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ORIGINAL ARTICLE

A prospective cohort study of ALI/ARDS in the Tohoku district of Japan (second report)

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Abstract
Purpose We previously reported a study of systemic inflammatory response syndrome (SIRS) cases in the Tohoku district of Japan in which the patients showed a 30-day mortality from acute lung injury/acute respiratory distress syndrome (ALI/ARDS) of about 20%. Cases in which chest X-ray findings did not meet ALI/ARDS criteria were diagnosed as acute hypoxemic respiratory failure (AHRF), but about 50% of these patients progressed to ALI/ARDS. The objective of this study was to verify the findings obtained in the earlier study and to gain further insights into the pathognomonic symptoms of AHRF associated with SIRS.

Methods A prospective cohort study was performed in SIRS patients admitted to the intensive care unit (ICU) with PaO_2/fractional inspired oxygen (FIO_2) $\leq$ 300 mmHg. Patients were assigned to ALI or ARDS groups based on symptoms at ICU entry. Cases in which chest X-ray showed no infiltration shadows in bilateral lung fields were classified as AHRF.

Results A total of 240 patients were enrolled in the study. The 30-day mortalities were 21.6% and 20.0% in the ALI and ARDS groups, respectively. Of the 88 AHRF patients, 49 progressed to ALI/ARDS, with progression occurring within 3 days after ICU entry in most cases; 39 patients recovered with no progression. Chest X-ray and computed tomography (CT) showed no findings indicating ALI/ARDS in 20 AHRF patients at ICU entry, but 7 of these patients progressed to ALI/ARDS.

Conclusion The mortality rates of ALI and ARDS were 21.6% and 20.5%, respectively. More than half of the AHRF patients progressed to ALI or ARDS. Some AHRF patients had normal findings on chest CT, but subsequently showed a bilateral shadow on a chest X-ray. This indicates that mild pathologic lesions may not show imaging abnormalities.

Keywords ALI · ARDS · AHRF · ICU · Computed tomography

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Introduction

Acute respiratory distress syndrome (ARDS) is a noncardiogenic pulmonary edema that develops in association with underlying diseases [1, 2] such as infection and pneumonia [3–5] and may also occur postoperatively [4, 6]. Since the first description of ARDS by Ashbaugh et al. [7],

many epidemiological studies have examined ARDS in terms of its underlying causes, incidence, mortality, and progression from other diseases [8–10]. Kraft et al. [8] found that mortality due to ARDS was about 50% from 1967 to 1994 in the United States and Europe, with considerable variation among studies, which reflected the difficulty of defining ARDS in this period due to the lack of standard diagnostic criteria. The acute lung injury (ALI)/ARDS criteria proposed at the American-European Consensus Conference on ARDS (AECC) in 1994 [11] are now widely accepted worldwide, and most epidemiological surveys conducted using these criteria have found ARDS mortality rates of 30%–40% [9, 10, 12, 13].

The first epidemiological survey of ALI/ARDS in Japan conducted using the AECC diagnostic criteria was reported by Tajimi et al. [14] in 1999. As far as we are aware, no other AECC criteria-based studies have been reported. Against this background, we launched the Tohoku Acute Pulmonary Disease Workshop, and an epidemiological survey was conducted in patients admitted to an intensive care unit (ICU) with systemic inflammatory response syndrome (SIRS) and deteriorated pulmonary oxygenation in the Tohoku district from April to September 2005. This survey showed a mortality rate from ALI/ARDS from 30 days after onset of about 20% [15]. We also found that about 23% of patients with acute hypoxemic respiratory failure (AHRF) had no shadows in the bilateral lung fields on chest X-ray, and therefore did not meet the criteria for a diagnosis of ALI/ARDS; however, about 50% of these patients progressed to ALI/ARDS based on shadows in the bilateral lung fields on follow-up chest X-ray. This suggests that pulmonary diseases cannot always be detected by chest X-ray in the initial stage of deteriorated pulmonary oxygenation. Therefore, we conducted a second study to verify these findings and to examine the progression of AHRF symptoms, using a chest computed tomography (CT) scan to complement the chest X-ray.

Methods

A prospective cohort study of patients who met the SIRS diagnostic criteria and were admitted to an ICU with deteriorated pulmonary function (PaO_2/fractional inspired oxygen (FIO_2) $\leq$ 300 mmHg) was performed in 34 hospitals in the Tohoku district. Prior to the commencement of this study, approval was obtained from the ethics committees of the individual hospitals. Patients meeting the above criteria were enrolled in the study from 29 June to 30 November 2007. Patients with cardiogenic syndromes were excluded. The entry route to the ICU, sex, age, primary illness, recent surgical history (within the last 3 months), onset date and cause of SIRS, diagnostic results for ALI/ARDS, respiratory management, diseases of organs other than the lung, and items for calculation of the Acute Physiology and Chronic Health Evaluation (APACHE) II score were recorded as background data on day 0 (the day of ICU entry). PaO_2, FIO_2, and chest radiography findings were recorded on days 0, 1, 2, 3, 5, 7, and up to the day before ICU discharge or 30 days after ICU entry. Infiltration shadows were determined in single or bilateral lung fields by chest X-ray and scores were calculated as the number of sections with an infiltration shadow, using a four-section system. A chest CT scan was conducted on day 0 whenever possible. Mortality was calculated based on death up to 30 days after ICU entry.

Patients who met the AECC diagnostic criteria for ALI or ARDS (using data on day 0) were assigned to the ALI or ARDs groups, respectively. Patients with $PaO_2/FIO_2 \leq 300$ mmHg who had no infiltration shadows in the bilateral lung fields or a shadow in only a single lung field on chest X-rays were assigned to the AHRF group, because these patients did not meet the diagnostic criteria for ALI/ARDS. PaO_2/FIO_2 values, chest X-ray scores, and pulmonary disease scores were calculated for these groups. The pulmonary disease score was calculated as the average of the positive end-expiratory pressure (PEEP) score, PaO_2/FIO_2, and the chest X-ray score, as described by Murray et al. [16] The method of Tamakuma et al. [17] ($\geq$12 cmH_2O) was used to obtain the PEEP score, because this approach is more appropriate in Japan.

Results are expressed as mean $\pm$ SD. Paired and unpaired t tests or analysis of variance (ANOVA) were used for intragroup and intergroup comparisons, respectively. Other statistical tests are indicated in the footnotes of Tables.

Results

The data at ICU entry (day 0) are shown in Tables 1 and 2. The mortality rate at 30 days after day 0 was 11.4% (10/88) in the AHRF group, 21.6% (8/37) in the ALI group, and 20.0% (23/115) in the ARDS group, with no significant differences among the groups (Table 3). The causes of death included multiple organ failure ($n = 27$, 65.9%), respiratory failure ($n = 13$, 31.7%), and septic shock ($n = 1$, 2.4%). Mortality rates based on primary illness and APACHE II score are shown in Tables 4 and 5, respectively.

The mean PaO_2/FIO_2 values and pulmonary disease scores improved in the ICU in all groups (Fig. 1a, b). The chest X-ray score tended to decrease on the day after day 0 in the ALI and ARDS groups, but increased and then peaked on days 3–5 in the AHRF group, before decreasing (Fig. 2). Changes in chest X-ray findings were examined in

Table 1 Background data

	AHRF	ALI	ARDS	*p* Value
No. of patients	88 (36.7%)	37 (15.4%)	115 (47.9%)	
Sex (male/female)	63:25	27:10	81:34	NS[b]
Age (years)[a]	61.7 ± 19.2	65.5 ± 11.2	68.3 ± 14.9	$p < 0.005$[c]
Route of ICU entry				
Emergency ambulance	51 (58.0%)	19 (51.4%)	44 (38.3%)	
Operation room	28 (31.8%)	13 (35.1%)	34 (29.6%)	$p < 0.005$[d]
General ward	7 (8.0%)	5 (13.5%)	34 (29.6%)	
Others	2 (2.3%)	0 (0%)	3 (2.6%)	
Underlying diseases				
Infectious disease	13 (14.8%)	10 (27.0%)	12 (10.4%)	NS[d]
Pneumonia	5 (5.7%)	5 (13.5%)	16 (13.9%)	NS[d]
Aspiration pneumonia	6 (6.8%)	1 (2.7%)	12 (10.4%)	NS[d]
Interstitial pneumonia	0 (0%)	0 (0%)	4 (3.5%)	NS[d]
Sepsis	9 (10.2%)	9 (24.3%)	4 (3.5%)	$p < 0.001$[d]
Tumor (postoperative)	5 (5.7%)	4 (10.8%)	22 (19.1%)	$p < 0.05$[d]
Trauma	22 (25.0%)	5 (13.5%)	8 (7.0%)	$p < 0.005$[d]
Burn	3 (3.4%)	0 (0%)	7 (6.1%)	NS[d]
Pancreatitis	2 (2.3%)	0 (0%)	2 (1.7%)	NS[d]
Heart disease (postoperative)	8 (9.1%)	2 (5.4%)	8 (7.0%)	NS[d]
Gastrointestinal perforation	11 (12.5%)	4 (10.8%)	6 (5.2%)	NS[d]
Aneurysm (thoracic/abdominal)	9 (10.2%)	5 (13.5%)	16 (13.9%)	NS[d]
Others	17 (19.3%)	8 (21.6%)	20 (17.4%)	NS[d]

AHRF acute hypoxemic respiratory failure, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *ICU* intensive care unit, *NS* not significant

[a] Ages are expressed as mean ± SD values

[b] χ^2 test

[c] Analysis of variance (ANOVA)

[d] Fisher's exact test

Table 2 Clinical characteristics

	AHRF	ALI	ARDS	*p* Value
Respiratory parameters[a]				
PEEP (cmH_2O)	4.6 ± 3.2	5.7 ± 3.4	5.7 ± 3.3	NS[c]
PaO_2/FIO_2 (mmHg)	200.3 ± 70.0	251.6 ± 26.8	130.0 ± 43.3	$p < 0.001$[c]
$PaCO_2$ (mmHg)	41.0 ± 11.1	41.3 ± 9.1	43.6 ± 15.2	NS[c]
Chest X-ray score	0.9 ± 0.9	3.4 ± 0.8	3.4 ± 0.7	$p < 0.001$[c]
Lung injury score	1.3 ± 0.6	2.0 ± 0.4	2.8 ± 0.6	$p < 0.001$[c]
Distribution of APACHE II score[b]	$n = 79$	$n = 35$	$n = 97$	
0–9	10 (12.7%)	3 (8.6%)	6 (6.2%)	
10–14	20 (25.3%)	8 (22.9%)	22 (22.7%)	
15–19	18 (22.8%)	9 (25.7%)	18 (18.6%)	NS[d]
20–24	17 (21.5%)	9 (25.7%)	17 (17.5%)	
25–29	9 (11.4%)	3 (8.6%)	19 (19.6%)	
30–34	4 (5.1%)	1 (2.9%)	11 (11.3%)	
35–	1 (1.3%)	2 (5.7%)	4 (4.1%)	
APACHE II[a]	17.7 ± 7.4	19.3 ± 8.3	20.6 ± 8.4	NS[c]

PEEP positive end-expiratory pressure, FIO_2 fractional inspired oxygen, *APACHE* acute physiology and chronic health evaluation

[a] Respiratory parameters and APACHE II scores are expressed as mean ± SD

[b] Patients whose APACHE II score could not be calculated because of missing data were excluded

[c] ANOVA

[d] Kruskal–Wallis test

detail in the 88 patients in the AHRF group. Infiltration shadows in the bilateral lung fields were found in 49 (55.7%) of these patients in follow-up chest X-rays, and 36 (40.9%) were subsequently diagnosed with ARDS and 13 (14.8%) with ALI (Fig. 3a). Forty-two AHRF patients (85.8%) progressed to ARDS/ALI within 3 days after day 0 (Fig. 3b). Mortality in the 49 AHRF patents who progressed to ALI/ARDS tended to be higher than that in the AHRF patients without disease progression [16.3% (8/49) vs. 5.6% (2/36), not significant] (Fig. 3c).

Changes in PaO_2/FIO_2 values and chest X-ray scores were also compared between patients with AHRF who did and did not progress to ALI/ARDS. PaO_2/FIO_2 values rapidly recovered starting from days 0 to 1 in patients who

Table 3 Mortality and causes of death

	AHRF ($n = 88$)	ALI ($n = 37$)	ARDS ($n = 115$)
Mortality up to day 30	10 (11.4%)[a]	8 (21.6%)[a]	23 (20.0%)
Cause of death			
MOF	7 (17.1%)	5 (12.2%)	15 (36.6%)
Respiratory failure	2 (4.9%)	3 (7.3%)	8 (19.5%)
Septic shock	1 (2.4%)	0 (0%)	0 (0%)
Causes of death and mortality for all fatal cases			
MOF	65.9% ($n = 27$)		
Respiratory failure	31.7% ($n = 13$)		
Septic shock	2.4% ($n = 1$)		

MOF multiple organ failure

[a] 8 of 10 fatal cases in the AHRF group and all 8 fatal cases in the ALI group progressed to ARDS before death

[b] Intergroup mortality comparison: AHRF versus ALI: NS, AHRF versus ARDS: NS, ALI versus ARDS: NS (χ^2 test)

Table 4 Mortality rates based on primary illnesses

Primary illness	Mortality
Infectious disease	10/35 (28.6%)
Pneumonia	8/26 (30.8%)
Aspiration pneumonia	7/19 (36.8%)
Interstitial pneumonia	2/4 (50.0%)
Sepsis	5/22 (22.7%)
Tumor (postoperative)	4/31 (12.9%)
Trauma	2/35 (5.7%)
Burn	1/10 (10.0%)
Pancreatitis	1/4 (25.0%)
Heart disease (postoperative)	1/18 (5.6%)
Gastrointestinal perforation	1/21 (4.8%)
Aneurysm (thoracic/abdominal)	4/30 (13.3%)
Others	9/45 (20.0%)

Table 5 Mortality rates based on APACHE II scores

APACHE II score	Mortality
0–9	1/19 (5.3%)
10–14	3/50 (6.0%)
15–19	7/45 (15.6%)
20–24	7/43 (16.3%)
25–29	6/31 (19.4%)
30–34	3/16 (18.8%)
35–	5/7 (71.4%)

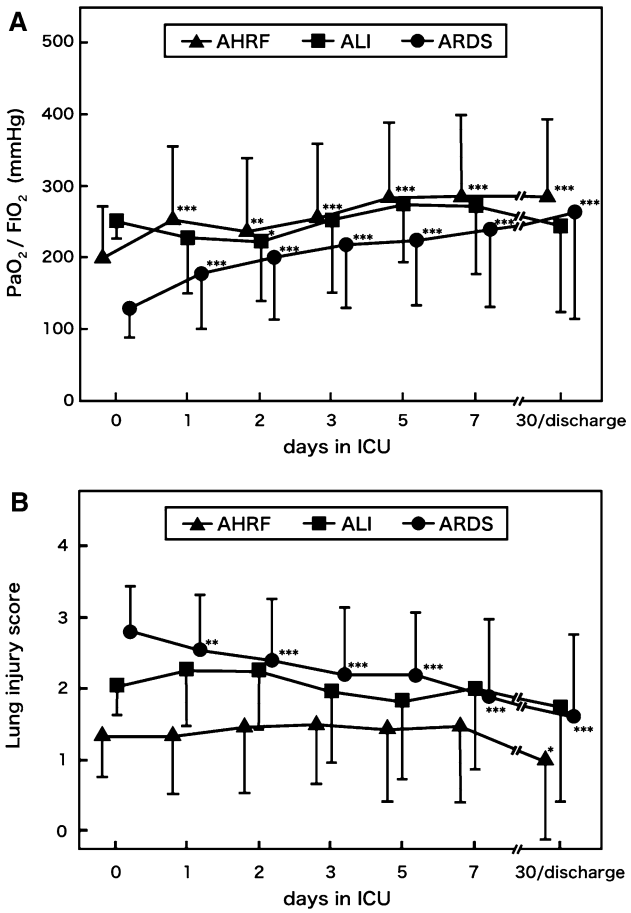

Fig. 1 Time-courses of **a** PaO_2/fractional inspired oxygen (FIO_2) and **b** lung injury score, from intensive care unit (*ICU*) entry (day 0) until the day immediately before ICU discharge or day 30. Data are shown as mean ± SD. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus day 0 by paired *t* test. *AHRF*, Acute hypoxemic respiratory failure; *ALI*, acute lung injury; *ARDS*, acute respiratory distress syndrome

did not progress to ALI/ARDS, whereas almost no change in these values was observed up to day 2 in those who did progress, although mild recovery did occur on day 3 or thereafter (Fig. 4a). Chest X-ray scores remained low on day 0 or thereafter in patients who did not progress to ALI/ARDS, whereas the value reached 2.0 ± 1.2 on day 1 in patients who progressed to ALI/ARDS and then decreased slowly until day 5 (Fig. 4b).

Chest X-rays conducted on day 0 showed no abnormal shadows in 38 patients with AHRF. Twenty-six of these patients underwent a chest CT scan (Fig. 5) and abnormal findings suspected to be due to ALI/ARDS were found in 6 patients. Five of these 6 patients were subsequently diagnosed with ALI/ARDS based on later chest X-ray findings. The CT scan showed no abnormal findings in 20 patients, but 7 of these patients were diagnosed with ALI/ARDS based on chest X-rays on the next day or thereafter. In the other 13 patients, chest X-rays showed abnormal shadows in the bilateral lung fields in 1 patient with $PaO_2/FIO_2 > 300$ mmHg; a shadow was shown in a single lung field in 2 patients; and no abnormal shadows were found in 10 patients, indicating recovery from deteriorated pulmonary oxygenation.

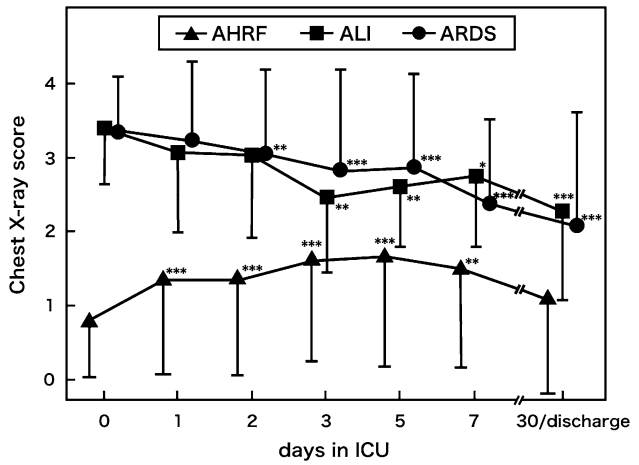

Fig. 2 Time-courses of X-ray scores from ICU entry (day 0) until the day immediately before ICU discharge or day 30. Data are shown as mean ± SD. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ versus day 0 by paired *t* test

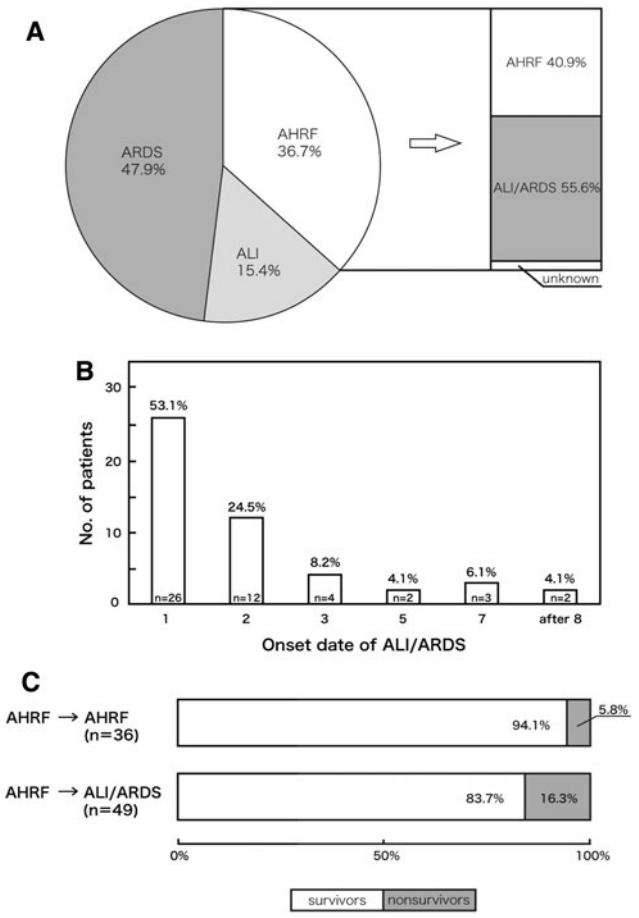

Fig. 3 **a** Rates of progression of patients with AHRF to ALI/ARDS. **b** Time-course of progression of patients with AHRF to ALI/ARDS from day 1 after ICU entry until day 8. **c** Mortality rates in the AHRF and ALI/ARDS groups

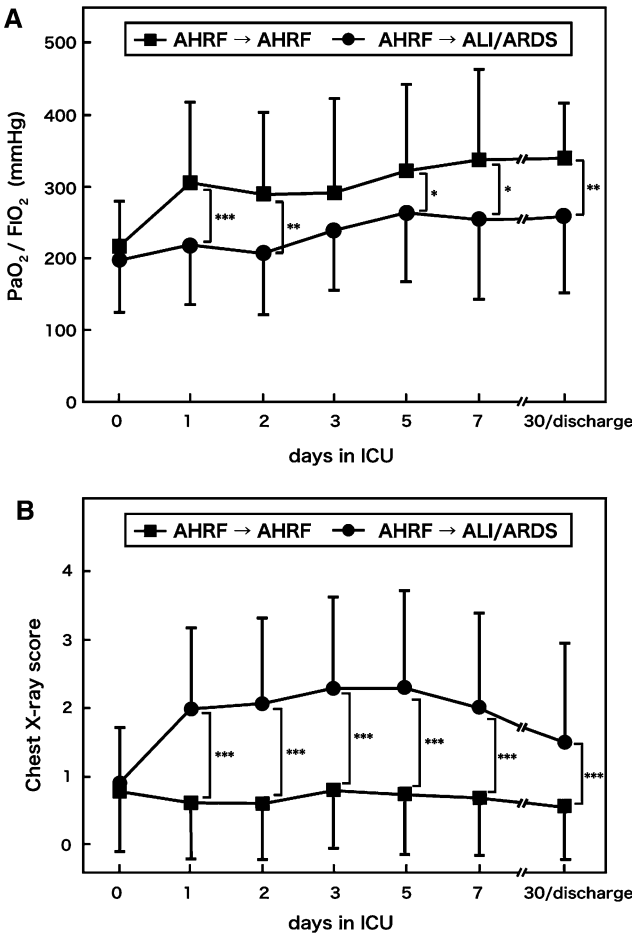

Fig. 4 Comparison of time-courses of **a** PaO_2/FIO_2 and **b** X-ray scores from ICU entry (day 0) until the day of ICU discharge or day 30 in patients with AHRF who progressed to ALI/ARDS ($n = 49$) and those who did not progress ($n = 36$). Data are shown as mean ± SD. **a** $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ versus day 0 by paired *t* test

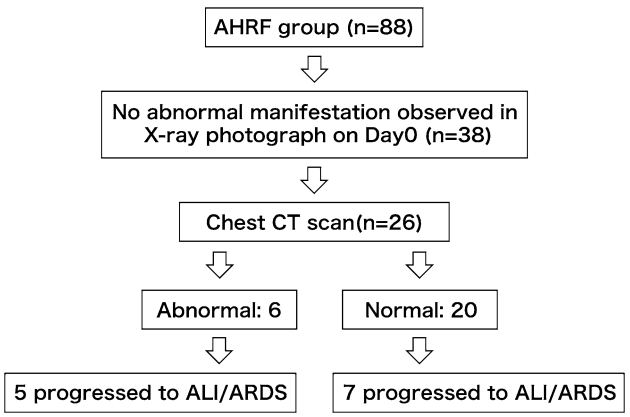

Fig. 5 Flowchart of disease progression for patients in the AHRF group. *CT* computed tomography

Discussion

There have been many epidemiological studies of ARDS [3–6, 8–10, 12–15] since Ashbaugh et al. [7] first described the condition in 1967. The pathology of ARDS revealed by these studies and advances in respiration [18–21] and infusion management [22] have contributed to a reduction in mortality. Kraft et al. [8] reported an ARDS mortality rate from 1967 to 1994 of about 50%, and also indicated the difficulty of comparing findings among studies because of the lack of standard diagnostic criteria. In 2008, Zambon and Vincent [10] reviewed studies performed since 1994 using AECC diagnostic criteria and found a mortality rate of 43%, with a 1.1% decrease per year, whereas Phua et al. [23] found mortality rates of 44.0% in observational studies and 36.2% in randomized controlled trials (RCTs) conducted since 1994. This suggests that the mortality rate has not improved significantly since the adoption of the AECC diagnostic criteria, and this lack of improvement may be due to a lack of effective standard treatment [23]. Thus, systematic reviews of risks for mortality are required, particularly because the mortality apparently depends on the type of study. An RCT designed to ensure safety and achieve optimal treatment efficacy may include higher percentages of mild cases, while observational studies include many patients who convalesce satisfactorily. Both types of studies are likely to underestimate the mortality rate. This background and recent epidemiological surveys [9, 10, 12, 13, 23, 24] suggest that the current mortality rate of ARDS is 30%–40%.

In an epidemiological survey performed in Japan in 1999 using the AECC criteria, Tajimi et al. [14] found mortality rates of 48.6% and 61.3% for ARDS patients in ICUs and in hospital wards, respectively. There have been no similar surveys conducted in Japan since that time. Therefore, we conducted an ALI/ARDS study in the Tohoku district in 2005, and found 30-day mortality rates of 19.5% and 23.0% for ALI and ARDS, respectively [15]. In the present study, these respective rates were 21.6% and 20.0%, which provides confidence in the reliability of the two studies. During the same period, Oda et al. [25] conducted an epidemiological survey of ALI/ARDS in Chiba Prefecture, and found an annual incidence of ALI/ARDS of 6.1/100,000 population and a 28-day mortality rate of 31.6%. These findings suggest that the mortality rates of ALI/ARDS patients are lower in the Tohoku district and Chiba Prefecture in Japan compared to the findings of studies in the United States and Europe [9, 10, 12, 13, 23, 24]. We note that the present study included patients who convalesced satisfactorily, and the mortality rates were only 5.7% in patients with trauma, 5.6% in those with heart disease (postoperative), 4.8% in patients with gastrointestinal perforation, and 13.3% in those with thoracic/abdominal aneurysm. Patients with sepsis were also included in the study, and such patients are generally assumed to have a higher mortality rate. However, the mortality among these patients was relatively low, at 22.7% (Table 4). Moreover, the mortality in patients with severe cases, with APACHE II scores of 30–34, was only 18.8% (Table 5). The low mortality rates may be due to multimodal patient management such as the treatment of AHRF and ALI/ARDS with similar approaches; e.g., the use of steroid drugs [25, 26], a neutrophil elastase inhibitor [27], and continuous hemodiafiltration (CHDF). Many studies have found multiple organ failure to be the primary cause of ALI/ARDS [4, 28, 29], and our present results also showed that this was the primary cause of death within 30 days of onset. Thus, reduction of mortality requires the prevention of multiple organ failure [28, 29], and we suggest that early-stage multimodal management might be useful for this purpose.

In our first study in 2005, chest X-rays showed infiltration shadows in bilateral lung fields in about half of the AHRF patients within 72 h of onset, indicating progression to ALI/ARDS [15]. In the present study we used a chest CT scan, in addition to a chest X-ray for AHRF patients, to examine the feasibility of early diagnosis. Six of 26 AHRF patients were suspected of having ALI/ARDS based on chest CT scans, but these patients were formally diagnosed with AHRF based on the AECC criteria, which do not include CT findings. However, 5 of the 6 patients (83.3%) were diagnosed with ALI/ARDS based on chest X-ray findings on the day after the CT scan, or thereafter. The chest CT scan showed normal findings in 20 patients, but 7 of these patients (35.0%) were also diagnosed with ALI/ARDS based on chest X-ray findings the day after the CT scan. In the other 13 patients, chest X-rays showed shadows in the bilateral lung fields in 1 patient with $PaO_2/FIO_2 \geq 300$ mmHg and shadows in a single lung field in 2 patients. The remaining 10 patients had no abnormal findings, indicating recovery from deteriorated pulmonary oxygenation, and they were discharged from the ICU. These findings suggest that the performance of a chest CT scan along with a chest X-ray is useful, but may still be insufficient to detect infiltration shadows in some AHRF patients in the initial stage. This indicates that other diagnostic techniques are also required.

In AHRF patients with no abnormal findings on a chest CT scan, PaO_2/FIO_2 values may decrease with respiratory failure due to an undetectable lung abnormality. For example, Martin et al. [30] measured the extravascular pulmonary fluid level in patients with serious sepsis, using the PiCCO system, and found that this level was increased in more than half of the 125 patients with $PaO_2/FIO_2 \leq 300$ mmHg (who were classified as non-ARDS patients because chest X-rays showed shadows at a lower

level than the AECC standard). These results and those in the present study suggest that clinical findings for patients with deteriorated pulmonary oxygenation who are clinically suspected of having ALI/ARDS do not always agree with chest X-ray and CT findings in the initial stage. This may indicate a limitation of ALI/ARDS diagnosis based on chest X-rays. Takeda et al. [31] have argued that the diagnostic criteria for ALI/ARDS are problematic because of uncertainty in diagnostic imaging. Clearly, PaO_2/FIO_2 values are also affected by factors such as the body position and the setting of an artificial respirator. Because mortality in ALI/ARDS varies with the type and seriousness of the primary illness (e.g., the higher mortality of septic patients compared to those with external injury or pneumonia), Takeda et al. [31] have recommended the classification of ARDS into several subgroups to limit the number of patients enrolled in an RCT. Regardless, mortality in ALI/ARDS remains high, and more efforts are required to improve diagnosis and treatment.

We conclude that the findings in our first study [15] were verified in the present study, which showed mortality rates of 21.6% in patients with ALI and 20.5% in those with ARDS. Out of 240 patients, 88 (36.7%) with SIRS and deteriorated pulmonary oxygenation were diagnosed with AHRF at ICU entry because they did not meet the AECC criteria for ALI/ARDS, due to the absence of shadows on chest X-rays. Forty-nine of these patients (55.7%) subsequently progressed to ALI/ARDS, with progression occurring within 3 days in most cases (85.8%). Moreover, chest X-rays showed abnormal findings indicating progression to ALI/ARDS in some AHRF patients on the days after ICU entry, despite a chest CT scan showing no abnormal findings on the day of entry. This suggests that abnormalities in the initial stage of deterioration of pulmonary oxygenation may not be detected by diagnostic imaging in patients with mild symptoms.

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