Prognosis of pathogen-proven acute respiratory distress syndrome diagnosed from a protocol that includes bronchoalveolar lavage: a retrospective observational study

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Abstract

Background: To treat patients with acute respiratory distress syndrome (ARDS), it is important to diagnose specific lung diseases and identify common risk factors. Our facility focuses on using bronchoalveolar lavage (BAL) to identify precise risk factors and determine the causative pathogen of ARDS within 24 h of intensive care unit (ICU) admission. This study evaluated the prognoses of pathogen-proven ARDS patients who were diagnosed or identified with risk factors using a diagnostic protocol, which included BAL, compared with the prognoses of pathogen-unproven ARDS patients.

Methods: This retrospective observational study was conducted in the ICU at a tertiary hospital from October 2015 to January 2019. We enrolled patients with respiratory distress who were on mechanical ventilation for more than 24 h in the ICU and who were subjected to our diagnostic protocol. We compared the disease characteristics and mortality rates between pathogen-proven and pathogen-unproven ARDS patients.

Results: Seventy ARDS patients were included, of whom, 50 (71%) had pathogen-proven ARDS as per our protocol. Mortality rates in both the ICU and the hospital were significantly lower among pathogen-proven ARDS patients than among pathogen-unproven ARDS patients (10% vs. 50%, \( p = 0.0006 \); 18% vs. 55%, \( p = 0.0038 \), respectively). Pathogen-proven ARDS patients were independently associated with hospital survival (adjusted hazard ratio, 0.238; 95% confidence interval, 0.096–0.587; \( p = 0.0021 \)).

Conclusions: Our diagnostic protocol, which included early initiation of BAL, enabled diagnosing pathogen-proven ARDS in 71% of ARDS patients. These patients were significantly associated with higher hospital survival rates. The diagnostic accuracy of our diagnostic protocol, which includes BAL, remains unclear.

Keywords: Pneumonia, BAL, Mimicker, Common risk factor, ARDS, Sepsis, ICU

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Background

Acute respiratory distress syndrome (ARDS) is a life-threatening disease with a mortality rate of ~40% [1]. The Berlin definition defines ARDS as respiratory distress occurring within 7 days of recognizing a common risk factor [2]. However, some patients are diagnosed with ARDS based on pathophysiological parameters but without a proven etiology or causative pathogen [3]. Thus, studies examining ARDS often include heterogeneous syndromes as well as ARDS mimickers [4].

The bronchoalveolar lavage (BAL) examination is used to differentially diagnose respiratory diseases, including ARDS. One study found that of ARDS patients who underwent BAL, 56% presented microbial pathogens and were definitively diagnosed with pneumonia, the leading risk factor for ARDS [5]. Therefore, BAL enables performing successful definitive therapy and reduces mortality from ARDS. Gibelin et al. reported that ARDS patients without common risk factors were diagnosed with autoimmune and malignant diseases via BAL examination, and these patients were associated with higher mortality risks [6]. BAL was recently recommended as a method for identifying the ARDS etiology and distinguishing interstitial pneumonia from ARDS [3, 7, 8]. However, the secondary analysis of the LUNG SAFE study revealed that only 9% of ARDS patients underwent BAL [9].

Our facility focuses on diagnosing lung diseases, differentiating interstitial pneumonia, and identifying the ARDS etiology using BAL. Furthermore, we started a protocol for diagnosing or identifying ARDS etiologies via sputum culture, gene analysis, serum testing, BAL analysis, and computed tomography (CT) scans in 2015. This study compared the prognoses of ARDS patients with or without proven causative pathogen using our diagnostic protocol, which includes BAL.

Methods

Study design and population

This observational study was conducted in the emergency and medical intensive care units (ICUs) of Hiroshima University Hospital from October 2015 to January 2019. The Institutional Review Board of Hiroshima University approved the study protocol (trial registration: E-1751, registered on 17 September 2019).

We retrospectively reviewed the medical records of ICU patients with respiratory failure at admission and included consecutive patients (aged ≥ 18 years) who were considered to have ARDS from pathophysiological parameters and stayed in the ICU for more than 24 h. Clinically defined ARDS was diagnosed and categorized as mild, moderate, or severe according to the Berlin definition. Patients with respiratory distress of unknown etiology were included. Patients who were postoperative or non-medical (including trauma and burns) admission, had interstitial pneumonia, or had do-not-resuscitate orders were excluded.

Diagnostic protocol

All ARDS patients underwent chest X-rays and CT scans at the timing of diagnosing ARDS if their condition allowed it. After patients were intubated, BAL was performed to determine the ARDS etiologies and causative pathogens. For the BAL procedure, 100–150 mL of normal saline was injected into the wedged bronchi, where a lobar infiltrate was observed on chest CT scans, and gently suctioned. The BAL fluid (BALF) was rapidly Gram-stained, cultured, and underwent cytological analysis on a weekday. When Gram staining of the BALF revealed no microorganisms, the BALF was analyzed via polymerase chain reaction (PCR) for Mycobacterium spp. and Mycoplasma pneumoniae, and Loop-mediated isothermal amplification (LAMP) for Legionella pneumophila. Urinary antigen testing was also performed for Streptococcus pneumoniae and Legionella pneumophila. For immunosuppressed patients, we measured the serum beta-D-glucan, analyzed the BALF for the Aspergillus antigen, and performed PCR for Pneumocystis carinii and cytology and C7-HRP to detect Cytomegalovirus spp. During the regional epidemic season, reverse-transcription PCR was performed on the BALF to test for the influenza virus. When causative pathogens were not identified or the precise cause of ARDS could not be determined, we further analyzed the BAL cell differentials to determine the etiology of ARDS, and this sometimes revealed evidence of interstitial pneumonia. However, potential pathogens were only identified during the initial analysis of the BAL fluid in the present study.

Immunological testing, including laboratory tests for proteinase-3-anti-neutrophil cytoplasmic antibodies (ANCA), myeloperoxidase-ANCA, anti-basement membrane antibody, and antinuclear antibody, were also performed.

Definition

ARDS etiology was determined via a diagnostic protocol, which included BAL. Pathogen-proven ARDS was defined according to the following risk factors: (1) pneumonia with an identified causative pathogen, (2) nonpulmonary sepsis with an identified causative pathogen, and (3) aspiration pneumonia. Pneumonia was diagnosed from at least one of the following: body temperature > 38.0°C; white blood cell count > 12,000/ 

mm³ or < 4000/mm³; altered mental status; and a positive microbial culture including bacteria, fungi, and/or a virus [10], in addition to new regional or lobar...
infiltration on chest radiographs and CT scans. Nonpulmonary sepsis was diagnosed as an increased Sequential Organ Failure Assessment (SOFA) score of \( \geq 2 \) points and identification of an infectious source other than the lungs. Aspiration pneumonia was diagnosed on the basis of a characteristic clinical history (witnessed aspiration), the presence of risk factors (lower level of consciousness, an impaired cough reflux or impaired swallowing), and radiographic findings, including the presence of infiltrates in gravity-dependent lung segments [11].

Management
The ventilator management was lung protective ventilation. Patients with partial pressure of arterial oxygen (PaO₂)/fraction of inspiratory oxygen (FIO₂) ratio < 100 were considered using neuromuscular blockage, initiating prone positioning and veno-venous extracorporeal membrane oxygenation (ECMO) which were performed for some but not all patients. Veno-venous ECMO was initiated according to the findings of the CESAR trial [12], i.e., when the Murray score (derived from all four variables: PaO₂/FIO₂ ratio, positive end-expiratory pressure, lung compliance, and chest radiographic appearance; and when FIO₂ = 1) was \( \geq 3.0 \) or the pH was < 7.20, or the patient did not respond to protective lung ventilation and prone positioning (SaO₂ < 90% or pH < 7.20).

Data collection
We collected demographic data, including age, sex, past illness history, SOFA score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and ARDS severity upon ICU admission. We also recorded the lowest PaO₂/FIO₂ ratio, tidal volume, ventilator parameters, and ARDS therapy used (e.g., neuromuscular-blocking agents, corticosteroid therapy, initiation of prone positioning, hemodialysis, ECMO, and tracheostomy). The clinical outcomes were ventilator management duration, length of the hospital and ICU stays, and mortality.

Statistical analysis
Values are presented as medians (interquartile range; IQR) or numbers (percentage) as appropriate. Categorical variables were compared between pathogen-proven and pathogen-unproven ARDS patients using Fisher’s exact tests. Continuous variables were compared using Mann-Whitney U tests. Cox regression analysis was performed to assess the pathogen-proven ARDS relative to hospital mortality, and the results are shown as hazard ratios. Factors with \( p \) value < 0.05 in the univariate analyses and pathogen-proven ARDS were entered into the multivariate model. All statistical analyses were conducted using the JMP statistical software (version 14.0.0; SAS, Cary, NC, USA).

Results
Prevalence of pathogen-proven ARDS
In total, 1446 patients were intubated, of which, 109 met the Berlin definition of ARDS and stayed in the ICU for more than 24 h. Finally, 70 ARDS patients who met the inclusion criteria were analyzed (Fig. 1). Fifty patients (71%) had pathogen-proven ARDS as per the diagnostic protocol that included BAL.
ARDS patient characteristics

Table 1 shows the patients’ baseline characteristics. The median age was 66 years (range, 57–74 years), and 42 patients (61%) were men. The median SOFA score was 11 (9–13); the median APACHE II score was 28 (24–32). In this cohort, age, SOFA score, APACHE II score, ARDS severity, and mechanical ventilation parameters did not significantly differ between pathogen-proven and pathogen-unproven ARDS patients.

ARDS etiology

In the 50 pathogen-proven ARDS patients, pneumonia was the most common risk factor (n = 31), followed by sepsis (n = 13), and aspiration (n = 6; Table 2). Of the 31 pneumonia patients, 20 had bacteria, 4 had viruses, 4 had fungi, and 3 had both viruses and fungi in their BAL. Streptococcus pneumoniae was predominant (n = 7) among the bacterial pneumonia patients. The influenza virus was predominant (n = 6) among viral pneumonia patients.

Treatment and outcomes of the ARDS patients

The treatment options used (e.g., neuromuscular-blocking agents, prone positioning, corticosteroid...
Factors associated with hospital mortality

Univariate analyses showed that pathogen-proven ARDS (hazard ratio [HR], 0.265; 95% confidence interval [CI], 0.109–0.647; \( p = 0.004 \)) and higher SOFA scores (HR, 1.211; 95% CI, 1.068–1.374; \( p = 0.0028 \)) were significantly associated factors with hospital mortality (Table 4). Pathogen-proven ARDS was significantly associated with hospital mortality after adjusting for SOFA score (HR, 0.238; 95% CI, 0.096–0.587; \( p = 0.0021 \)).

Discussion

In the present study, 71% of ARDS patients had pathogen-proven ARDS. To our knowledge, this was the first study to investigate the prognostic impact of a diagnostic protocol that included BAL in ARDS patients. The hospital mortality rate of pathogen-proven ARDS patients was lower than that of pathogen-unproven patients after adjusting for SOFA scores.

A nationwide survey in Japan revealed that 34% of ARDS patients had pneumonia, and all ARDS patients had risk factors [13]. Conversely, a survey conducted in the USA from 2006 to 2014 revealed that approximately 45% of ARDS patients had pneumonia, and 16% had no specific risk factors [14]. The discrepancy between these findings may have occurred because of the ambiguous diagnosis of ARDS risk factors, which depends on BAL for detecting microorganisms that cause pneumonia or the vague clinical criteria for pneumonia. In our setting, BAL-based detection systems, especially LAMP for *Legionella pneumophila* and PCR for *Pneumocystis jiroveci*, *influenza viruses*, and *cytomegaloviruses*, contributed to detecting many causative organisms. This is consistent with the findings of previous studies and supports aggressively using BAL to increase the ability to diagnose pneumonia as an ARDS etiology [15–17].

The reduced mortality of pathogen-proven ARDS patients in this study may be explained as follows. First, ARDS patients with no common risk factors included those with autoimmune and idiopathic diseases, and the absence of common risk factors has been associated with increased mortality in ICUs [6, 18]. Second, the outcomes (i.e., development of acute lung injury/ARDS or mortality) of patients with infections can be improved via early and appropriate antimicrobial therapy [19–21]. In addition, precise detection of microorganisms shortens the duration of empiric antibiotic therapy [22], resulting in fewer adverse events. Given the overall low performance of BAL (9.4%) in a large-scale epidemiological study (LUNG SAFE study) [9], BAL-based diagnostic approaches should be more widely applied for ARDS patients to help improve their outcomes.

| Table 3 Therapy and outcome |
|-----------------------------|
| All patients (\( N = 70 \)) | Pathogen-proven ARDS group (\( N = 50 \)) | Pathogen-unproven ARDS group (\( N = 20 \)) | \( p \) |
| **Therapy** | | | |
| Neuromuscular blocking agents | 12 (17) | 8 (16) | 4 (20) | 0.732 |
| Corticosteroid therapy | 29 (41) | 20 (40) | 9 (45) | 0.791 |
| Prone position | 5 (7) | 3 (6) | 2 (10) | 0.619 |
| Hemodialysis | 21 (30) | 15 (30) | 6 (30) | 1.000 |
| VA ECMO | 5 (7) | 4 (8) | 1 (5) | 1.000 |
| VV ECMO | 12 (17) | 11 (22) | 1 (5) | 0.158 |
| Tracheostomy | 28 (40) | 20 (40) | 8 (40) | 1.000 |
| Appropriate antibiotic therapy for causative pathogens within day 3 | – | 48 (96) | – | – |
| **Outcome** | | | |
| Ventilator-free days of 28 days | 16 (0–20) | 18 (7–20) | 4 (0–22) | 0.112 |
| ICU-free days of 28 days | 13 (0–16) | 13 (5–16) | 1 (0–15) | 0.034 |
| ICU mortality | 15 (21) | 5 (10) | 10 (50) | 0.0006 |
| Hospital-free days of 28 days | 0 (0–6) | 0 (0–6) | 0 (0–7) | 0.613 |
| Hospital mortality | 20 (29) | 9 (18) | 11 (55) | 0.0038 |

Values are given as the median (interquartile range) or number (%). \( p \) values were calculated using Fisher's exact test or the Mann-Whitney \( U \) test.
This study had several limitations. First, it was a single-center, retrospective observational study of relatively few patients. In addition, the etiology of the pathogen-unproven ARDS was not determined (Supplementary Table 1). We excluded potential participants with several major ARDS etiologies (e.g., burn, trauma, and drug-induced) and other etiologies (e.g., interstitial pneumonia). Analysis of the BAL fluid revealed no significant pathogens in the pathogen-unproven ARDS patients, and they also did not have non-septic shock or other significant risk factors, such as transfusion or pancreatitis. However, this group could have included “ARDS mimickers” as defined in a previous study [3] and hematological malignancy-related ARDS. The survival rate of ARDS mimickers and hematological malignancy-related ARDS is poor [23], which may explain the poor outcomes in the pathogen-unproven ARDS cohort in the present study, even though there were fewer patients with septic shock in this group. Further studies are required to investigate the clinical characteristics of these subtypes of ARDS. Second, our hospital is a tertiary hospital, and 37% of our patients were transported from other hospitals after antibiotic administration, which may differ among settings. Third, the selection of wedged bronchi for BAL might have affected the sensitivity of pathogen detection. Fourth, regarding viruses, we only tested for cytomegaloviruses and influenza viruses. Therefore, presence of other causative viruses, such as rhinoviruses, adenoviruses, and herpesviruses, is unknown. Applications of currently available, easy-to-use, comprehensive, molecular-based diagnostic systems, such as FilmArray™, would help increase pathogen detection rates and enable faster treatment, especially for viruses [24]. In addition, we included patients who were on mechanical ventilation for more than 24 h; thus, some severely ill patients may have been excluded, affecting the mortality analysis. Finally, the definition of “pathogen-unproven ARDS” has not been standardized and may include ARDS “mimickers” [3]. However, the definition of ARDS “mimickers” has also not been standardized. These two terms should be precisely defined to accurately categorize the heterogeneity of ARDS.

**Conclusion**

Pathogen-proven ARDS patients who were diagnosed via diagnostic work-up that included BAL had lower mortality rates than did pathogen-unproven ARDS patients. Pathogen-unproven ARDS was significantly associated with hospital mortality. The diagnostic accuracy and significance for treatment of the diagnostic protocol, including BAL, should be determined in further studies.

**Supplementary information**

Supplementary information accompanies this paper at https://doi.org/10.1186/s40560-020-00469-w.

**Additional file 1: Table S1.** Etiologies of pathogen-unproven ARDS (n=20).

| Variables               | Univariable HR | 95% CI       | p     | Multivariable HR | 95% CI       | p     |
|-------------------------|----------------|--------------|-------|-----------------|--------------|-------|
| Pathogen-proven ARDS    | 0.265          | 0.109–0.647  | 0.004 | 0.238           | 0.096–0.587  | 0.0021|
| Age (per year decrease) | 0.974          | 0.942–1.008  | 0.126 |
| Male                    | 0.751          | 0.302–1.869  | 0.542 |
| SOFA score (per 1 increase) | 1.211       | 1.068–1.374  | 0.0028| 1.226           | 1.082–1.390  | 0.0015|
| APACHE II score (per 1 increase) | 1.030     | 0.966–1.101  | 0.363 |
| PaO2/FIO2               | 1.014          | 0.940–1.090  | 0.715 |
| COPD                    | 1.941          | 0.560–6.730  | 0.332 |
| Liver failure           | 1.869          | 0.762–4.586  | 0.184 |
| Corticosteroids         | 1.164          | 0.478–2.830  | 0.739 |
| Hemodialysis            | 2.356          | 0.956–5.806  | 0.069 |
| VV ECMO                 | 0.834          | 0.243–2.867  | 0.769 |

**Abbreviations**

ANCA: Anti-neutrophil cytoplasmic antibodies; APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute respiratory distress syndrome; BAL: Bronchoalveolar lavage; BALF: Bronchoalveolar lavage fluid; CI: Confidence interval; CT: Computed tomography; ECMO: Extracorporeal membrane oxygenation; FIO2: Fraction of inspiratory oxygen; HR: Hazard ratio; LAMP: Loop-mediated isothermal amplification; PaO2: Partial pressure of arterial oxygen; PCR: Polymerase chain reaction; SOFA: Sequential Organ Failure Assessment

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Authors’ contributions
MK drafted the manuscript. MK collected the data. KH, SQ, KY, YT, and NS helped to draft the manuscript. MK and NS participated in the design of the study and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The institutional review boards in Hiroshima University (trial registration: E-1751, registered on 17 September 2019) approved an opt-out method of informed consent.

Consent for publication
Not applicable

Competing interests
Nothing to declare

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