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Clinical characteristics and prognosis of drug-associated acute respiratory distress syndrome compared with non-drug-associated acute respiratory distress syndrome: a single-centre retrospective study in Japan

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ABSTRACT

Objectives To report the clinical features and prognosis of drug-associatedacute respiratory distress syndrome (ARDS).

Design A retrospective analysis of data collected during a prospective cohort study.

Setting Intensive care unit in a teaching hospital.

Participants A total of 197 Japanese patients with ARDS diagnosed by the Berlin definition who were admitted to the Division of Respiratory Medicine from October 2004 to December 2015 were enrolled in the study and were classified as two groups according to their causes: a drug-associated ARDS group (n=27) and a non-drug-associated ARDS group (n=170). Primary outcome measure is 28-day mortality, and the secondaryoutcome measure is ventilator-free days.

Results The Acute Physiology and Chronic Health Evaluation II scores were significantly lower in the drug-associated ARDS group than in the non-drug-associated ARDS group (median (IQR): 18.0 (16.5–21.0) vs 23.0 (18.0–26.0), p<0.001), and the arterial oxygen tension/fractional inspired oxygen ratio was higher (148.0 (114.1–177.5) vs 101.0 (71.5–134.0), p=0.003). In the drug-associated ARDS group, although high-resolution CT scores indicative of the extent of fibroproliferation (301.6 (244.1–339.8) vs 208.3 (183.4–271.6), p<0.001), serum lactate dehydrogenase levels (477 (365–585) vs 322 (246–434), p=0.003) and the McCabe scores (score 1/2/3, n (%): 20 (74)/4 (15)/3 (11)vs154 (91)/7 (4)/9 (5), p=0.04) were significantly higher, ventilator weaning was earlier (p<0.001) and 28-day mortality was better (p=0.043). After adjusting for potentially confounding covariates, drug-associated ARDS group was associated with lower 28-day mortality (adjusted HR (HR) 0.275; 95% CI 0.106 to 0.711; p=0.008).

Conclusions Although more severe lung damage with fibroproliferation was observed in patients with drug-associated ARDS, ventilator weaning was earlier, and their prognosis was better than the others. Further well-designed prospective studies are needed.

Strengths and limitations of this study

- ► All data were collected prospectively as part of an ongoing high-resolution CT study in acute respiratory distress syndrome (ARDS).
- ► The first report on the prognostic factors associated with drug-associated ARDS (DARDS) performed for the purpose of elucidating differences in the clinical characteristics of DARDS and non-DARDS.
- ► This is a single-centre, retrospective cohort study, and the number of patients in the DARDS group was relatively small.
- ► There are some difficulties in judging whether a certain drug is causative in drug-associated ARDS group and whether underlying illness is actually ARDS.
- ► Approximately half of the cases underwent bronchoalveolar lavage, and no histopathological investigations were performed.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a condition that presents with acute respiratory failure and has a poor prognosis. Most cases are evidently due to infectious diseases such as pneumonia or sepsis.

Certain drugs are also reportedly capable of causing ARDS. For example, it has been reported that some new molecular target drugs such as gefitinib, amiodarone and dipeptidyl peptidase 4 inhibitor can induce severe interstitial lung disease.[1–3] There are also reports of severe respiratory failure or ARDS resulting from the use of drugs such as methotrexate[4] and certain herbal medicines.[5] Most of these reports were case studies, and there are very few reports on the incidence or prognosis of drug-associated ARDS (DARDS).

It has been reported that the hospital mortality rate of patients with drug-induced 'diffuse alveolar damage (DAD)', which has been the strongest prognostic factor in ARDS, diagnosed by surgical lung biopsy was only 17%.[6] We hypothesised that clinical characteristics would differ between DARDS and non-drug-associated ARDS (non-DARDS), and patients with DARDS would have better outcomes. However, since the Berlin definition of ARDS was published in 2012,[7] there have been no reports of definitively confirmed DARDS. In the current study, we compared the clinical characteristics of DARDS with those of non-DARDS.

MATERIALS AND METHODS

Patients

This was a retrospective analysis of data collected during an ongoing prospective cohort study of ARDS with high-resolution CT (HRCT), some of which have been published previously.[8 9] A total of 197 Japanese patients with ARDS diagnosed by the Berlin definition[7] were admitted to the Division of Respiratory Medicine at our hospital from October 2004 to December 2015. Our hospital is an acute medicine teaching hospital in an urban area, with 400 beds. We reviewed the patients with ARDS using the prior ARDS definition[10] before 2012 and included those patients that met the criteria. Written informed consent was obtained from all patients or their families. Details of excluded cases are shown in the CONSORT diagram (figure 1). We did not include patients with chronic interstitial lung disease including idiopathic pulmonary fibrosis, those with vasculitis or alveolar haemorrhage or those diagnosed with acute organising pneumonia, hypersensitivity pneumonitis or acute eosinophilic pneumonia.

Definition of DARDS

We classified the patients with ARDS into DARDS group and non-DARDS groups according to ARDS aetiology. We used the definition of drug-associated acute lung injury (DALI) described by Dhokarh *et al*[11] using traditional risk factors for acute lung injury (ALI): sepsis, septic shock, pneumonia, pancreatitis, trauma, massive blood transfusion and gastric aspiration. Probable DALI was considered in patients with no established ALI risk factors except specific drug exposure within 1 year. Patients with possible DALI had at least one risk factor for ALI and a history of specific drug exposure within 1 year. Those with conditional DALI had received drugs not previously reported to cause ALI but with similarity to known causative agents. Non-DALI patients who were not exposed to drugs reported or assumed to cause ALI. Drug exposure data in the year prior to ARDS onset was obtained from 'medicine notebooks' that list all drugs prescribed to the patients. This is a unique system in Japan.

Treatment

Ventilator management and ventilator weaning were conducted in accordance with evidence-based guidelines[12] with reference to the lower tidal volume (V_T) strategy and predicted body weight (PBW) (6 mL/kg PBW < V_T < 8 mL/kg PBW) in the ARDS Clinical Trial[13] and to the guidelines for weaning and discontinuing ventilatory support from the American College of Chest Physicians.[14] Plateau pressure was limited to less than 30 cmH_2O, with a positive end-expiratory pressure (PEEP) of 8–12 cmH_2O. At the first day, PEEP, peak inspiratory pressure and V_T

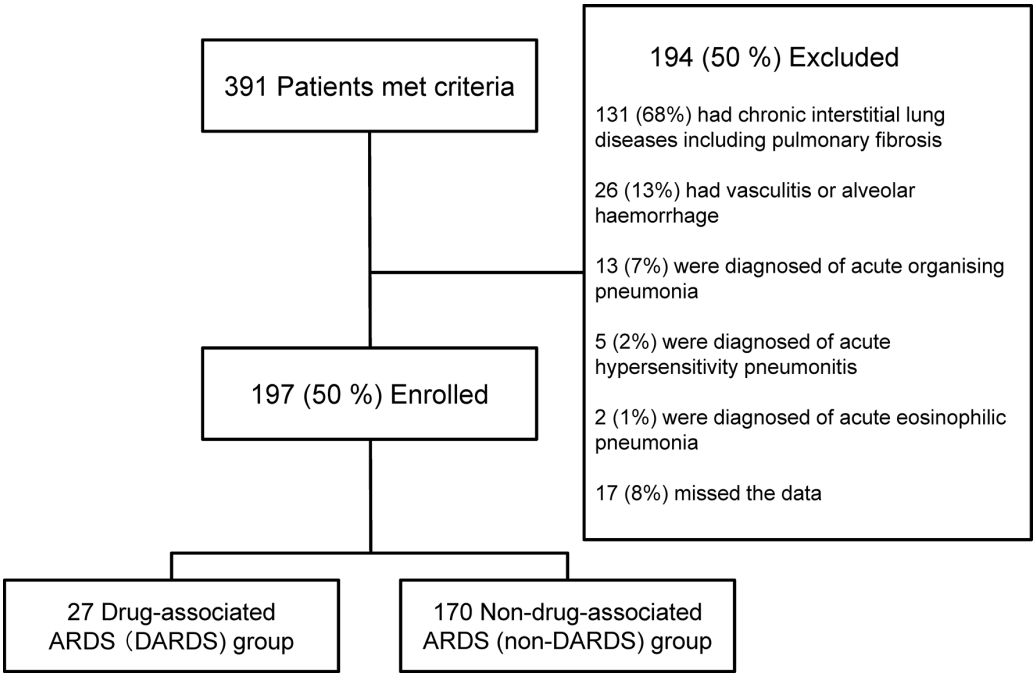

Figure 1 Flow chart of the study design.

were daily recorded. High-dose corticosteroids therapy was defined that the patient was administered more than 2 mg/kg/day. There were no patients treated with extracorporeal membrane oxygenation therapy in this study cohort.

Comparison of prognostic factors and outcome

We performed a comparative investigation using patient age, gender, 28-day mortality, duration of mechanical ventilation, Acute Physiology and Chronic Health Evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, HRCT score indicative of the extent of fibroproliferation,[8] McCabe score, arterial oxygen tension (PaO_2)/fractional inspired oxygen (FiO_2) ratio and blood test results. As previously published,[15] HRCT score was graded on a scale of 1–6: score of 1: normal attenuation; score of 2: ground-glass attenuation; score of 3: consolidation; score of 4: ground-grass attenuation with traction bronchiolectasis or bronchiectasis; score of 5: consolidation with traction bronchiolectasis or bronchiectasis and score of 6: honeycombing. The presence of each of these six abnormalities was assessed independently in upper, middle and lower zones of each lung. The extent of each abnormality was determined by visually estimating the percentage of the affected lung parenchyma in each zone. Each abnormality score was calculated by multiplying the percentage area by each grading score. The six zone scores were averaged to determine the total score for each abnormality in each patient. The overall CT score was obtained by adding the six averaged scores. The McCabe score was recorded as one of three possible values: non-fatal: score 1; near-fatal: score 2; fatal: score 3.[16] The primary outcome was 28-day mortality, and the secondary outcome was the duration of mechanical ventilation.

Statistical analysis

Continuous variables were expressed as the median values and IQR. In the univariate analysis of the two groups, categorical variables were compared using the χ^2

Table 1 Clinical characteristics of the patients

Risk factor of acute lung injury	DARDS group (n=27) Sepsis: 1 (4), pneumonia: 2 (7), aspiration: 2 (7), others: 0 (0)	Non-DARDS group (n=170) Sepsis: 75 (44), pneumonia: 57 (33), aspiration: 35 (21), others: 4 (3)	p Value
Age (years)	76.0 (70.5–78.5)	76.5 (67.0–83.0)	0.742
Sex (male/female)	10 (37)/17 (63)	113 (66)/57 (34)	0.004
White cell count (per mm^3)	12 000 (9150–15 250)	9900 (5100–14 800)	0.658
C reactive protein (mg/dL)	15.3 (13.4–21.5)	15.4 (8.8–25.0)	0.977
Lactate dehydrogenase (IU/L)	477 (365–585)	322 (246–434)	0.003
Albumin (g/dL)	2.9 (2.7–3.1)	2.9 (2.4–3.2)	0.536
Platelet count (per mm^3)	22.5 (12.4–29.9)	18.0 (10.8–24.7)	0.391
PEEP (cmH_2O)	9.0 (8.0–10.0)	8.0 (8.0–10.0)	0.796
PIP (cmH_2O)*	19.5 (11.0–24.0)	22.0 (18.0–25.0)	0.231
Tidal volume (mL)†	410 (350–500)	425 (350–486)	0.583
APACHE II score	18.0 (16.5–21.0)	23.0 (18.0–26.0)	<0.001
SOFA score	6.0 (3.0–7.5)	7.0 (5.0–11.0)	0.057
HRCT score	301.6 (244.1–339.8)	208.3 (183.4–271.6)	<0.001
McCabe score (1/2/3)	20 (74)/4 (15)/3 (11)	154 (91)/7 (4)/9 (5)	0.04
PaO_2/FiO_2	148.0 (114.1–177.5)	101.0 (71.5–134.0)	0.003
Severity (mild/moderate/severe)	3 (11)/18 (67)/6 (22)	10 (6)/76 (45)/84 (49)	0.029
Ventilator-free days	19.0 (10.0–21.5)	0 (0–18.0)	<0.001‡
28-day mortality	5 (19)	64 (38)	0.043‡

Continuous variables are reported as median and IQR and compared with the use of the Mann-Whitney U test. Categorical variables are reported as number (percentage) and compared with the χ^2 test or Fisher's exact test.
*DARDS group (n=22), non-DARDS group (n=131).
†DARDS group (n=22), non-DARDS group (n=116).
‡Calculated using the log-rank tests.
APACHE II, Acute Physiology and Chronic Health Evaluation II; DARDS, drug-associated acute respiratory distress syndrome; FiO_2, fractional inspired oxygen; HRCT, high-resolution CT; PaO_2, arterial oxygen tension; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; SOFA, sequential organ failure assessment.

Table 2 Aetiological agents of drug-associated ARDS

DARDS (n=27)	
Probable DARDS (n=22, 81%)	
Possible DARDS (n=5, 19%)	
Drug	**Number**
Antineoplastic drug	7
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)	2
Gefitinib	1
Irinotecan	1
Bicalutamide	1
Docetaxel	1
Epirubicin	1
Chinese herbal medicine	5
Antibiotics	4
Cephalosporin	2
Penicillin	1
Daptomycin	1
Antiarrhythmic drug	
Amiodarone	4
Antirheumatic drug	3
Non-steroidal anti-inflammatory drugs	2
Novel oral anticoagulant	1
Antiviral agents	
Daclatasvir and asunaprevir	1

ARDS, acute respiratory distress syndrome; DARDS, drug-associated ARDS.

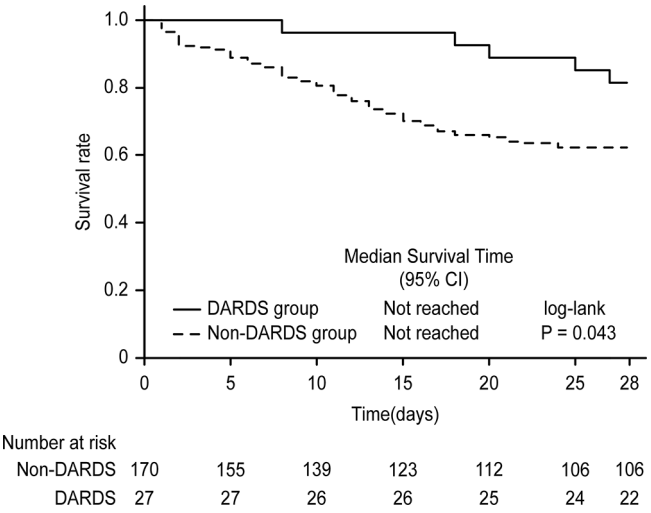

Figure 2 Kaplan-Meier curves show the distribution of 28-day mortality. Patients in the drug-associated acute respiratory distress syndrome (DARDS) group (n=27, solid line) had a significantly better mortality rate than did those in the non-DARDS group (n=170, dotted line) (log-rank test, p=0.043).

test or Fisher's exact test, and continuous variables were compared using the Mann-Whitney test. Clinically significant variables with a p Value <0.05 at univariate analysis were included in the multivariate analysis. We excluded the variables that had an r value of >0.4 in the factor analysis from multivariate analysis. The multivariate analysis was performed using a Cox proportional hazard model with a backward-selection procedure. Unadjusted and adjusted survival curves were plotted using the Kaplan-Meier method. Log-rank tests were used to compare differences in survival. The time to successful discontinuation of mechanical ventilation was also evaluated. We also estimated adjusted relationships between diagnosing DARDS and outcome using the Cox proportional hazards regression model via inverse probability of treatment weighting (IPTW) using a propensity score. The propensity score model for DARDS versus non-DARDS was constructed using a logistic regression including main term for age, sex, white cell count, C reactive protein, lactate dehydrogenase, albumin, platelet count, APACHE II score, SOFA score, McCabe score, HRCT score and PaO_2/FiO_2. Propensity score model discrimination was assessed by the area under the curve. The weights were based on the probability of diagnosing DARDS. Potential factors of 28-day mortality in the DARDS group were analysed by univariate Cox regression analysis. We used the SPSS software (V.22.0) for the statistical analyses, and generated survival plots with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R VV.3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria). A p value of less than 0.05 was considered significant.

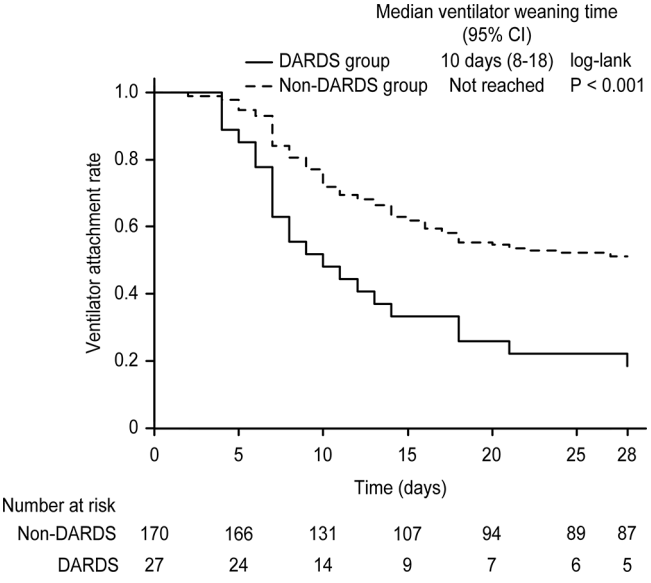

Figure 3 Kaplan-Meier curves show the distribution of ventilator-free days. In the drug-associated acute respiratory distress syndrome (DARDS) group (n=27, solid line), the duration of ventilator weaning was significantly shorter than in the non-DARDS group (p=170, dotted line) (log-lank test, p<0.001).

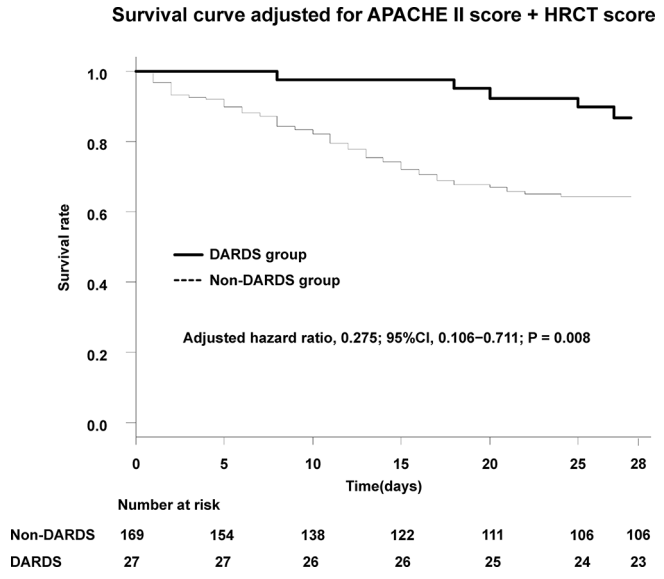

Figure 4 Survival curve for the association between DARDS and 28-day mortality from the Cox proportional hazards model, adjusted for Acute Physiology and Chronic Health Evaluation (APACHE) II and high-resolution CT (HRCT) score. DARDS, drug-associated acute respiratory distress syndrome.

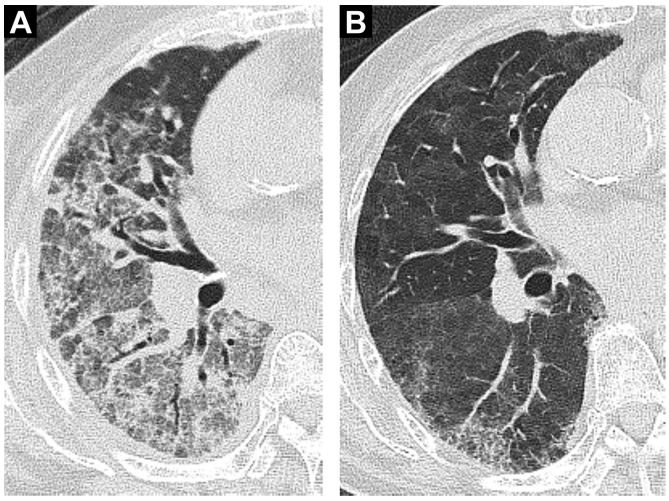

Figure 5 The patient was an 80-year-old woman with acute respiratory distress syndrome due to herbal medicine. High-resolution CT (HRCT) shows extensive ground-glass attenuation with bronchiectasis (A). We determined a diffuse alveolar damage pattern. After starting corticosteroid therapy, hypoxaemia was markedly improved, and she was discharged from the hospital on day 22 with room air. HRCT on day 20 shows improvement of the diffuse ground-glass attenuation with bronchiectasis (B).

RESULTS

There were 27 patients in the DARDS group and 170 in the non-DARDS group. The causes of the non-DARDS group were sepsis (n=75; 44%), pneumonia (n=56; 33%), aspiration (n=35; 21%) and others (n=3; 2%).

Clinical characteristics

The background information of the patients in the DARDS and non-DARDS groups is shown in table 1.

The aetiological agents in the DARDS group are shown in table 2. In our study, causative agents were anticancer drugs in seven cases (26%), the Chinese herbal medicine 'kampo' in 5 (19%), antibiotics in 4 (15%), the antiarrhythmic drug amiodarone in 4 (15%), antirheumatic drugs in 3 (11%) and the others in 4 (15%).

Prognostic implications

Five of the 27 patients (19%) in the DARDS group and 64 of the 170 (38%) in the non-DARDS group died within 28 days. The Kaplan-Meier survival curves for each group at 28 days are shown in figure 2. The 28-day mortality was significantly better in the DARDS group than in the non-DARDS group (19% vs 38%, p=0.043). The duration of mechanical ventilation was significantly shorter in the DARDS group than in the non-DARDS group: the median ventilator time was 10 days (95% CI 7 to 18) in the DARDS group and not reached (95% CI 18 to not reached) in the non-DARDS group (p<0.001, figure 3). After adjustment for confounding covariates including PaO_2/FiO_2, DARDS was independently associated with lower mortality (adjusted HR 0.275; 95% CI 0.106 to 0.711; p=0.008) (figure 4) and shorter duration of mechanical ventilation (adjusted HR 3.791; 95% CI 2.197 to 6.539; p<0.001). In the adjusted analysis, APACHE II score (adjusted HR 1.058; 95% CI 1.007 to 1.113; p=0.026) and HRCT score (adjusted HR 1.220; 95% CI 1.105 to 1.315; p<0.001) were also independently associated with a poor prognosis in the regression model (table 3).

IPTW estimators with propensity adjustment also showed that diagnosis and treatment for ARDS caused by drug was associated with lower mortality (HR 0.139; 95% CI 0.044 to 0.440; p=0.001) and shorter duration of mechanical ventilation (HR 3.602; 95% CI 2.045 to 6.344; p<0.001). The area under the curve for the calculated propensity score was 0.903 (95% CI 0.850 to 0.955). Figure 5 shows an examples of HRCT scans of a survivor.

Table 3 Cox proportional hazards model results for 28-day mortality

Factor	HR (95% CI)	p Value
APACHE II score	1.058 (1.007 to 1.113)	0.026
HRCT score	1.220* (1.105 to 1.315)	<0.001
Drug-associated ARDS	0.274 (0.106 to 0.711)	0.008

*Expressed as mortality change per 10% increase in area of attenuation with traction bronchiectasis on HRCT.
ARDS, acute respiratory distress syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; HRCT, high-resolution CT.

Comparison of prognostic factors

We compared the clinical parameters in both groups. In the DARDS group, the APACHE II scores were significantly lower, the PaO_2/FiO_2 ratios were significantly higher, and the SOFA scores tended to be lower than in the non-DARDS group, suggesting that the general

Table 4 Univariate analysis of predictors of 28-day mortality in drug-associated ARDS

Characteristic	HR	95% CI	p Value
Age (years)	1.149	0.948 to 1.394	0.158
Sex (male)	7.984	0.891 to 71.56	0.063
White cell count (per mm^3)	0.999	0.999 to 1.000	0.095
C reactive protein (mg/dL)	1.065	0.964 to 1.177	0.214
Lactate dehydrogenase (IU/L)	1.001	1.000 to 1.002	0.147
Albumin (g/dL)	0.088	0.018 to 0.428	0.003
Platelet count (per mm^3)	0.848	0.742 to 0.969	0.015
APACHE II score	0.951	0.730 to 1.237	0.706
SOFA score	0.970	0.714 to 1.317	0.844
HRCT score	1.133	0.798 to 1.601	0.510
McCabe score	5.343	1.763 to 16.19	0.003
PaO_2/FiO_2	1.018	1.005 to 1.032	0.009

APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; FiO_2, fractional inspired oxygen; HRCT, high-resolution CT; PaO_2, arterial oxygen tension; SOFA, sequential organ failure assessment.

severity of the condition and the extent of multiorgan failure were lower in the DARDS group. In addition, the McCabe scores, HRCT scores and lactate dehydrogenase values were significantly higher in the DARDS group, suggesting that the prognosis of the underlying disease was poor, and the degree of lung injury was severe. We analysed clinical factors of 28-day mortality in the DARDS group with univariate analysis and found that albumin, platelet count, PaO_2/FiO_2 and McCabe score were significant predictors for 28-day mortality (table 4).

Corticosteroid treatment

There were 17/27 (63.0%) patients in the DARDS group and 32/170 (18.8%) in the non-DARDS group who initially received high-dose corticosteroids, and significantly higher doses were administered in the DARDS group (p<0.001).

Bronchoalveolar lavage (BAL) findings

Of the 27 patients in the DARDS group, BAL was performed in 13 and the median (IQR) for each cellular fraction was 16.0% (13.5–44.0) for neutrophils, 29.1% (19.0–66.0) for lymphocytes and 1.0% (0.0–3.5) for eosinophils. Neutrophils were predominant in five patients, lymphocytes were predominant in seven and eosinophils were predominant in one.

DISCUSSION

Unlike the result of the previous studies, the current study showed that patients with DARDS did not necessarily show poorer prognosis than those with the other causes of ARDS. These differences might depend on whether the causative agents are anticancer drugs, and whether the prognosis of the underlying disease is poor.

Dhokarh *et al*[11] reported that a DALI group had a poorer prognosis than a non-drug-associated group. Similarly, Gibelin *et al*[17] recently reported that there was a trend towards a higher intensive care unit mortality rate in ARDS patients without common risk factors, including drug-induced ARDS, as compared with ARDS patients with common risk factors. In these reports, the most common suspected drugs were anticancer drugs. The rate of anticancer drugs reported in their studies by Dhokarh *et al*[11] was 48% and that by Gibelin *et al*[17] was 69%, respectively. In contrast to these studies, only 26% of the patients with DARDS in our study received anticancer drug, which accounted for less than those in the previous studies, and there is a possibility that the difference in the population of patients with DARDS reflect difference of prognosis. One of the factors that predicted mortality within 28 days in the DARDS group was the McCabe score in this study. Four of the seven patients (57%) with DARDS who received antineoplastic drug therapy died within 28 days. Although the 28-day mortality was better in the DARDS group, the 28-day mortality rate in patients who received antineoplastic drug therapy was as high as those in the results of previous investigations.[11] It is expected that the patients with poor prognosis of underlying disease might be more susceptible to lung injury when anticancer drug being administered and that dysregulated immune system in those patients could affect increased risk for mortality compared with patients without cancer. We believe that the fact that the McCabe score was higher in tumour-bearing patients may reflect the poor prognoses of the underlying diseases reported in studies by Dhokarh *et al*[11] and Gibelin *et al*.[17]

There are two reported types of drug-associated lung injury: those caused by a cytotoxic mechanism that is sensitive to the total dosage and those caused by an immunostimulatory mechanism.[18] It is widely held that anticancer drugs act via a cytotoxic mechanism, and the results of corticosteroid therapy are considered to be limited.[1] Conversely, corticosteroids are expected to be effective when treating cases caused by immunostimulatory agents.[17] These differences may reflect differences in the mechanisms of lung injury and differences in responsiveness to treatment, even where a similar extent of fibroproliferation occurred in the lungs. It was reported that histopathological findings of DAD were present in only 45% of ARDS cases diagnosed based on the Berlin definition at autopsy.[19] This implies that cases that fulfil the criteria for ARDS do not necessarily exhibit the histopathological features of DAD. In our previous study, the HRCT findings reflected the pathological staging of DAD, and ARDS cases with high HRCT scores—indicating extensive fibroproliferative lesions—needed prolonged ventilation and ultimately suffered from multiorgan failure caused by ventilator-associated lung injury.[8] Although the HRCT score indicating fibroproliferative lesions was higher in the DARDS group, which suggested DAD, the prognoses as well as the extent of multiorgan failure were significantly better than

non-DARDS group. We believe there may be two potential reasons for this. The first is that there might be the differences in the pathological profiles in DARDS cases that develop fibroproliferative lesions, and the corticosteroid therapy could be more effective to DARDS. In the current study, there were varied cellular fractions in the 13 patients who underwent BAL. Furthermore, only 5/13 patients (39%) showed a predominance of neutrophils, while 8/13 patients (62%) showed a predominance of lymphocytes or eosinophils. Neutrophilic BAL in patients with ARDS suggests a DAD pattern reportedly associated with the poorest prognosis.[20 21] In addition, the ARDS patients with a predominantly haemorrhagic or lymphocytic BAL fluid cytology, as opposed to those with predominantly macrophagic or neutrophilic one, had more often chance of corticosteroid therapy and showed a better prognosis.[17] Although BAL was performed only 13/27 patients in our DARDS group, BAL lymphocytosis in these patients might have reflected good response to corticosteroid therapy. If the cause of ARDS is suspected to be a certain drug and the BAL lymphocytosis is observed, corticosteroid therapy may be supposed to be more beneficial. The results of our study are concordant with this previous report,[17] in terms of better responses to corticosteroid therapy and subsequent improvement in survival in patients with DARDS.

Various questions remain unresolved with regard to the use of corticosteroid therapy for the treatment of ARDS.[22–26] However, initial high-dose corticosteroid administration followed by a tapering regimen has been reported to be effective in some immune disorders.[27 28] In Japan, in cases of acute respiratory failure due to DALI or interstitial pneumonias, initial high-dose corticosteroids followed by a gradually tapering regimen is recommended by the Practical Guidelines of the Japanese Respiratory Society.[29] Significantly lower mortality in the patients with DARDS in the current study treated with initial high-dose steroid therapy may reflect the immunomodulatory effect of corticosteroids in the context of lung injury caused by drugs.

A second potential explanation is even where patients with DARDS exhibit histological DAD, the prognosis may be better than those with non-DARDS. It has been reported that the hospital mortality rate of patients with drug-induced DAD diagnosed by surgical lung biopsy was only 17%.[6]Compared with the hospital mortality with 40% of DAD due to major cause of ARDS such as infection, that of drug-induced DAD was the lowest among the causes in the report. It is suggested that the cause of ARDS should be taken into account in the therapeutic reactivity even if DAD is pathologically proven.

Given the above considerations, we propose the following hypotheses: (1) there may have been a few patients with histological DAD in the DARDS group in our study, and corticosteroid therapy may have been effective in these patients and (2) even where patients with DARDS exhibit histological DAD, the prognosis may be good in cases of non-fatal underlying disease.

Notably, drug-associated lung injury has frequently been reported to exhibit differences based on ethnicity.[30–35] These ethnicity-based differences suggest that there may be differences in the genes related to lung fragility in Japanese and other East Asian patients.

There were some limitations to the present study. First, it was a retrospective analysis by use of prospective collected cohort study data, and it is possible that this may have biased the results or that multiple unmeasured variables may have affected the outcomes. However, compared with a typical retrospective design, these problems might be minimised. Second, it was a single-centre study, and the number of patients in the DARDS group was relatively small. Therefore, we used statistical analysis such as IPTW to compensate for the small number of patients. Third, it only included Japanese patients, and ethnic differences need to be considered. Fourth, there is some difficulties in judging whether a certain drug is causative in DARDS group. For example, whether cephalosporin really caused the ARDS or the infection for which the patient was receiving the cephalosporin caused it was uncertain in the strict sense. However, this is unavoidable problem on this topic because specific markers, histological findings and diagnostic clinical features are generally unremarkable, and there are no criterion standard diagnostic tests for drug-associated lung disease. Fifth, there is some possibility of underlying illness that is not actually ARDS. For example, some patients may actually have hypersensitivity pneumonitis, underlying diffuse alveolar haemorrhage or another disease with a favourable outcome. That may create an unequal comparison between DARDS and non-DARDS group. Finally, approximately half of the cases underwent BAL, and no histopathological investigations were performed. Notably however, the cases of ARDS were severe, and to date, the clinical relevance of BAL and biopsy have not yet been established. Further investigation of DARDS including assessments of the potential influences of ethnic differences is required, as are further studies investigating the individual aetiologies of ARDS itself.

In conclusion, patients with DARDS may not necessarily show poor prognosis than those with the other causes of ARDS, depending on the causative agents or prognosis of underlying disease. Another well-designed prospective study is needed to determine whether the prognosis is better in patients with DARDS than in patients without DARDS.

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