous reports and suggested that a clinically early time point does not necessarily  
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8 correspond to a pathologically early phase of ARDS. Given that no significant  
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10 difference in the cause of ARDS was apparent between the survivors and non-survivors  
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12 in this study, no correlation between the HRCT score and the clinical duration of ARDS  
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14 may also be attributable to differences in individual sensitivity to lung injury and in the  
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16 intensity of the consequent exaggerated inflammation that occurs between the onset of  
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18 injury and progression to ARDS. The term “fibroproliferative” ARDS may not  
19  
20 necessarily apply only to “late phase” ARDS but possibly also to “early phase”.  
21  
22 Accordingly, extent of fibroproliferative changes on HRCT scan, together with  
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24 N-PCP-III concentration in BALF, may be a potential clue to differentiate “real” late  
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26 ARDS from the early one.  
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35 Currently, there have been few prospective clinical studies to validate the  
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37 susceptibility to ventilator-associated outcomes. The ARDS Network low tidal  
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39 volume study has suggested that excessive large tidal ventilation induces  
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41 inflammatory cytokines and is associated with a known risk factor for ventilator  
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43 associated lung injury<sup>27</sup>. In the present study, patients with extensive  
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45 fibroproliferation shown as higher HRCT score on the day of ARDS onset needed a  
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47 longer duration of mechanical ventilation with subsequent ventilator-associated  
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49 pneumonia and had shorter organ-failure free days, and subsequently suffered from  
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51 multiple organ failure.  
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6 Barotraumas occurring in critically ill patients independently affects intensive care  
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8 unit mortality<sup>38</sup>. Barotrauma events occur late in the course of ARDS and are related to  
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10 lung structural changes such as cystic or fibroproliferative lesions that develop over  
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12 time<sup>39</sup>. In our study, barotrauma occurred more than 10 days (mean  $\pm$  SD, 12.7  $\pm$  9.4  
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14 days) after the onset of ARDS and was more frequent in patients with a higher HRCT  
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16 score (score  $\geq$  235) than in those with a lower HRCT score (score  $<$  235) during the first  
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18 28 days. Given that a higher HRCT score at diagnosis suggests advanced  
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20 fibroproliferation, our data support the relationship between pulmonary  
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22 fibroproliferation and its susceptibility to barotraumas.  
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30 Ventilator-associated pneumonia (VAP) has been a causative factor of subsequent  
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32 systemic inflammatory syndrome resulting in multi-organ failure<sup>33</sup>. The risk of VAP  
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34 increases with prolonged mechanical ventilation<sup>34</sup>. **Furthermore, sustained and**  
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36 **intense inflammatory responses in unresolving ARDS increase the bi-directional**  
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38 **effects on bacterial growth**<sup>40</sup>. More extensive fibroproliferative changes on HRCT  
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40 scan shown as a higher CT score were associated with a longer ventilator dependency  
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42 that was more susceptible to VAP onset. These results support that pulmonary  
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44 fibroproliferation of ARDS increases risk for ventilator dependency and its associated  
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46 complications.  
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53 In a previous study of 45 cases of ARDS confirmed at biopsy, patients whose  
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55 conditions were shown histologically to be in the acute exudative phase had a better  
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6 prognosis than did those whose condition was shown to be in the fibroproliferative  
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8 phases<sup>41</sup>. **Persistent dysregulated systemic inflammation leading to maladaptive**  
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10 **lung repair results in pulmonary fibroproliferation and progression of**  
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12 **extrapulmonary organ dysfunction**<sup>29</sup>. **Prolonged corticosteroid therapy attenuates**  
13  
14 **systemic inflammation and reduced duration of mechanical ventilation**<sup>29</sup>. In our  
15  
16 study, the group of patients who had less fibroproliferative changes on HRCT scans  
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18 (HRCT score, < 210) showed lower mortality and more ventilator-free days than those  
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20 who had more extensive areas of fibroproliferation (HRCT score, ≥ 210). This may  
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22 suggest a relationship between the pathologic phases of ARDS and responsiveness to  
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24 treatment. **More extensive and rapidly progressive pulmonary fibroproliferation**  
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26 **resulting from intense exaggerated systemic inflammation at presentation occurs,**  
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28 **less effective even prolonged corticosteroid therapy may be.** Whether the patients  
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30 with fibroproliferative predominance have different treatment strategies compared to  
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32 those with exudative predominance has been a vexing question<sup>4</sup>. Improving our  
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34 understanding of disease state and evolution of the disease may be key to the  
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36 development of the optimal therapy and their timing. A method that could be used to  
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38 evaluate and calibrate the clinical to pathologic stages may help prognosticate, alter  
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40 supportive or therapeutic approach to ARDS such as ventilator management and define  
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42 the treatment window for those interventions. Further prospective studies are needed to  
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44 examine the efficacy of the drugs such as corticosteroids according to the extent of  
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6 fibroproliferation on HRCT scans.  
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9       There were some potential limitations. First, our study included few patients with  
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11 ARDS caused by major trauma, multiple transfusion and others, although it included  
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13 approximately 90% of the patients who had ARDS caused by three major etiologies  
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15 (pneumonia, aspiration, sepsis) of ARDS; thus, our study may not sufficiently reflect all  
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17 forms of ARDS. However, previous large randomized control studies also included  
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19 more than 70% of patients with these three etiologies<sup>26,31</sup>. Therefore, our results may  
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21 be applicable to most forms of ARDS.  
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27       Second, many elderly patients (mean age, 75.0 years) were included. Clinically,  
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29 elderly ARDS patients show higher morbidity and need longer duration of mechanical  
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31 ventilation with subsequent poorer prognosis than the younger patients<sup>2,37</sup>. The  
32  
33 age-related differences in mortality and outcomes have been considered to be due to the  
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35 greater number of comorbid illness and higher frequency of non-pulmonary organ  
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37 system failure in older patients<sup>37</sup>. In this study, preexisting pulmonary emphysema was  
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39 seen in 32 (38 %) of 85 patients. Although no significant differences were seen between  
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41 survivors and non-survivors in the number of a history of cigarette smoking and a  
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43 presence of emphysema, we could not evaluate the severity of emphysema before the  
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45 onset of ARDS. Such a smoking-induced chronic lung disease could potentially affect  
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47 ventilator-dependency or prognosis. Although it was problematic whether aging  
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49 increase susceptibility to lung injury and to pulmonary fibroproliferation, further  
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6 investigation of younger patients with ARDS is needed to confirm the consistency of  
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8 the results of our study.  
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11 Third, no correlation was provided with either clinical parameters or pathologic  
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13 findings in the present study. Further investigation is necessary to compare HRCT  
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15 findings with other predictors of morbidity/mortality-i.e. inflammatory biomarkers such  
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17 as serum IL-6 or BAL PCP III levels. Recent studies of biopsy findings from ARDS  
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19 patients have reported the pathologic diversity and only half proportion of typical  
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21 diffuse alveolar damage<sup>5,6</sup>. Regardless of the cause or pathology of ARDS, our study  
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23 highlighted the extent of lung architectural distortion (areas with traction  
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25 bronchiectasis) indicating that pulmonary fibroproliferation on HRCT scans. Although  
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27 fibroproliferative ARDS does not warrant different treatment strategies up to the present,  
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29 prospective evaluation of HRCT findings in patients with ARDS would help therapeutic  
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31 implications in the development of treatment strategies based on the extent of  
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33 fibroproliferation, as well as its prognostic implications.  
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43 **Fourth, when using our cutoff values of HRCT scores, there were**  
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45 **approximately 25 % of our patients who did not fit for prediction of poor**  
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47 **prognosis or ventilator dependency. Recently, multiple organ failure in ARDS**  
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49 **patients is considered to be either as the predisposing condition or as a**  
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51 **consequence of ARDS<sup>42</sup>. If ARDS occurs as one of multiple organ failure, even**  
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53 **though pulmonary fibroproliferation was mild, extra-pulmonary dysfunction**  
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6 **could be the determinant of the outcome.**  
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9       On the basis of our results, extensive HRCT abnormalities indicative of  
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11 fibroproliferative changes on the day of ARDS diagnosis were independently predictive  
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13 of poor prognosis and prolonged mechanical ventilation, and were also associated with  
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15 subsequent multiple organ failure. Pulmonary fibroproliferation that occurs early in  
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17 ARDS patients increases mortality risk by increasing susceptibility to ventilator  
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19 dependency and its associated complications.  
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## ACKNOWLEDGEMENTS

**Author contributions:** Dr Suga takes full responsibility for the integrity of all the data and the accuracy of the data analysis.

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.

Dr Habashi: contributed to reanalyzing the data and revising the manuscript.

Dr Fujimoto: contributed to reanalyzing the data and revising the manuscript.

Dr Johkoh: contributed to reanalyzing the data and revising the manuscript.

Dr Iwamoto: contributed to collecting the data and revising the manuscript.

Dr Kawamura: contributed to collecting the data and revising the manuscript.

Dr Nagano: contributed to collecting the data and revising the manuscript.

Dr Fukuda: contributed to collecting the data and revising the manuscript.

Dr Hirata: contributed to collecting the data and revising the manuscript.

Dr Yoshinaga: contributed to reanalyzing the data and revising the manuscript.

Dr Ichiyasu: contributed to collecting the data and revising the manuscript.

Dr Tsumura: contributed to collecting the data and revising the manuscript.

Dr Kohrogi: contributed to reanalyzing the data and revising the manuscript.

Dr Kawaguchi: contributed to reanalyzing the data and revising the manuscript.

Dr Yoshioka: contributed to reanalyzing the data and revising the manuscript.

Dr Sakuma: contributed to reanalyzing the data and revising the manuscript.

**Other persons contributing to this study:** We appreciate Michael A. Matthay, MD<sup>1</sup>, and

Hiroshi Kubo, MD, PhD<sup>2</sup> for their editorial assistance and also thank Isamu Cho, MD, PhD<sup>3</sup>,

Tomoki Tanaka, MD<sup>3</sup>, Junichi Maehara, MD<sup>4</sup>, Shigeo Hiroshige, MD<sup>5</sup>, Makoto Takaki, MD<sup>5</sup>,

Mitsuko Honda, MD<sup>5</sup>, Naoko Arakawa, MD<sup>5</sup>, Yuko Yasuda, MD<sup>5</sup>, Makiko Takeguchi, MD<sup>5</sup>,

Aoi Teruya, MD<sup>5</sup>, Yoshitomo Eguchi, MD<sup>5</sup>, Naoki Shingu, MD<sup>5</sup>, and Yoshihiko Sakata, MD<sup>5</sup>

for their clinical assistance.

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

| Characteristic                                   | Total<br>(n = 85) | 60 days               |                                       | p value |
|--|-------------------|-----------------------|---------------------------------------|---------|
|  |                   | Survivors<br>(n = 54) | Outcomes<br>Non-survivors<br>(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 <sub>2</sub> :FiO <sub>2</sub>               | 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<br>(per mm <sup>3</sup> ) | 10600 ± 6788      | 10600 ± 6178          | 10600 ± 7839                          | 0.63    |

|  |             |             |             |        |
|--|-------------|-------------|-------------|--------|
| C-reactive protein (CRP)<br>(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<br>(LDH) (IU/L)        | 308 ± 185   | 301 ± 147   | 339 ± 235   | 0.29   |
| Platelet count (per mm <sup>3</sup> )        | 20.1 ± 10.7 | 20.7 ± 11.0 | 18.9 ± 10.3 | 0.94   |
| Days of CT scanning<br>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<br>predicted body weight | 8.0 ± 0.8   | 8.0 ± 0.7   | 8.0 ± 0.9   | 0.54   |
| Plateau pressure, cmH <sub>2</sub> O         | 21.5 ± 4.2  | 21.0 ± 3.8  | 23.0 ± 4.7  | 0.34   |
| Initial PEEP, cmH <sub>2</sub> O             | 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<br>(n = 54) | Non-survivors<br>(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<br>or bronchiectasis            | 88.0 ± 22.0           | 78.2 ± 22.5               | 0.01    |
| Ground-glass attenuation plus traction<br>bronchiolectasis or bronchiectasis | 9.3 ± 17.8            | 16.6 ± 21.7               | 0.08    |
| Air-space consolidation plus traction<br>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<br>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-resolution CT at the onset of**

**ARDS**

| Variable                                   | High-Resolution Computed Tomographic<br>(CT) score |                   | p value  |
|--|--|-------------------|----------|
|  | < 210<br>(n = 47)                                  | ≥ 210<br>(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 <sub>2</sub> / FiO <sub>2</sub> 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 <sub>2</sub> / FiO <sub>2</sub> 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 pneumoniae*.

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 pneumoniae*. (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).

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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.

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

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6 score ( $\geq 210$ ) significantly increased from day 1 to day 14 ( $p = 0.027$ ). Four patients  
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8 with a lower CT score ( $< 210$ ) and 9 patients with a higher CT score ( $\geq 210$ ) who died  
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10 within 14 days were excluded.  
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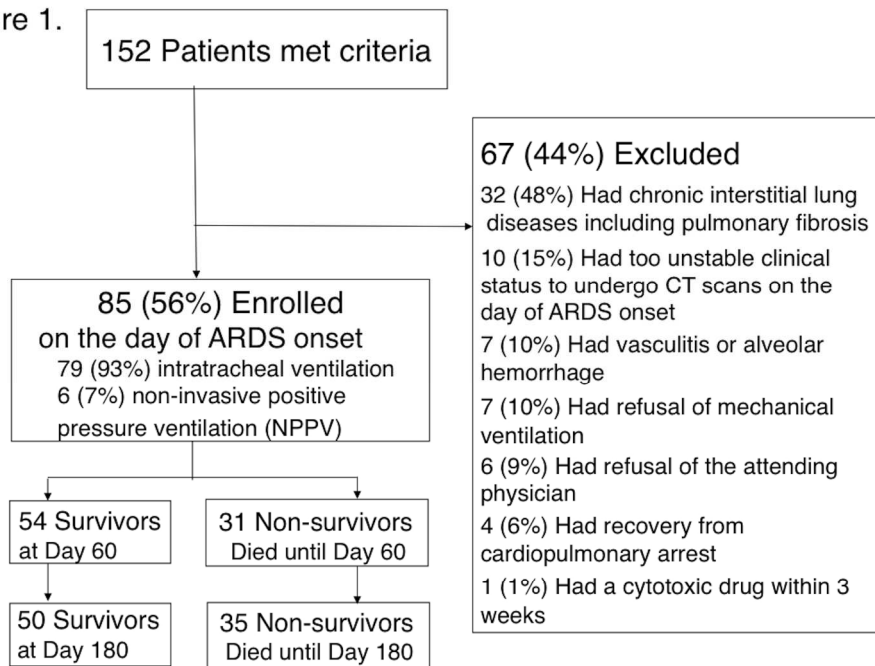
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Figure 1.



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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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|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID:                  | bmjopen-2011-000545.R2   |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 18-Jan-2012  |
| Complete List of Authors:       | <p>Ichikado, Kazuya; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Muranaka, Hiroyuki; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Gushima, Yasuhiro; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Kotani, Toru; Tokyo Women's Medical University, Department of Anesthesiology and Intensive Care<br/> Nader, Habashi; R Adams Cowley Shock Trauma Center, Multi-trauma Intensive Care Unit<br/> Fujimoto, Kiminori; Kurume University School of Medicine, Department of Radiology; Kurume University Hospital, Center for Diagnostic Imaging<br/> Johkoh, Takeshi; Kinki Central Hospital of Mutual Aid Association of Public Teachers, Department of Radiology<br/> Iwamoto, Norihiro; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Kawamura, Kodai; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Nagano, Junji; Kumamoto City Hospital, Pulmonary Division<br/> Fukuda, Kohichiro; Kumamoto City Hospital, Pulmonary Division<br/> Hirata, Naomi; Kumamoto Chu-oh Hospital, Pulmonary Division<br/> Yoshinaga, Takeshi; Kumamoto Chu-oh Hospital, Pulmonary Division<br/> Ichiyasu, Hidenori; Kumamoto University Graduate School of Medical Sciences, Department of Respiratory Medicine<br/> Tsumura, Shinsuke; Kumamoto University Graduate School of Medical Sciences, Department of Respiratory Medicine<br/> Kohrogi, Hirotsugu; Kumamoto University Graduate School of Medical Sciences, Department of Respiratory Medicine<br/> Kawaguchi, Atsushi; Biostatistics Center, Kurume University School of Medicine<br/> Yoshioka, Masakazu; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine<br/> Sakuma, Tsutomu; Kanazawa Medical University, Thoracic Surgery<br/> Suga, Moritaka; Saiseikai Kumamoto Hospital, Division of Respiratory Medicine</p> |
| <b>Primary Subject Heading</b>: | Respiratory medicine   |

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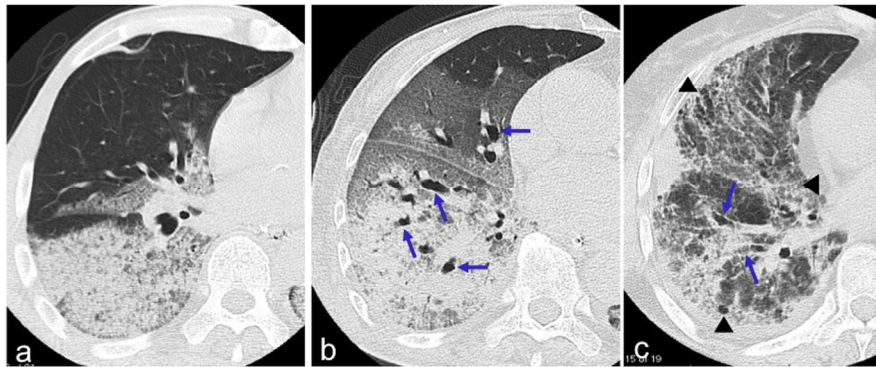


Figure 2a: High-resolution CT findings corresponding to exudative phase of ARDS. HRCT scan at the level of right middle lobe shows dependent airspace consolidation and nondependent areas of sparing. The patient was a 68-year-old man with ARDS due to *Streptococcus pneumoniae* pneumonia.

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.

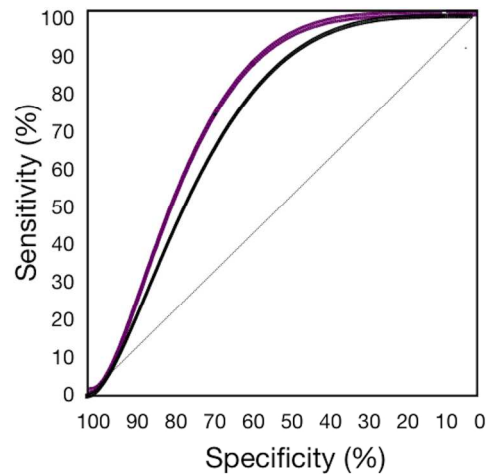
Figure 2c: High-resolution CT findings corresponding to fibrotic phase of ARDS. HRCT scan at the level of right inferior pulmonary vein shows extensive ground-glass attenuation associated with traction bronchiectasis (arrows), coarse reticulation and cystic changes (arrowheads). The patient was a 65-year-old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



— Day 60 mortality; AUC, 0.71 (0.61-0.82); sensitivity, 71 %, specificity, 72 %  
— Day 180 mortality; AUC 0.73 (0.62-0.84); sensitivity, 71 %, specificity, 76 %

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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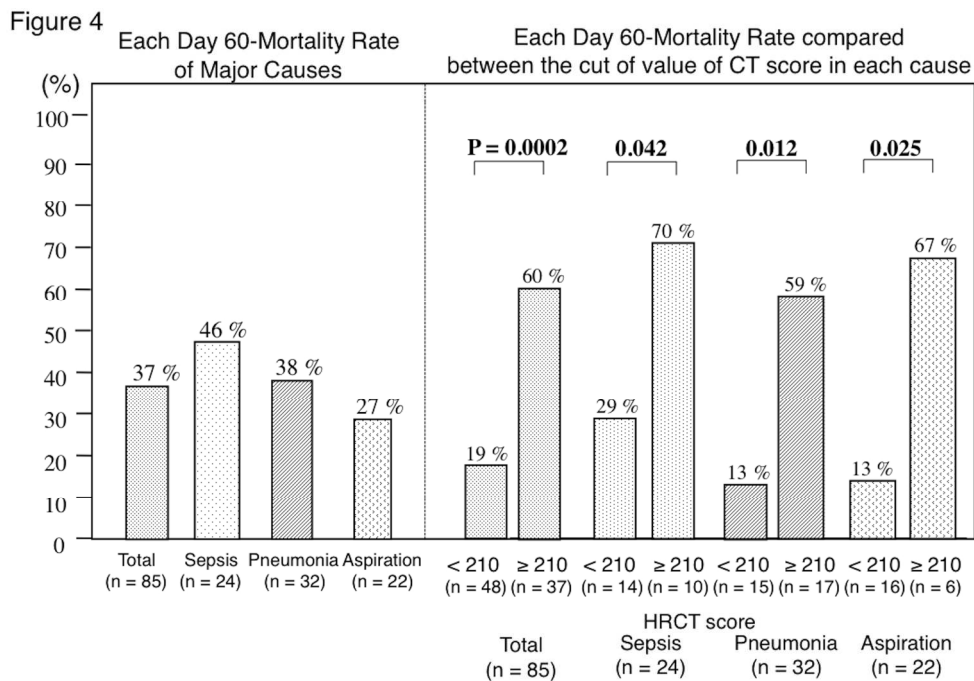
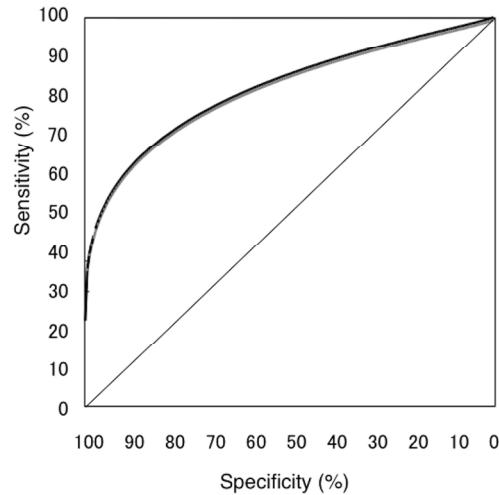


Figure 4a. Day 60-mortality rate of each major cause of ARDS.

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

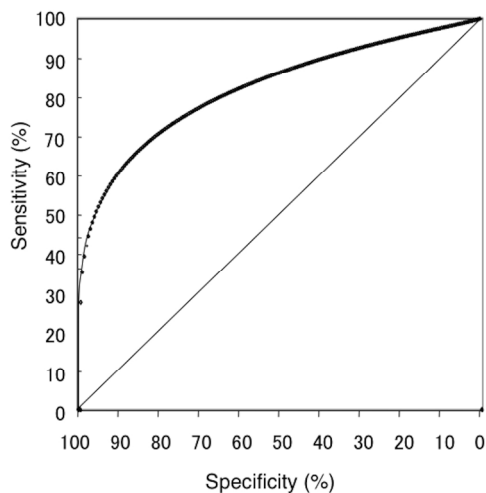


AUC, 0.77 (0.67-0.88); sensitivity, 75 %, specificity, 76 %

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 operating characteristics curve of the prediction  
of the onset of barotrauma



AUC, 0.77 (0.59-0.95); sensitivity, 73 %, specificity, 77 %

Figure 6b.  
Incidence of barotrauma  
Compared between the cut of value  
of CT score

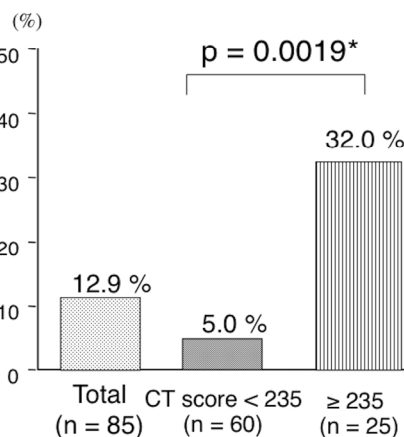
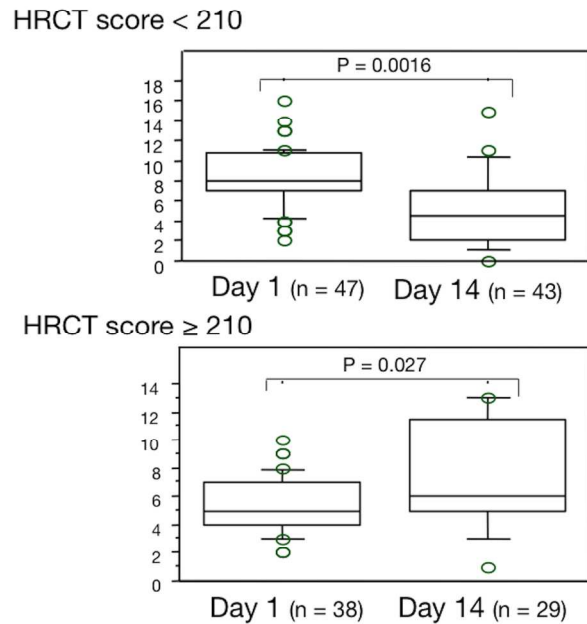


Figure 6a. Receiver operator characteristic (ROC) curve of prediction of the onset of barotrauma from high-resolution computed tomography (HRCT) score. ROC curve identified the optimal cut-off value of 235 determined by the Youden Index for prediction of barotraumias onset with 73 % sensitivity and 77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

Figure 6b. Comparison of the incidence of barotraumias 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 ( $\geq 210$ ) 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 ( $\geq 210$ ) 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*

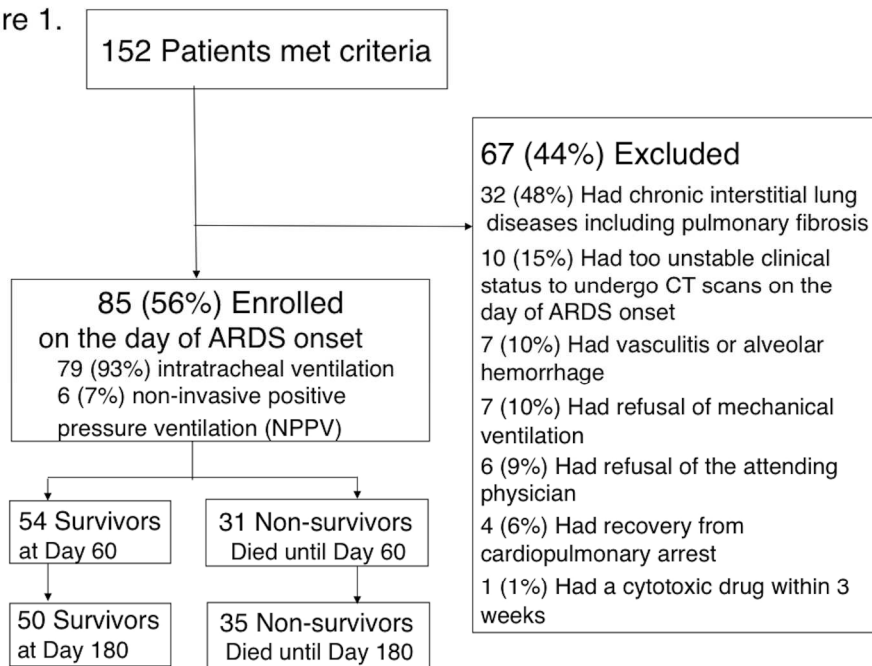
| Section/Topic                | Item # | Recommendation   | Reported on page # |
|------------------------------|--------|--|--------------------|
| Title and abstract           | 1      | (a) Indicate the study's design with a commonly used term in the title or the abstract   | Page 4             |
|                              |        | (b) Provide in the abstract an informative and balanced summary of what was done and what was found  | Page 4             |
| <b>Introduction</b>          |        |  | <b>Page 7-8</b>    |
| 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             |
| <b>Methods</b>               |        |  | <b>Page 8-13</b>   |
| 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/<br>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            |
| <b>Results</b>               |        |  | <b>Page 14-17</b>  |

|                          |     |  |                       |
|--------------------------|-----|--|-----------------------|
| 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            |
| <b>Discussion</b>        |     |  | Page 18-23            |
| Key results              | 18  | Summarise key results with reference to study objectives   | Page 3                |
| <b>Limitations</b>       |     |  | 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            |
| <b>Other information</b> |     |  | 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](http://www.strobe-statement.org).

Figure 1.



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8 Tomography in the Acute Respiratory Distress Syndrome  
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11 Predict Mortality and Ventilator Dependency: A Prospective  
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14 Observational Cohort Study  
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6 **Conflict of interest disclosures:** None of the authors has declared any conflict of interest  
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13 **Keywords**

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15 acute respiratory distress syndrome, high-resolution computed tomography,  
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### 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



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6 **Objectives:** To examine whether the extent of fibroproliferative changes on  
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8 high-resolution computed tomography (HRCT) scan influences prognosis, ventilator  
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10 dependency, and the associated outcomes in patients with early acute respiratory  
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12 distress syndrome (ARDS).  
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16 **Design:** A prospective observational cohort study  
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19 **Setting:** Intensive care unit in a teaching hospital  
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22 **Participants:** Eighty-five patients with ARDS who met American-European Consensus  
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24 Conference Criteria and eligible criteria.  
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27 **Interventions:** HRCT scans were performed and prospectively evaluated by two  
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29 independent observers on the day of diagnosis and graded into six findings according to  
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31 the extent of fibroproliferation. An overall HRCT score was obtained by previously  
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33 published method.  
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37 **Primary and secondary outcomes: The primary outcome was 60-day mortality.**  
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40 Secondary outcomes included the number of ventilator-free days, organ failure-free  
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42 days, the incidence of barotraumas, and the occurrence of ventilator-associated  
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44 pneumonia.  
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48 **Results:** Higher HRCT scores were associated with statistically significant decreases in  
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50 organ-failure free days as well as ventilator-free days. Multivariate Cox proportional  
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52 hazards model showed that the HRCT score remained an independent risk factor for  
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54 mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36;  $p = 0.005$ ).  
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6 Multivariate analysis also revealed that the CT score had predictive value for  
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8 ventilator-weaning within 28 days (odds ratio 0.63; 95% CI 0.48, 0.82; p = 0.0006) as  
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10 well as for an incidence of barotraumas (1.61; 95%CI 1.08, 2.38; p = 0.018) and for an  
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12 occurrence of ventilator-associated pneumonia (1.46; 95%CI 1.13,1.89; p = 0.004). **An**  
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14 **HRCT score < 210 enabled prediction of 60 day survival with 71 % sensitivity and**  
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16 **72 % specificity** and of ventilator-weaning failure within 28 days with 75 % sensitivity  
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18 and 76 % specificity.  
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24 **Conclusions:** Pulmonary fibroproliferation assessed by HRCT in patients with early  
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26 ARDS predicts increased mortality with an increased susceptibility to multiple organ  
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28 failure, including ventilator dependency and its associated outcomes.  
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#### 34 **Data sharing statement**

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37 There is no additional data available.  
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#### 40 **Research grant**

41  
42  
43 This research received no specific grant from any funding agency in the public,  
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45 commercial or not-for-profit sectors.  
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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<sup>1,2</sup>. ARDS is considered to have an early and a late phase and is pathologically classified into three stages<sup>3</sup> 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<sup>3,4</sup>. **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 (fibroproliferation 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<sup>5</sup>. Although pathologic staging may be conceptually useful, improvement vs. worsening in physiological parameters (i.e., PaO<sub>2</sub>/FiO<sub>2</sub> 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,

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6 however, few features, except probably time, allow them to distinguish these  
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8 pathological phases without a lung biopsy<sup>6,7</sup>.  
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11 Data regarding the significance of a fibroproliferative response on mortality  
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13 risk assessed using bronchoalveolar lavage or tracheal aspirate in ARDS patients is  
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15 available<sup>8-11</sup>. High-resolution computed tomographic (HRCT) findings correlate with  
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17 the pathologic phases of diffuse alveolar damage<sup>12-15</sup>. Furthermore, we have previously  
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19 reported on the prognostic value of HRCT in determining the extent of  
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21 fibroproliferation in ARDS patients<sup>16</sup>. Based on HRCT appearance, less  
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23 fibroproliferation in early ARDS was associated with greater ventilator-free days and  
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25 less barotraumas<sup>16</sup>. **Because ARDS is a systemic disease with systemic inflammation,**  
26  
27 **core pathogenetic process affects the lung as well as extra-pulmonary vital organs.**  
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29 **In this prospective study, we evaluated not only what was found in the**  
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31 **retrospective study<sup>16</sup> but also the relationship between early fibroproliferation and**  
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33 **the progression to multiple organ failure;** whether the extent of fibroproliferation on  
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35 HRCT scan at the time diagnosis of ARDS would impact the susceptibility for ventilator  
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37 dependency and its associated complications and on the mortality.  
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## 48 METHODS

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50 One hundred and fifty two patients with ARDS diagnosed according to the  
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52 American-European Consensus Conference Criteria<sup>17</sup> were enrolled from October 1,  
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54 2004 to July 31, 2008 at our institution. This study was approved by an institutional  
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6 review board of our hospital, and informed consent was obtained from the participants  
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8 or their families. On the basis of the survival in our retrospective study of 44 patients<sup>16</sup>,  
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10 we designated the number of patients more than 80 at least.  
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### 13 **Patients**

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

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42 All patients underwent whole lung volumetric HRCT scanning of the chest on the day  
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44 of diagnosis of ARDS using a multidetector-row CT (MDCT) scan. All MDCT scans  
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46 were obtained with 2-mm thickness and 15-mm table speed per rotation and were  
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48 performed at full inspiration from the lung apex to base. Contiguous CT slices were  
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50 reconstructed using of a high-spatial frequency algorithm. Sections were displayed at  
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52 10-mm intervals throughout the chest with the patient in the supine position and without  
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6 intravenous contrast medium. The process did not negatively affect the patients'  
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9 condition. In this study, we evaluated single CT scan acquired at day one of the ARDS  
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11 diagnosis, because sequential CT scans were hard to be performed after high positive  
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13 end-expiratory pressure ventilation was introduced. HRCT scans were evaluated on the  
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15 day of ARDS diagnosis by two independent observers (K.Fujimoto. and T.J.) who were  
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17 chest radiologists with 23 and 20 years of experience, respectively, and were unaware of  
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19 patient condition. The presence and extent of areas of ground-glass attenuation,  
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22 air-space consolidation, traction bronchiectasis, traction bronchiolectasis, and  
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25 honeycombing were assessed. Ground-glass attenuation was defined as a hazy area with  
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27 increased opacification without obscuration of underlying vascular markings. Air-space  
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29 consolidation was considered present when the vascular markings were obscured. When  
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31 bronchi were irregular in contour, the dilated bronchus within areas of parenchymal  
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33 abnormality was recognized as traction bronchiectasis. Traction bronchiolectasis was  
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35 identified by the presence of dilated bronchioles within areas with parenchymal  
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37 abnormality. Honeycombing was defined as the presence of cystic airspaces measuring  
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46 2-10 mm in diameter with well-defined walls.

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48 HRCT findings were graded on a scale of 1-6 based on the classification  
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50 system correlating with previously described pathology (Fig. 2) <sup>14,16</sup>: 1, normal  
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52 attenuation; 2, ground-glass attenuation; 3, consolidation; 4, ground-glass attenuation  
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54 with traction bronchiolectasis or bronchiectasis; 5, consolidation with traction  
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6 bronchiolectasis or bronchiectasis; 6, honeycombing. The presence of each of these six  
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9 abnormalities was assessed independently in three (upper, middle, lower) zones of each  
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11 lung. The upper zone was defined as the area above the level of the carina, the middle  
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13 zone as the area between the level of the carina and that of the infrapulmonary vein, and  
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15 the lower zone as the area below the level of the infrapulmonary vein. The extent of  
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17 each abnormality was determined by visually estimating the percentage (to the nearest  
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19 10%) of the affected lung parenchyma in each zone. The assessments of the two  
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21 observers were averaged. The abnormality score for each zone was calculated by  
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23 multiplying the percentage area by the point value (1-6). The six zone scores were  
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25 averaged to determine the total score for each abnormality in each patient. The overall  
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27 CT score for each patient was obtained by adding the six averaged scores. The scoring  
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29 system is previously reported<sup>14,16</sup> and has been evaluated in the other diseases<sup>18,19</sup>.

### 37 38 **Treatment Protocol**

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

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53 **While there is contradicting reports for a survival benefit, all randomized**  
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55 **trials have shown a significant reduction in duration of mechanical ventilation<sup>27-30</sup>.**  
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6 When this study protocol was made, the efficacy of prolonged corticosteroids to the  
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8 fibroproliferative ARDS had been reported in a small randomized control study<sup>30</sup>. In the  
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10 current study, we examined the relationship between the efficacy of steroids and the  
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12 extent of fibroproliferation on HRCT scans. According to our previous study<sup>16</sup>, early  
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14 fibroproliferation on HRCT scans was observed in 64 % of 44 patients with ARDS.  
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16 Therefore, we started corticosteroid therapy after performing HRCT scans at the  
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18 diagnosis of ARDS. Initial administration of methylprednisolone with a moderate dose  
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20 (2 mg/kg/day) (n = 71) or high-dose (1000 mg/day for three days followed by a  
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22 moderate dose) (n = 14) was introduced and was gradually tapered over one month  
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24 according to the previous study<sup>30</sup>. Ventilator management and ventilator weaning was  
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26 introduced by the evidence-based guidelines<sup>23, 24</sup> with reference to the lower tidal  
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28 volume ( $V_T$ ) strategy (6 ml/kg predicted body weight (PBW) <  $V_T$  < 10 ml/kg PBW) in  
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30 the ARDS Clinical Trial<sup>31</sup> and to the guidelines for weaning and discontinuing  
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32 ventilatory support from the American College of Chest Physicians<sup>32</sup>.  
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### 43 **Screening of ventilator associated outcomes**

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45 For each patient, we recorded the number of ventilator-free days. Barotrauma,  
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47 defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema,  
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49 was noted as present or absent on routine chest radiographs or chest tube insertions for  
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51 known or suspected spontaneous pneumothorax during the first 28 days<sup>33</sup>.  
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56 Ventilator associated pneumonia (VAP) surveillance was incorporated into the  
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6 routine examinations of cultures of sputum obtained using a sterile intratracheal suction  
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8 tube<sup>34</sup>. VAP was defined as pneumonia occurring after more than 48 hours of  
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10 mechanical ventilation and for up to 72 hours after weaning.  
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### 13 14 **Organ or system failure**

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16 Patients were monitored daily for 28 days for signs of the failure of  
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18 extrapulmonary organs and systems according to the ARDS Clinical Trial<sup>31</sup>. The  
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20 number of days without organ or system failure was calculated by subtracting the  
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22 number of days with organ failure from the lesser of 28 days or the number of days to  
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24 death. The Sequential Organ Failure Assessment (SOFA) score was sequentially  
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26 monitored at Day 7 and 14, except for patients who died within 7 days or 14 days.  
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### 32 **Outcome measurements**

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35 **The primary outcome was mortality 60 days after ARDS diagnosis. Patients**  
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37 **discharged from the hospital while alive for 60 days were defined as survivors.**

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40 **Their prognoses were eventually followed until 180 days.** Non-survivors were  
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42 defined as patients who died in the hospital. Secondary outcome variables included the  
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44 number of ventilator-free days, organ failure-free days, the incidence of barotraumas,  
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46 and the occurrence of ventilator-associated pneumonia.  
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### 50 **Statistical analysis**

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53 Cox proportional hazards regression analysis was used to examine the influence on  
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55 survival of 10 % change of radiologically fibroproliferation on HRCT while adjusting  
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6 for other prognostic clinical factors such as age, severity of illness, non-pulmonary  
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8 organ dysfunctions, that had been reported<sup>35-37</sup>. Multivariate regression analysis was  
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10 also performed to assess the impact on ventilator-weaning failure within 28 days, an  
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12 incidence of barotraumas, and ventilator-associated pneumonia. To analyze the CT  
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14 score as a predictor of survival, or of the failure of ventilator weaning or of the  
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16 occurrence of barotrauma within 28 days after the onset of ARDS, we used  
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18 receiver-operator characteristic (ROC) curves and the corresponding area under the  
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20 curve (AUC) to evaluate how the prediction model performed on the test data and to  
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22 determine the cutoff value of the CT score yielding the highest sensitivity and  
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24 specificity which were determined by the Youden index (i.e., sensitivity + specificity –  
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26 1). Statistical analyses were performed by using the SPSS package (version 18.0J; SPSS,  
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28 Tokyo, Japan). For all statistical analyses,  $p < 0.05$  was considered significant.  
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## 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  $\pm$  SD, 195.7  $\pm$  53.7; range,

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6 133.4-325.0) was significantly smaller than that of non-survivors ( $233.1 \pm 46.2$ ;  
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8 174.8-384.8). Construction of a ROC curve yielded an optimal cut-off value of the  
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10 HRCT score of 210 which was determined for prediction of survival at Day 60 with  
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12 71 % sensitivity of and 72 % specificity (AUC, 0.71; 95% confidence interval (CI),  
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14 0.61-0.82) and for prediction of survival at Day 180 with 71 % sensitivity and 76 %  
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16 specificity (AUC, 0.73; 95% CI, 0.62-0.84) (Fig. 3). A significant difference was  
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18 observed in the 60-day mortality rate between patients with CT score < 210 and those  
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20 with CT score  $\geq$  210 ( $p < 0.0001$ ) as well as in the ventilator-free days at day 28 ( $p <$   
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22 0.0001) (Table 3). The difference in the 60-day mortality rate between patients with  
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24 more or less fibroproliferative changes on HRCT scan persisted regardless of causes of  
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26 ARDS (Fig. 4). Multivariate Cox proportional hazards model with adjustment for  
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28 demographic characteristics, severity of illness, non-pulmonary organ dysfunctions, and  
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30 HRCT score at diagnosis, the HRCT score remained an independent risk factor for  
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32 mortality (hazard ratio 1.20; 95% confidence interval 1.06, 1.36;  $p = 0.005$ ) when  
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34 expressed as mortality change per 10% increase in the area of attenuation with traction  
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36 bronchiolectasis or bronchiectasis on HRCT scans (Table 4).  
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48 **Relation between the HRCT score and the number of ventilator-free days, and the**  
49 **number of organ-failure-free days and sequential changes of SOFA score**  
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51 An ROC curve determined the best cut-off value of the CT score of 210 for  
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53 prediction of ventilator-weaning failure within 28 days with 75 % sensitivity and 76 %  
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6 specificity (AUC, 0.77; 95% CI, 0.67-0.88) (Fig. 5a). Regardless of significantly higher  
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8 SOFA score ( $8.0 \pm 3.0$  versus  $5.0 \pm 2.0$ ;  $p < 0.0001$ ) and higher DIC score ( $2.8 \pm 1.5$   
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10 versus  $1.9 \pm 1.8$ ;  $p < 0.002$ ) at diagnosis, patients with a CT score of  $< 210$  had a  
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12 significantly higher number of ventilator-free days ( $14.0 \pm 7.8$  versus  $5.2 \pm 8.0$  days;  $p <$   
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14  $0.0001$ ). Those patients with a lower CT score were associated with less severe  
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16 subsequent multiorgan failure as shown by a significantly higher number of  
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18 organ-failure-free days (Table 3) and by significant decrease of sequential SOFA score  
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20 than that of patients with a higher CT score (Fig.7). Multivariate regression analysis,  
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22 with adjustment for demographic characteristics, general severity, and occurrence of  
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24 barotraumas, showed that the CT score was independently associated with  
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26 ventilator-weaning within 28 days with an odds ratio of 0.63 when expressed as  
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28 weaning failure change per 10% increase in the area of attenuation with traction  
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30 bronchiolectasis or bronchiectasis on HRCT scans ( $p = 0.0006$ ) (Table 5a).  
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#### 40 **Relation between the HRCT score and the incidence of barotraumas or** 41 42 **ventilator-associated pneumonia** 43 44

45 All eleven patients with barotrauma had pneumothorax. Barotrauma occurred  
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47 3-28 days (mean  $\pm$  SD,  $12.7 \pm 9.4$  days) after ARDS onset. An ROC curve identified the  
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49 optimal cutoff value of the CT score of 235 for prediction of barotrauma onset with  
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51 73 % sensitivity and 77 % specificity (AUC, 0.77; 95% CI, 0.59-0.95) (Fig. 6a).  
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56 Patients with the CT score  $< 235$  had a significantly lower incidence of barotrauma (5.0  
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6 versus 32.0 %;  $p = 0.0019$ ) within 28 days after the onset of ARDS than those with CT  
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8 score of  $\geq 235$  (Fig. 5b). The CT score was also independently associated with the  
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10 occurrence of barotraumas with an odds ratio of 1.61 by multivariate regression analysis  
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12 ( $p = 0.018$ ) (Table 6b). Ventilator-associated pneumonia (VAP) was documented in 36  
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14 patients (42.3%) after day 5 since ARDS onset. The percentage of patients complicated  
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16 with VAP in the higher CT score group tended to be higher than those in the lower CT  
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18 score groups (51.4 and 35.4 percent, respectively;  $p = 0.14$ ). Multivariate analysis also  
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20 demonstrated that the CT score was independently associated with the complication of  
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22 VAP with an odds ratio of 1.46 ( $p = 0.0041$ ) (Table 5c).  
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## 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<sup>8-11</sup>. 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<sup>8-11</sup>. 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



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6 previous reports and suggested that a clinically early time point does not necessarily  
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8 correspond to a pathologically early phase of ARDS. Given that no significant  
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10 difference in the cause of ARDS was apparent between the survivors and non-survivors  
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12 in this study, no correlation between the HRCT score and the clinical duration of ARDS  
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14 may also be attributable to differences in individual sensitivity to lung injury and in the  
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16 intensity of the consequent exaggerated inflammation that occurs between the onset of  
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18 injury and progression to ARDS. The term “fibroproliferative” ARDS may not  
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20 necessarily apply only to “late phase” ARDS but possibly also to “early phase”.  
21  
22 Accordingly, extent of fibroproliferative changes on HRCT scan, together with  
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24 N-PCP-III concentration in BALF, may be a potential clue to differentiate “real” late  
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26 ARDS from the early one.  
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35 Currently, there have been few prospective clinical studies to validate the  
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37 susceptibility to ventilator-associated outcomes. The ARDS Network low tidal  
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39 volume study has suggested that excessive large tidal ventilation induces  
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41 inflammatory cytokines and is associated with a known risk factor for ventilator  
42  
43 associated lung injury<sup>31</sup>. In the present study, patients with extensive  
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45 fibroproliferation shown as higher HRCT score on the day of ARDS onset needed a  
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47 longer duration of mechanical ventilation with subsequent ventilator-associated  
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49 pneumonia and had shorter organ-failure free days, and subsequently suffered from  
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51 multiple organ failure.  
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6 Barotraumas occurring in critically ill patients independently affects intensive care  
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8 unit mortality<sup>38</sup>. Barotrauma events occur late in the course of ARDS and are related to  
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10 lung structural changes such as cystic or fibroproliferative lesions that develop over  
11  
12 time<sup>39</sup>. In our study, barotrauma occurred more than 10 days (mean  $\pm$  SD, 12.7  $\pm$  9.4  
13  
14 days) after the onset of ARDS and was more frequent in patients with a higher HRCT  
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16 score (score  $\geq$  235) than in those with a lower HRCT score (score  $<$  235) during the first  
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18 28 days. Given that a higher HRCT score at diagnosis suggests advanced  
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20 fibroproliferation, our data support the relationship between pulmonary  
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22 fibroproliferation and its susceptibility to barotraumas.  
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30 Ventilator-associated pneumonia (VAP) has been a causative factor of subsequent  
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32 systemic inflammatory syndrome resulting in multi-organ failure<sup>33</sup>. The risk of VAP  
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34 increases with prolonged mechanical ventilation<sup>34</sup>. **Furthermore, sustained and**  
35  
36 **intense inflammatory responses in unresolving ARDS increase intracellular and**  
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38 **extra-cellular growth of nosocomial pathogens and increase the risk for nosocomial**  
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40 **infections**<sup>40</sup>. More extensive fibroproliferative changes on HRCT scan shown as a  
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42 higher CT score were associated with a longer ventilator dependency that was more  
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44 susceptible to VAP onset. These results support that pulmonary fibroproliferation of  
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46 ARDS increases risk for ventilator dependency and its associated complications.  
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53 In a previous study of 45 cases of ARDS confirmed at biopsy, patients whose  
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55 conditions were shown histologically to be in the acute exudative phase had a better  
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6 prognosis than did those whose condition was shown to be in the fibroproliferative  
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8 phases<sup>41</sup>. Persistent dysregulated systemic inflammation leading to maladaptive lung  
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10 repair results in pulmonary fibroproliferation and progression of extrapulmonary organ  
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12 dysfunction<sup>5</sup>. Prolonged corticosteroid therapy attenuates systemic inflammation and  
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14 reduced duration of mechanical ventilation<sup>5</sup>. In our study, the group of patients who had  
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16 less fibroproliferative changes on HRCT scans (HRCT score, < 210) showed lower  
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18 mortality and more ventilator-free days than those who had more extensive areas of  
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20 fibroproliferation (HRCT score,  $\geq$  210). This may suggest a relationship between the  
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22 pathologic phases of ARDS and responsiveness to treatment. **When more extensive**  
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24 **and rapidly progressive pulmonary fibroproliferation resulting from intense**  
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26 **exaggerated systemic inflammation at presentation occurs, even prolonged**  
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28 **corticosteroid therapy may not be effective.** Whether the patients with  
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30 fibroproliferative predominance have different treatment strategies compared to those  
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32 with exudative predominance has been a vexing question<sup>4</sup>. Improving our  
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34 understanding of disease state and evolution of the disease may be key to the  
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36 development of the optimal therapy and their timing. A method that could be used to  
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38 evaluate and calibrate the clinical to pathologic stages may help prognosticate, alter  
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40 supportive or therapeutic approach to ARDS such as ventilator management and define  
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42 the treatment window for those interventions. Further prospective studies are needed to  
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44 examine the efficacy of the drugs such as corticosteroids according to the extent of  
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6 fibroproliferation on HRCT scans.  
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9       There were some potential limitations. First, our study included few patients with  
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11 ARDS caused by major trauma, multiple transfusion and others, although it included  
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13 approximately 90% of the patients who had ARDS caused by three major etiologies  
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15 (pneumonia, aspiration, sepsis) of ARDS; thus, our study may not sufficiently reflect all  
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17 forms of ARDS. However, previous large randomized control studies also included  
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19 more than 70% of patients with these three etiologies<sup>27,31</sup>. Therefore, our results may  
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21 be applicable to most forms of ARDS.  
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27       Second, many elderly patients (mean age, 75.0 years) were included. Clinically,  
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29 elderly ARDS patients show higher morbidity and need longer duration of mechanical  
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31 ventilation with subsequent poorer prognosis than the younger patients<sup>2,37</sup>. The  
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33 age-related differences in mortality and outcomes have been considered to be due to the  
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35 greater number of comorbid illness and higher frequency of non-pulmonary organ  
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37 system failure in older patients<sup>37</sup>. In this study, preexisting pulmonary emphysema was  
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39 seen in 32 (38 %) of 85 patients. Although no significant differences were seen between  
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41 survivors and non-survivors in the number of a history of cigarette smoking and a  
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43 presence of emphysema, we could not evaluate the severity of emphysema before the  
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45 onset of ARDS. Such a smoking-induced chronic lung disease could potentially affect  
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47 ventilator-dependency or prognosis. Although it was problematic whether aging  
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49 increase susceptibility to lung injury and to pulmonary fibroproliferation, further  
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6 investigation of younger patients with ARDS is needed to confirm the consistency of  
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8 the results of our study.  
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11 Third, no correlation was provided with either clinical parameters or pathologic  
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13 findings in the present study. Further investigation is necessary to compare HRCT  
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15 findings with other predictors of morbidity/mortality-i.e. inflammatory biomarkers such  
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17 as serum IL-6 or BAL PCP III levels. Recent studies of biopsy findings from ARDS  
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19 patients have reported the pathologic diversity and only half proportion of typical  
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21 diffuse alveolar damage<sup>6,7</sup>. Regardless of the cause or pathology of ARDS, our study  
22  
23 highlighted the extent of lung architectural distortion (areas with traction  
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25 bronchiectasis) indicating that pulmonary fibroproliferation on HRCT scans. Although  
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27 fibroproliferative ARDS does not warrant different treatment strategies up to the present,  
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29 prospective evaluation of HRCT findings in patients with ARDS would help therapeutic  
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31 implications in the development of treatment strategies based on the extent of  
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33 fibroproliferation, as well as its prognostic implications.  
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43 Fourth, when using our cutoff values of HRCT scores, there were approximately  
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45 30 % of our patients who did not fit for prediction of poor prognosis or ventilator  
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47 dependency. Recently, multiple organ failure in ARDS patients is considered to be either  
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49 as the predisposing condition or as a consequence of ARDS<sup>42</sup>. If ARDS occurs as one of  
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51 multiple organ failure, even though pulmonary fibroproliferation was mild,  
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53 extra-pulmonary dysfunction could be the determinant of the outcome.  
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6 On the basis of our results, extensive HRCT abnormalities indicative of  
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8 fibroproliferative changes on the day of ARDS diagnosis were independently predictive  
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10 of poor prognosis and prolonged mechanical ventilation, and were also associated with  
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12 of poor prognosis and prolonged mechanical ventilation, and were also associated with  
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14 subsequent multiple organ failure. Pulmonary fibroproliferation that occurs early in  
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16 ARDS patients increases mortality risk by increasing susceptibility to ventilator  
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18 dependency and its associated complications.  
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## ACKNOWLEDGEMENTS

**Author contributions:** Dr Suga takes full responsibility for the integrity of all the data and the accuracy of the data analysis.

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.

Dr Habashi: contributed to reanalyzing the data and revising the manuscript.

Dr Fujimoto: contributed to reanalyzing the data and revising the manuscript.

Dr Johkoh: contributed to reanalyzing the data and revising the manuscript.

Dr Iwamoto: contributed to collecting the data and revising the manuscript.

Dr Kawamura: contributed to collecting the data and revising the manuscript.

Dr Nagano: contributed to collecting the data and revising the manuscript.

Dr Fukuda: contributed to collecting the data and revising the manuscript.

Dr Hirata: contributed to collecting the data and revising the manuscript.

Dr Yoshinaga: contributed to reanalyzing the data and revising the manuscript.

Dr Ichiyasu: contributed to collecting the data and revising the manuscript.

Dr Tsumura: contributed to collecting the data and revising the manuscript.

Dr Kohrogi: contributed to reanalyzing the data and revising the manuscript.

Dr Kawaguchi: contributed to reanalyzing the data and revising the manuscript.

Dr Yoshioka: contributed to reanalyzing the data and revising the manuscript.

Dr Sakuma: contributed to reanalyzing the data and revising the manuscript.

**Other persons contributing to this study:** We appreciate Michael A. Matthay, MD<sup>1</sup>, and

Hiroshi Kubo, MD, PhD<sup>2</sup> for their editorial assistance and also thank Isamu Cho, MD, PhD<sup>3</sup>,

Tomoki Tanaka, MD<sup>3</sup>, Junichi Maehara, MD<sup>4</sup>, Shigeo Hiroshige, MD<sup>5</sup>, Makoto Takaki, MD<sup>5</sup>,

Mitsuko Honda, MD<sup>5</sup>, Naoko Arakawa, MD<sup>5</sup>, Yuko Yasuda, MD<sup>5</sup>, Makiko Takeguchi, MD<sup>5</sup>,

Aoi Teruya, MD<sup>5</sup>, Yoshitomo Eguchi, MD<sup>5</sup>, Naoki Shingu, MD<sup>5</sup>, Yoshihiko Sakata, MD<sup>5</sup>, and

Azusa Katsume, MD<sup>5</sup> for their clinical assistance.

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For peer review only



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

| Characteristic                                   | Total<br>(n = 85) | 60 days               |                                       | p value |
|--|-------------------|-----------------------|---------------------------------------|---------|
|  |                   | Survivors<br>(n = 54) | Outcomes<br>Non-survivors<br>(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 <sub>2</sub> :FiO <sub>2</sub>               | 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<br>(per mm <sup>3</sup> ) | 10600 ± 6788      | 10600 ± 6178          | 10600 ± 7839                          | 0.63    |

|  |             |             |             |        |
|--|-------------|-------------|-------------|--------|
| C-reactive protein (CRP)<br>(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<br>(LDH) (IU/L)        | 308 ± 185   | 301 ± 147   | 339 ± 235   | 0.29   |
| Platelet count (per mm <sup>3</sup> )        | 20.1 ± 10.7 | 20.7 ± 11.0 | 18.9 ± 10.3 | 0.94   |
| Days of CT scanning<br>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<br>predicted body weight | 8.0 ± 0.8   | 8.0 ± 0.7   | 8.0 ± 0.9   | 0.54   |
| Plateau pressure, cmH <sub>2</sub> O         | 21.5 ± 4.2  | 21.0 ± 3.8  | 23.0 ± 4.7  | 0.34   |
| Initial PEEP, cmH <sub>2</sub> O             | 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<br>(n = 54) | Non-survivors<br>(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<br>or bronchiectasis            | 88.0 ± 22.0           | 78.2 ± 22.5               | 0.01    |
| Ground-glass attenuation plus traction<br>bronchiolectasis or bronchiectasis | 9.3 ± 17.8            | 16.6 ± 21.7               | 0.08    |
| Air-space consolidation plus traction<br>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<br>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-resolution CT at the onset of**

**ARDS**

| Variable                                   | High-Resolution Computed Tomographic<br>(CT) score |                   | p value  |
|--|--|-------------------|----------|
|  | < 210<br>(n = 47)                                  | ≥ 210<br>(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 <sub>2</sub> / FiO <sub>2</sub> 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 <sub>2</sub> / FiO <sub>2</sub> 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 pneumoniae*.

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 pneumoniae*. (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).



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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.

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

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5 score ( $\geq 210$ ) significantly increased from day 1 to day 14 ( $p = 0.027$ ). Four patients  
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7 with a lower CT score ( $< 210$ ) and 9 patients with a higher CT score ( $\geq 210$ ) who died  
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9 within 14 days were excluded.  
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**Patient confidentiality**

Details have been removed from this case description.

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