Clinical Phenotypes from Fatal Cases of Acute Respiratory Distress Syndrome Caused by Pneumonia

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Research

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Abstract

Background: The COVID-19 pandemic has renewed interest and discussion about clinical phenotypes of acute respiratory distress syndrome (ARDS). Since the Berlin definition, various clinical disease courses with fatal outcome have been described but early objective indicators predicting distinct clinical courses have remained elusive.

Objectives: Identify clinically available predictors that distinguish between two phenotypes of fatal ARDS due to pneumonia.

Methods: 104 Japanese patients with pneumonia induced ARDS were extracted from our prospectively collected database. Fatal cases were divided into early (< 7 days after diagnosis) and late death ($\geq$ 7 days) groups and their clinical variables and prognostic factors were statistically evaluated.

Results: Of 50 cases, fatal within 180 days, 18 (36%) comprised the early death group (median 2 days, IQR [1, 5]) and 32 (64%), the late death group (median 16 days, IQR [13, 29]). Multivariate regression analyses showed APACHE II score (HR 1.14, 95%CI 1.01-1.28, p 0.047) was the only independent prognostic factor for early death. Late deaths were associated with disseminated intravascular coagulation score (HR 1.30, 95%CI 1.07-1.58, p 0.007), culture sensitivity to initial antimicrobials (HR 3.42, 95%CI 1.86-6.29, p <0.0001), and high-resolution computed tomography (HRCT) score indicating early fibroproliferation. ROC analyses estimated a late death propensity score for HRCT score $\geq$ 211, of 5.42 (95%CI 1.54–19.12; p 0.008).

Conclusions: The extent of fibroproliferation on HRCT, along with coagulation abnormalities and APACHE II scores, should be considered for use in predictive trial enrichment and personalized medicine for patients with ARDS due to pneumonia.

Introduction

Acute respiratory distress syndrome (ARDS) has diverse etiologies and varied clinical courses (1–3). Two clinical phenotypes of this syndrome have recently been described, phenotype 1/hypoinflammation and phenotype 2/hyperinflammation, evidenced by statistical extraction independent of clinical outcomes (4,5). Phenotype 1 and 2 account for approximately 65% and 35% of ARDS patients, respectively. The latter is often caused by sepsis associated with shock and metabolic acidosis, resulting in significantly higher mortality with fewer ventilator-free days and organ-failure-free days compared to those with hypoinflammation. Previous studies of causes and timing of death from ARDS in the 1980s and 1990s reported and classified fatal cases into early and late death and emphasized primary or secondary septic syndrome as common causes of deaths (6,7). Such categorization, based on timing and cause of death, can likely define subgroups within the hypo- and hyperinflammation clinical phenotypes. Due to the clinical heterogeneity of ARDS, it is critical for clinicians to understand and recognize ARDS phenotypes, with associated prognostic factors that contribute to varied outcomes, in order to optimize individual treatment of patients.

Severe community-acquired pneumonia (CAP) is the most common cause of ARDS (8). ARDS due to pneumonia fulfilling the Berlin criteria concurrently satisfies the latest sepsis definition (9). Thus, the intensity of systemic inflammation caused by pneumonia in each patient may reflect clinical phenotypes predictive of clinical course and outcome.

Another viewpoint regarding clinical characteristics of ARDS has been reported from lung pathology. Recent studies on the autopsy and biopsy of ARDS report only half of patients who met ARDS clinical criteria had diffuse alveolar damage (DAD) and those with DAD had poorer outcomes than those without (10–13). ARDS patients with DAD of pulmonary origin, including pneumonia, showed more extensive pulmonary fibrosis at autopsy than non-pulmonary ARDS cases, even with adjustment for time from onset to death (10). We previously reported the clinical significance and prognostic value of high-resolution computed tomography (HRCT) for prediction of mortality or ventilator associated outcomes associated with secondary septic syndrome in ARDS (14,15)

With the goal of refining therapeutic strategies against each clinical course, we clarified the differences in clinical course and relevant prognostic factors among patients with pneumonia associated ARDS. We hypothesized that (1) early death within one week was associated with severe general condition due to primary septic syndrome, and (2) late death was due to pulmonary fibroproliferation and secondary sepsis syndrome.

Methods

Online supplementary materials describe detailed methods. Although this study was a retrospective, single-center study, the data were prospectively collected during the ongoing high-resolution CT (HRCT) study in patients with ARDS. Part of the study data were previously published [14–21]. A total of 210 Japanese patients, with ARDS diagnosis based on the International definition of ARDS were extracted from our HRCT database constructed from October 1, 2004 to May 31 2017. We reviewed data to determine if individual cases that occurred prior to the 2012 publication of the Berlin definition [4] met those diagnostic criteria. Patient outcomes were evaluated through 180 days after diagnosis of ARDS.

Written informed consent was obtained from all patients or their families.

The study was approved by our institutional review board (Permission number 238), and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

All patients underwent HRCT on the day of diagnosis of ARDS. Exclusions and screening and enrollment flow are shown in Fig. 1.

Analysis of this study provided historical data to support a randomized, open-label multicentre phase-II study evaluating efficacy and safety of MultiStem® cells [HLCM051], an allogeneic bone marrow-derived stem cell product, in patients with ARDS due to pneumonia (NCT03807804), ongoing since February 2019.

Patients

Of the 210 cases, 104 diagnosed with ARDS due to pneumonia were extracted from our database (Fig. 1). Patient demographics and severity characteristics are in Table 1. Microbial etiology, anti-microbial treatment and sensitivity to initial anti-microbial agents are in Table 2.

Table 1 Background and Prognosis of Patients with ARDS Due to Pneumonia

	Entire cohort	Patients prognosis			p-value	
		All patients	Survivors	Early death		Late death
				(< 7 days from diagnosis)		(≥ 7 days after diagnosis)
Subject, n (%)	104 (100)	54 (51.9)	18 (17.3)	32 (30.7)		
Follow-up days		180 [180, 180]	2 [1, 5]	16 [13, 29]	<0.001	
Age	72 [65, 81]	73 [65, 82]	77 [67, 83]	70 [65, 80]	0.592	
sex (%)						
Female	38 (39.5)	20 (37.0)	8 (44.4)	10 (31.2)	0.645	
Male	66 (60.5)	34 (63.0)	10 (55.6)	22 (68.8)		
Comorbidity #						
Chronic respiratory disease						
COPD	26 (25)	11 (20)	7 (39)	8 (25)	0.291	
Others*	4 (4)	1 (2)	0 (0)	3 (9)	0.223	
Chronic cardiovascular disease	9 (9)	6 (11)	2 (11)	1 (3)	0.4	
Diabetes mellitus	26 (25)	9 (17)	4 (22)	13 (41)	0.044	
Neurological disease	13 (13)	10 (18)	1 (5)	2 (6)	0.155	
Chronic liver disease	13 (13)	6 (11)	1 (5)	6 (19)	0.362	
Chronic renal disease	8 (8)	4 (7)	1 (6)	3 (9)	0.883	
Immunological disease	7 (7)	2 (4)	2 (11)	3 (9)	0.429	
Malignancy	12 (12)	5 (9)	1 (6)	6 (19)	0.281	
Severity of ARD & n (%)						
Mild	20 (10)	3 (6)	1 (6)	4 (12)	0.023	
Moderate	101 (48)	31 (57)	3 (17)	15 (47)		
Severe	89 (42)	20 (37)	14 (78)	13 (41)		
Extent of infiltration on Chest X-ray						
2	13 (13)	9 (17)	4 (22)	0 (20)	0.008	
3	53 (51)	31 (57)	9 (50)	13 (41)		
4	38 (36)	14 (26)	5 (28)	19 (59)		
High-resolution CT pattern						
Definite diffuse alveolar damage pattern	46 (56)	18 (33)	6 (33)	22 (67)	0.002	
Possible diffuse alveolar damage pattern	18 (15)	11 (21)	1 (5.6)	6 (19)		
Inconsistent with diffuse alveolar damage pattern	40 (29)	25 (46)	11 (61)	4 (12)		
HRCT score	216 [185, 291]	193 [170, 221]	206 [166, 253]	254 [212, 314]	<0.001	
McCabe score						
1	178 (85)	51 (94)	17 (94)	26 (81)	0.159	
2	17 (8)	3 (6)	0 (0)	4 (13)		
3	15 (7)	0 (0)	1 (6)	2 (6)		
APACHE II score	22 [18, 25]	21 [19, 25]	28 [24, 31]	21 [17, 25]	<0.001	
SOFA score	7 [5, 10]	7 [5, 10]	12 [9, 14]	7 [5, 9]	0.004	
PaO2/FiO2 ratio	108 [78, 157]	111 [83, 155]	74 [64, 96]	109 [78, 139]	0.017	
PEEP, cm	9 [8, 12]	9 [8, 12]	10 [8, 13]	10 [8, 12]	0.44	
Tidal volume, ml	425 [360, 500]	420 [350, 500]	430 [400, 490]	425 [375, 481]	0.96	
Peak inspiratory pressure, cmH2O	21 [18, 24]	21 [18, 24]	22 [17.5, 24]	21 [19, 24]	0.998	
JAAM DIC score						
0	3 (2.9)	1 (1.9)	0 (0.0)	2 (6.2)	0.082	
1	18 (17.5)	14 (26.4)	1 (5.6)	3 (9.4)		
2	26 (25.2)	18 (34.0)	1 (5.6)	7 (21.9)		
3	16 (15.5)	6 (11.3)	4 (22.2)	6 (18.8)		
4	17 (16.5)	6 (11.3)	4 (22.2)	7 (21.9)		
5	12 (11.7)	4 (7.5)	4 (22.2)	4 (12.5)		
6	5 (4.9)	2 (3.8)	1 (5.6)	2 (6.2)		
7	6 (5.8)	2 (3.8)	3 (16.7)	1 (3.1)		
DIC score (≥ 4)	40 (38.4)	14 (25.9)	12 (66.7)	14 (43.7)	0.007	
Albumin, (g/dL)	2.9 [2.4, 3.2]	3.0 [2.4, 3.4]	2.8 [2.4, 3.2]	2.9 [2.5, 3.1]	0.623	
WBC	9650 [6025, 14750]	9450 [5175, 13025]	4400 [2475, 9975]	11450 [5050, 14225]	0.093	
CRP, mg/dl	15.8 [9.3, 24.9]	19.5 [10.7, 26.0]	19.9 [13.2, 32.9]	15.2 [8.0, 23.5]	0.311	
LDH, IU/L	328 [249, 461]	256 [218, 337]	311 [263, 362]	364 [256, 495]	0.004	
Platelet, X 10 ⁴	18.0 [11.3, 24.7]	17.2 [13.1, 27.1]	15.2 [7.3, 25.6]	16.2 [8.9, 21.1]	0.417	

Data are presented as median values [IQR] or N (%).

Abbreviations

APACHE: acute physiology and chronic health evaluation

CRP:C reactive protein

HRCT: high-resolution computed tomography

JAAM; Japanese Association for Acute Medicine

LDH: Lactate dehydrogenase

PEEP: positive end expiratory pressure

SOFA: sequential organ failure assessment

WBC: white blood cell count

Spp:species

Table 2 Microbiological Etiology and Use of Anti-pathogen Agents

	Entire cohort	Patients prognoses			p-value
		All patients	Survivors	Early death patients (<7 days from diagnosis)	Late death patients (≥7 days after diagnosis)
Subject, n (%)	104 (100)	54 (52)	18 (17)	32 (31)	
Pathogen of pneumonia					
<i>Streptococcus pneumoniae</i>	43 (41)	26 (48)	9 (50)	8 (25)	0.076
<i>Influenza virus</i>	8 (7)	6 (11)	1 (5)	1 (3)	0.431
<i>Legionella pneumophila</i>	4 (4)	2 (4)	1 (5)	1 (3)	1
<i>Pneumocystis jirovecii</i>	4 (4)	2 (4)	0 (0)	2 (6)	0.648
<i>Klebsiella spp.</i>	2 (2)	1 (2)	1 (5)	0 (0)	0.41
<i>Haemophilus influenzae</i>	1 (1)	1 (2)	0 (0)	0 (0)	1
<i>Nocardia</i>	2 (2)	0 (0)	1 (5)	1 (3)	0.229
<i>Pseudomonas</i>	2 (2)	0 (0)	2 (11)	0 (0)	0.028
<i>E. coli</i>	3 (3)	2 (4)	0 (0)	1 (3)	1
<i>Cytomegalovirus</i>	1 (1)	0 (0)	0 (0)	1 (3)	0.481
MRSA	1 (1)	1 (2)	0 (0)	0 (0)	1
Unknown	33 (32)	13 (24)	3 (17)	17 (53)	0.007
Sensitivity of Initial Antimicrobial agents					0.002
Sensitive	68 (65)	42 (78)	13 (72)	13 (41)	
Non-sensitive	5 (5)	1 (2)	2 (11)	2 (6)	
Indeterminate	31 (30)	11 (20)	3 (17)	17 (53)	
Prior administration of antibiotics					0.033
Yes	39 (37)	15 (28)	6 (33)	18 (56)	
No	65 (63)	39 (72)	12 (67)	14 (43)	

Agreement of pathogen sensitivity with initial empiric antimicrobial agents

Except cases immediately diagnosed by urine antigens such as *S. pneumoniae* and *Legionella pneumophila* or nasopharyngeal flu antigen, empiric antibiotics were selected per Japanese Respiratory Society guidelines for management of respiratory infections (22, 23). When necessary, anti-microbials were adjusted according to in-vitro sensitivity of cultured pathogens. Pathogen sensitivity to initial empiric antimicrobial was graded: sensitive, non-sensitive, and indeterminate. “Indeterminate” was assigned when no significant pathogens were cultured.

Assessment of chest radiograph and HRCT findings

Extent of chest radiography lung infiltration was scored by Murray score (24) as follows: 1-quadrant, 2-quadrants; 3-quadrants; 4-quadrants. All patients underwent helical HRCT of the chest on the day of ARDS diagnosis using multidetector-row CT (MDCT). This study evaluated single HRCTs acquired on the day of ARDS diagnosis because of the difficulty of obtaining sequential CTs in patients receiving positive pressure ventilation. HRCTs were independently evaluated by two experienced chest radiologists (T.J. and K.F.) who were unaware of patients’ clinical condition.

Evaluation of HRCT patterns and HRCT score

On HRCT scans, DAD pattern is characterized by patchy ground-glass attenuation and/or air-space consolidation associated with bronchial dilation, reticular opacities, and cystic changes depending on the pathologic fibroproliferative phase of DAD according to the most recent international multidisciplinary consensus statement of idiopathic interstitial pneumonias (24). Each patient’s HRCT was assigned one of three patterns (definite DAD pattern, possible DAD pattern, and inconsistent with DAD pattern) consistent with the international guideline (Supplement Fig. 1). HRCT findings were graded a score of 1–6 based on the following classification system correlating with the previously described pathology (25). The scoring system was previously reported (14,15, 25).

Assignment of ventilator-associated outcomes

The number of ventilator-free days were recorded for each patient. Air leak syndrome defined as any pneumothorax, pneumomediastinum or subcutaneous emphysema was noted as present or absent on regular chest radiographs.

We also recorded diagnoses of culture confirmed ventilator-associated tracheobronchitis or pneumonia requiring newly prescribed antibiotics.

Evaluation of Coagulative and Fibrinolytic Abnormalities

Coagulative and fibrinolytic abnormalities at diagnosis of ARDS were assessed by the disseminated intravascular coagulation (DIC) score criteria of the Japanese Association of Acute Medicine (JAAM) (26)

Statistical analysis

Continuous variables, expressed as medians and interquartile ranges (IQRs) were compared using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test. Interobserver variation of HRCT findings and patterns was analyzed using the weighted *kappa* statistic and classified as follows: poor (*kappa* = 0-0.20), fair (*kappa* = 0.21–0.40), moderate (*kappa* = 0.41–0.60), substantial (*kappa* = 0.61–0.80), and almost perfect (*kappa* = 0.81-1.00). Interobserver variation of the extent of the HRCT findings was assessed by Spearman's rank correlation coefficient. The HRCT scores assigned by two independent observers' were compared by the Bland-Altman method. Univariate and multivariate analyses using Cox proportional hazard models were performed to identify independent factors predicting early death (< 7-day mortality) and 180-day mortality. Using ROC curves, we examined the sensitivity, specificity and predictive values of the APACHE II score and HRCT score and identified the best cut-off value for each by using Youden's index. The propensity score model for the best cut-off value of HRCT score was constructed with a logistic regression model including significant covariates. Unadjusted and adjusted survival curves were plotted using the Kaplan-Meier method. Log-rank tests were used to compare differences in survival. For all analyses, a p-value less than 0.05 was considered to indicate a statistically significant difference.

Results

The timing and causes of death

The distribution of days from diagnosis to death in this study is shown in Fig. 2. Fifty of 104 patients (48%) died during the 180 days-study period. Forty-one (82% of deaths) occurred within the first 28 days. Eighteen (36%) died less than 7 days following diagnosis (median, 2 days, IQR [1, 5]; early death group), almost all (88%), due to sepsis syndrome associated with multiple organ failure or shock. Of 32 patients (64%) who died after ≥ 7 days (median, 16 days, IQR [13, 29]; late death group), 22 (68%) died of sepsis syndrome and 10 (32%) of irreversible respiratory failure.

Differences of clinical characteristics

There were distinct clinical differences between early and late death groups. Demographics and clinical characteristics of patients in the three outcome groups (survivors, early deaths and late deaths) are summarized in Table 1. The early death group had significantly more severe general condition reflected by APACHE II score and more severe ARDS itself than those in the late death group. The early death group also showed significantly higher SOFA scores and DIC scores compared to the late death group. Conversely, the extent of infiltration on chest X-ray at diagnosis was significantly less extensive in the early death group than the late death group. Early decedent x-ray infiltrate scores were similar to those in the survivor group. Pneumonia microbial pathogen was identified in 70% of patients (Table 2). Pathogen was identified most frequently in the early death group (83%) and least frequently in the late death group (47%). Prior administration of antimicrobial agents at referring hospitals was significantly more frequent in the late death group (56%) than the early death group (33%) and survivors (28%) ($p = 0.029$). Similarly,

“indeterminate” anti-microbial sensitivity was more frequent in the late death group (53%) compared with the other groups ($p = 0.002$). *Streptococcus pneumonia* was the most frequent pathogen isolated (41% of all cases), tended to be the major bacteria caused the early death (50%).

Difference of high-resolution CT features

Substantial agreement (weighted kappa 0.78) between the 2 experts’ evaluation of HRCT findings was confirmed.

The consistency of HRCT scores between the 2 observers was shown in the Bland-Altman plots with 95% limits of agreement (Supplement Fig.

2). HRCT patterns of all patients were assessed as; definite (56%), possible (15%), and inconsistent with DAD (29%). Among the late death group, definite DAD pattern was most frequent (67%). Whereas the inconsistent with DAD pattern was seen in 61% of the patients who died early. The severity of fibroproliferation, evidenced by the extent of areas with traction bronchiectasis (contributing to high HRCT scores) was significantly higher in the late death group (median, 254; IQR [212, 314]) compared to those in the early death group (median, 206; IQR [166, 253]) ($P < 0.001$).

Prognostic Implications

Predictor for Early death

Among APACHE II, HRCT and DIC scores, only APACHE II score (HR 1.14, 95%CI 1.01–1.28, $p = 0.03$) was independently associated with early death (< 7 days) using a multivariate regression analysis (Table 3). A ROC curve showed that the APACHE II score of 27 was appropriate for prediction of early death with 67% sensitivity and 84% specificity (AUC, 0.79; 95%CI, 0.68–0.91) (Fig. 3)

Table 3. Univariate and Multivariate Analyses for Mortality

Variable	Univariate for 180-day mortality			Multivariate for Early death (<7 days)			Multivariate for Late death (≥ 7 days)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	1.01	0.98–1.03	0.486						
Sex	1.31	0.71–2.40	0.383						
Comorbidity									
Diabetes mellitus	1.68	0.93–3.02	0.082						
Neurological disease	0.37	0.12–1.20	0.096						
COPD	1.53	0.84–2.81	0.165						
Other chronic respiratory disease	1.68	0.52–5.41	0.384						
Cardiovascular disease	0.62	0.19–2.01	0.429						
Chronic liver disease	0.98	0.44–2.18	0.964						
Chronic renal disease	0.97	0.35–2.70	0.956						
Malignancy	1.18	0.53–2.63	0.682						
Immunological disease	2.01	0.80–5.07	0.139						
McCabe	1.53	0.87–2.68	0.138						
APACHE II score	1.06	0.99–1.11	0.05	1.14	1.01–1.28	0.047	1.01	0.93–1.08	0.84
SOFA score	1.08	1.00–1.17	0.05						
PaO ₂ /FIO ₂ ratio	0.99	0.99–1.00	0.157						
Severity of the Berlin definition	1.41	0.87–2.26	0.16						
Extent of infiltration on chest X-ray	1.48	0.95–2.31	0.087						
JAAM DIC score	1.25	1.085–1.45	0.0002	1.02	0.89–1.49	0.93	1.31	1.07–1.58	0.007
HRCT score*	1.13	1.05–1.25	0.004	1.11	0.76–1.64	0.59	1.28	1.13–1.45	< 0.001
HRCT pattern									
Definite diffuse alveolar damage	1.74	0.99–3.06	0.051						
Possible diffuse alveolar damage	0.66	0.30–1.47	0.307						
Inconsistent with diffuse alveolar damage	0.7	0.36–1.28	0.249						
Prior antibiotics	1.72	0.96–2.99	0.056						
Sensitivity of initial antibiotics	1.84	1.18–2.85	0.006	0.83	0.31–2.24	0.71	3.42	1.86–6.29	< 0.001

SOFA: sequential organ failure assessment

JAAM DIC score: Japanese Association of Acute Medicine disseminated intravascular coagulation score

HRCT score: high-resolution computed tomography score

*Hazard ratio of HRCT score is expressed as mortality change per 10 % increase in area of attenuation with traction bronchiectasis on high-resolution CT

Predictor for Late death

Multivariate regression analysis after adjusted characteristics showed that sensitivity to initial antimicrobial agent(s), the HRCT score, and the DIC score were independently associated with late death (Table 3). ROC curve yielded an optimal cut-off value of the HRCT score of 211, which was determined by the Youden Index to predict death from day 7 to day 180 with 81% sensitivity and 63% specificity (AUC, 0.72; 95% CI, 0.58–0.87) (Fig. 4A). Mortality rate of the patients with HRCT scores less than 211 were in the 20% range at each time point, while those with an HRCT score of 211 or higher had a mortality rate in the 60% range (Fig. 4B). When applied for overt DIC criteria of DIC score ≥ 4, the HRCT score ≥ 211 (HR 5.90, 95%CI 2.29–15.17, $p < 0.001$) was the most relevant factor for the late death compared with the sensitivity of initial administration of antimicrobial agents (HR 3.28, 95%CI 1.72–6.27, $p < 0.001$) and the DIC score ≥ 4 (HR 2.51, 95%CI 1.69–5.39, $p = 0.01$). The adjusted HR of HRCT score ≥ 211 estimated using the propensity score was 5.42 (95%CI 1.54–19.12; $P = 0.008$) for late death (Table 4, Fig. 5).

Table 4. Comparison of prognostic variables for the late death (≥ 7 days)

Variables	Hazard Ratio	95% CI	P value
HRCT score ≥ 211	5.9	2.29–15.17	< 0.001
Sensitivity of initial antibiotics	3.28	1.72–6.27	< 0.001
JAAM DIC score ≥ 4	2.51	1.69–5.39	0.01
Propensity score matching for the late death			
HRCT score ≥ 211	5.42	1.54–19.12	0.008

JAAM DIC score: Japanese Association of Acute Medicine disseminated intravascular coagulation score

HRCT score: high-resolution computed tomography score

Definite DAD pattern on HRCT scans was significantly worse than possible DAD pattern and inconsistent with DAD pattern ($p = 0.046$) and was independently prognostic for late death (HR 2.91, 95%CI 1.34–6.30, $p = 0.006$). However, because HRCT patterns correlated well with HRCT scores ($r_s = 0.728$, $p < 0.001$), HRCT patterns did not reach significant value when the HRCT score was included as a covariate.

Predictors for Ventilator-Associated Outcomes

In the adjusted analysis, the APACHE II score (OR 0.89, 95%CI 0.81–0.98, $p = 0.02$), the HRCT score (OR 0.60, 95%CI 0.46–0.78, $p < 0.0001$), and the DIC score (OR 0.63, 95%CI 0.48–0.83, $p < 0.001$) were independently associated with ventilator-weaning within 28 days after diagnosis. As for the onset of air-leak syndrome, only the HRCT score (OR 1.28, 95%CI 1.00–1.28, $p = 0.03$) was extracted from the other variables. Multivariate analysis also demonstrated that the HRCT score was independently associated with the anti-biotic treated ventilator-associated infection, with an OR 1.28 ($p = 0.041$)

Discussion

We demonstrated here the distinct differences and prognostic factors between the early and late death groups and clarified two clinical phenotypes from fatal cases in our patients with ARDS due to pneumonia. Patients who died early accounted for 36% of deaths, and experienced more severe general condition caused by the so called “cytokine storm”, which was evidenced by higher APACHE II score, higher SOFA score, and higher DIC score as well as higher disease severity in spite of less extensive radiological features. Conversely, patients who died late accounted for 64% of deaths, and were characterized by more extensive radiographic infiltration, more severe lung fibroproliferation on HRCT scans, and typically experienced prolonged mechanical ventilation followed by secondary multiple organ failure. We also demonstrated here for the first time the radiological differences as well as other clinical differences between the two fatal groups. Similar to our study, previous studies of causes and timing of deaths among ARDS cases from the 1980s and 1990s showed that fatal cases were classified into early (< 72 hours after diagnosis) and late (> 72 h) death and emphasized the common cause of death as sepsis syndrome (6,7). However, our data suggest that different processes were involved in sepsis syndrome deaths early and late. Contrast that approximately 90% of patients who died early succumbed to primary sepsis syndrome, which was also the cause of ARDS itself, whereas 60% of those who died late suffered secondary sepsis syndrome following prolonged mechanical ventilation. Recently, ARDS has been classified into two clinical phenotypes by using a latent class analysis: hypoinflammation (phenotype 1) and hyperinflammation (phenotype 2) (4,5). Although personalized medicine for ARDS would be expected according to the phenotypes (5), two phenotypes from our fatal cases may be subgroup of these phenotype 1 and 2.

We reported that evidence of early fibroproliferation based on HRCT scans at diagnosis was independently associated with the ventilator-associated outcomes and subsequent multiple organ failure, as well as refractory respiratory failure (14,15). In a prospective cohort study evaluating 159 autopsy lungs from ARDS patients, Thille et al (10) described that early fibroproliferation occurred within one week and fibrosis formation was observed after one week at earliest. Interestingly, fibrosis was more frequent in ARDS of pulmonary origin compared to that of the other origins. Since our study patients' ARDS was caused by pneumonia, early progression of lung fibro-proliferation evaluated by HRCT score was the most relevant risk factor for the late death and was considered the most crucial.

A new frontier in ARDS clinical trials, where phenotyping of patients before randomization has been proposed. Personalized mechanical ventilation tailored to the type of CT pattern of the patient (focal or non-focal) has already been reported in this field (29). This study was analyzed to plan the study design for a randomized, open-label multicentre phase II study to evaluate the efficacy and safety of MultiStem® cells [HLCM051], an allogeneic bone marrow-derived stem cell product, in patients with ARDS due to pneumonia (NCT03807804). Using the cut-off value of APACHE II score ≥ 27 , patients who are likely to die of severe systemic organ failure in a few days without confirming the effect of the investigational new drug would be excluded. On the other hand, patients who are at high risk of progressive pulmonary fibroproliferation associated with secondary septic syndrome and could hardly be rescued by any conventional treatment, were extracted by using the value of HRCT score ≥ 211 .

Coagulation and fibrinolytic abnormalities which result in DIC, and excessive systemic inflammation lead to multiple organ failure (28). Although these abnormalities have garnered relatively little attention among ARDS researchers previously (18, 20), there has been emerging concern around these abnormalities as coronavirus infections in 2019 (COVID-19) are reported to evoke prominent coagulopathy associated with an increased risk of death (29). Because DIC score was one of the independent predictive factors in our study, a new assessment of these abnormalities may be necessary in patients with ARDS caused by the other pneumonia pathogens as well as COVID-19.

Recent studies indicated that approximately one-half of patients with ARDS who met the Berlin definition, exhibit DAD, and that the prognosis of patients with DAD was inferior to those who do not have DAD (12,13). In our study, the definite DAD pattern was most frequently observed in the late death group, while the inconsistent with DAD pattern significantly dominated the early death group. Sarmiento et al (30) who studied 36 autopsy cases of ARDS due to pneumonia reported that pathological alterations of DAD were seen in less than 50% of patients who died within six days. The distinct difference in HRCT findings between the early and late death groups may reflect a difference of the underlying pathology. It is of critical value to identify DAD without using invasive procedures (31). Although HRCT patterns correlated well with HRCT scores and tended to be a prognostic value in our study, further study is needed to evaluate the relationship between HRCT patterns and prognosis.

In a study of 432 patients requiring mechanical ventilation for severe community-acquired pneumonia (CAP) including 125 (29%) cases of ARDS, multivariate logistic regression analyses showed that previous

antibiotic use and inadequate antibiotic therapy were independently associated with 30-day mortality, respectively (8). In our study, “previous antibiotic use” and “indeterminate” sensitivity of initial antimicrobial agents were significantly more frequent in the late death group, and the latter was one of the predictive factors for the late death, but not for the early death. It was reported that duration of use of antibiotic therapy over 24 hours lead to lower sensitivity to detect significant pathogens (32). Longer use of broad-spectrum antibiotics without de-escalation according to the sensitivity for cultured pathogens could have resulted in inducing the antibiotics treated ventilator-associated infection which was the most often observed in the late death group.

Our study has several limitations. First, it was a retrospective evaluation using a prospective collected dataset. Compared with a typical retrospective design however, our study is strengthened by the use of a prospectively collected cohort including prospective identification of acute respiratory failure as a suspected ARDS. Second, this study included a relatively small number of patients and was conducted at a single center, which necessitates cautious extrapolation of the findings to other settings. Although we have previously reported the critical utility of HRCT findings and scoring, and the prognostic value of DIC score for care of ARDS patients (19,20), CT findings and coagulative and fibrinolytic abnormalities have only recently gained more widespread consideration during the current pandemic of severe acute respiratory syndrome of COVID-19. Third, the long period of recruitment (14 years) may have affected patient care.

We did introduce advances in ventilatory management (33) and other supportive care over time. However, the fundamental management including lung protective ventilation strategy did not change during our cohort. Finally, respiratory viruses except for flu could not routinely be identified because of diagnostic techniques over the period. In cases for which no significant pathogen was identified in our study, these patients might have been infected with other respiratory viruses. Even if these viruses were involved in the disease, only supportive care could be taken in addition to lung protective ventilation.

Conclusions

There are distinct differences in clinical characteristics and prognostic factors between the early and late death in patients with ARDS due to pneumonia. Early deaths are largely caused by high severity of general condition characterized by cytokine storm and late deaths are associated with early fibroproliferation with coagulation abnormalities. Systemic severity, the extent of early fibroproliferation on HRCT scans, and coagulation abnormalities should be taken into consideration in personalized medicine towards ARDS caused by pneumonia.

Abbreviations

ARDS

Acute respiratory distress syndrome

DAD

Diffuse alveolar damage
APACHE
Acute Physiology and Chronic Health Evaluation
HRCT
High-resolution computed tomography
IQR
Interquartile range
PBW
Predicted body weight
PEEP
Positive end-expiratory pressure
PIP
Peak inspiratory pressure
SOFA
Sequential organ failure assessment
 V_T
Tidal volume

Declarations

Ethics approval and consent to participate: Yes

Consent for publication: Not applicable

Availability of data and materials: Yes

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1.

Figure 1

Screening and Enrollment of Patients with Acute Respiratory Distress Syndrome

Figure 2.

Figure 2

The correlation between the number of patients who died and days from diagnosis to death Fifty (48%) of 104 patients in our series died during the 180 days study period, and 82% (41 deaths) of all deaths occurred within the first 28 days. Eighteen (36%) of the 50 non-survivors died within six days (<7 days) from diagnosis (median, 2 days, IQR [1, 5]; early death group). The other 32 patients (64%) died after the Day 7 (≥ 7 days) (median, 16 days, IQR [13, 29]; late death group).

Figure 3.

Figure 3

Receiver operator characteristic (ROC) curve of predictive value for early death (< 7 days from diagnosis) of APACHE II score ROC identified the optimal cut-off value of 27 determined by Youden Index for prediction of death within 6 days with a 67% sensitivity and 84% specificity (AUC, 0.79; 95%CI, 0.68-0.91).

Figure 4A.

Figure 4B.

Figure 4

4A. Receiver operator characteristic (ROC) curve of predictive value for late death (≥ 7 days from diagnosis) of high-resolution CT score ROC curve yielded an optimal cut-off value of the HRCT score of 211 which was determined by the Youden Index for prediction of death from day 7 to day 180 with 81 % sensitivity and 63 % specificity (AUC, 0.72; 95% CI, 0.58-0.87). 4B. Each mortality rate compared between the optimal cut-off value of high-resolution CT score. Mortality rate of the patients with HRCT scores less than 211 ranged between 20 – 30% at any time point, while those with an HRCT score of 211 or greater ranged between 58 – 66%. Statistical difference was noted between the 2 groups at any time point.

Figure 5

Survival curves for the optimal high-resolution CT score and the late death (≥ 7 days from diagnosis) from the Cox proportional hazards model, adjusted for sensitivity of initial antibiotics to cultured pathogens and disseminated intravascular coagulation scores. The HRs of HRCT score ≥ 211 estimated using the propensity score were 5.42 (95%CI 1.54–19.12; P = 0.008) for the late death mortality after adjusted for sensitivity of antibiotics to cultured pathogens and the DIC score.

Supplementary Files

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