SHOCK, Vol. 47, No. 5, pp. 615–620, 2017

OPEN

COINFECTION AND MORTALITY IN PNEUMONIA-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME PATIENTS WITH BRONCHOALVEOLAR LAVAGE: A PROSPECTIVE OBSERVATIONAL STUDY

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Received 13 Sep 2016; first review completed 4 Oct 2016; accepted in final form 11 Nov 2016

ABSTRACT—**Background:** Pneumonia is the leading risk factor of acute respiratory distress syndrome (ARDS). It is increasing studies in patients with pneumonia to reveal that coinfection with viral and bacterial infection can lead to poorer outcomes than no coinfection. This study evaluated the role of coinfection identified through bronchoalveolar lavage (BAL) examination on the outcomes of pneumonia-related ARDS. **Methods:** We performed a prospective observational study at Chang Gung Memorial Hospital from October 2012 to May 2015. Adult patients were included if they met the Berlin definition of ARDS. The indications for BAL were clinically suspected pneumonia-related ARDS and no definite microbial sample identified from tracheal aspirate or sputum. The presence of microbial pathogens and clinical outcomes were analyzed. **Results:** Of the 19,936 patients screened, 902 (4.5%) fulfilled the Berlin definition of ARDS. Of these patients, 255 (22.7%) had pneumonia-related ARDS and were included for analysis. A total of 142 (55.7%) patients were identified to have a microbial pathogen through BAL and were classified into three groups: a virus-only group (n = 41 [28.9%]), no virus group (n = 60 [42.2%]), and coinfection group (n = 41 [28.9%]). ARDS severity did not differ significantly between the groups ($P = 0.43$). The hospital mortality rates were 53.7% in virus-only identified group, 63.3% in no virus identified group, and 80.5% in coinfection identified group. The coinfection group had significantly higher mortality than virus-only group (80.5% vs. 53.7%; $P = 0.01$). **Conclusion:** In patients with pneumonia-related ARDS, the BAL pathogen-positive patients had a trend of higher mortality rate than pathogen-negative patients. Coinfection with a virus and another pathogen was associated with increased hospital mortality in pneumonia-related ARDS patients.

KEYWORDS—Acute respiratory distress syndrome, bronchoalveolar lavage, coinfection, outcomes, pneumonia

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is defined as an acute inflammatory lung injury associated with increased pulmonary vascular permeability, decreased lung compliance, and bilateral lung infiltrates and hypoxemia (1). Several factors increase the risk of ARDS, including sepsis, aspiration, major trauma, pulmonary contusion, acute pancreatitis, drug, massive transfusions, pulmonary vasculitis, and drowning (2), with pneumonia being the most common risk factor, reported in 33% to 59% of cases (3–6). Furthermore, pneumonia is the only infection associated with an increased risk of developing ARDS in critically ill patients (7).

Pneumonia-related ARDS can be caused by bacterial, viral, fungal, and even parasitic pathogens (8). Because of the treatability and potential reversibility of pneumonia, intensivists must thoroughly explore the infectious etiology of pneumonia-related ARDS. Community-acquired pneumonia is probably the most common cause of ARDS, and common pathogens include *Streptococcus pneumoniae*, *Staphylococcus aureus*, various respiratory viruses, *Legionella pneumophila, Pneumocystis jirovecii*, and enteric gram-negative organisms (4). Nosocomial pneumonias can also develop into ARDS, and the most commonly implicated pathogens include *S aureus, Pseudomonas aeruginosa,* and other enteric gram-negative bacteria (9).

In adult patients with severe community-acquired pneumonia that required hospitalization or intensive care unit (ICU) admission, respiratory viruses were detected more frequently than bacteria (10, 11). The mortality rates of severe community-acquired pneumonia in patients with viral infection, bacterial infection, and viral–bacterial coinfection were not significantly different (11, 12). However, little is known about the distribution of different identified pathogens on the outcome of pneumonia-related ARDS. The main objective of this prospective study was to evaluate the role of coinfection on the outcomes of pneumonia-related ARDS.

METHORDS

Study design and study population

This study was approved by the Chang Gung Memorial Hospital's Institutional Review Board Ethics Committee (CGMH IRB No.102-1729B). A prospective observational cohort study was conducted from October 2012 to May 2015 at Chang Gung Memorial Hospital, a referral medical center with 278 adult ICU beds in nine medical ICUs, seven surgical ICUs, and one burn ICU. All of the admitted adult patients with mechanical ventilation were screened for

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This study was not supported by any grant.

The authors report no conflicts of interest.

DOI: 10.1097/SHK.0000000000000802

eligibility. Patients were included if they met the Berlin definition of ARDS (1): onset within 1 week of a known clinical insult or new or worsening respiratory symptoms; bilateral opacities not fully explained by effusions, lobar or lung collapse, or nodules; respiratory failure not fully explained by cardiac failure or fluid overload and need for objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor was present; and PaO_2/FiO_2 ratio $\leq$300 mm Hg with positive-end expiratory pressure (PEEP) or continuous positive airway pressure $\geq$5 cm H_2O. ARDS was classified as mild if the PaO_2/FiO_2 ratio was between 201 mm Hg and 300 mm Hg, moderate if PaO_2/FiO_2 was between 101 mm Hg and 200 mm Hg, and severe if PaO_2/FiO_2 was less than or equal to 100 mm Hg. Patients were excluded if they were younger than 18 years old or were referred from other hospitals with an ARDS diagnosis.

The The bronchoalveolar lavage (BAL) indications for ARDS patients were clinically suspected pneumonia-related ARDS and no identification of a definite microbial sample in tracheal aspirate or sputum examination. Pneumonia was suspected clinically if the following two or more criteria were fulfilled: new airspace opacity on a chest radiograph; body temperature >38.3°C or <36.0°C, white blood count >12,000/mm^3 or <4,000/mm^3, or >10% bandemia; and a positive microbial culture. The site for BAL sampling was selected on the basis of the most recent chest X-ray or high-resolution computer tomography of the chest (if available). BAL was performed using a fibrobronchoscope by introducing 200 mL of a sterile, warm saline solution into a bronchial subsegment and aspirating it back in four 50-mL aliquots. The BAL samples were analyzed in the hospital's microbiology and pathology laboratories for the presence of bacteria, fungi, and viruses in accordance with normal practice. The bacteria analyzed included aerobic and anaerobic bacteria, legionella, *Mycoplasma pneumoniae*, and mycobacteria. Urinary antigen testing was performed for the detection of *S pneumoniae* and *L pneumophila* (BinaxNOW, Alere, Scarborough, USA). The fungal analysis involved candida culture, an aspergillosis antigen and culture, and *P jirovecii* testing. The BAL samples were subjected to Giemsa and Gomori methenamine silver staining and qualitative pneumocystis DNA analysis by using polymerase chain reaction (PCR) for *P jirovecii*. Viral identification from BAL samples was performed using PCR and viral culture: reverse-transcription PCR for influenza viruses A and B, shell vial culture for cytomegalovirus (CMV), and viral culture for herpes simplex virus (HSV), parainfluenza virus, adenovirus, respiratory syncytial virus, human metapneumovirus, and enterovirus. BAL culture results were deemed positive when at minimum one microorganism grew to a concentration of $>10^4$ colony-forming units per milliliter. We collected the samples of all the ARDS patients who had received BAL for microbial examination during the study period for analysis.

The recommended management of ARDS patients entailed lung protective ventilation using a low tidal volume, 4 mL/kg to 8 mL/kg of the predicted body weight, plus the PEEP setting guided by the FiO_2 level for volume-controlled or pressure-controlled ventilation (3). Oxygenation was monitored through pulse oximetry (SpO_2) and the FiO_2 level was adjusted to maintain SpO_2 >90%. PiCCO plus monitoring (version 5.2.2; Pulsion Medical System AG, Muenchen, Germany) was applied for hemodynamic and lung water monitoring if the clinical condition indicated it. The general medical management included the empirical use of antibiotics, fluid replacement, vasopressor agent use, corticosteroid use (if applicable), sedation with midazolam, and paralysis with cisatracurium as directed by the treating physicians.

Data collection

Demographics and baseline clinical characteristics were collected on enrollment. The following data were recorded upon ARDS diagnosis or ICU admission: the date of hospital and ICU admission, age, gender, body mass index, Charlson comorbidity index (13), Acute Physiology and Chronic Health Evaluation II score (14), Sequential Organ Failure Assessment score (15), Multiple Organ Dysfunction score (16), Lung Injury score (17), and severity of ARDS. Arterial blood gas, the tidal volume, the lowest PaO_2/FiO_2 ratio with the highest PEEP, and the peak airway pressure were collected during mechanical ventilation. The patients were followed up until mortality, ICU or hospital discharge, or 90 days after the day of inclusion. The final BAL examinations for microbial identification were traced until 90 days after the day of inclusion.

Classification of pneumonia-related ARDS patients

The patients were classified into two main groups: a pathogen-negative group, patients without bacterial, viral, or fungal pathogens identified through BAL, and a pathogen-positive group, patients with $\geq$1 pathogen identified through BAL. The ARDS patients in the pathogen-positive group were further classified as follows: a virus-only group (only viruses were identified), no virus group (only bacterium and/or fungus were identified), and coinfection group (virus and bacterium and/or fungus were identified).

Statistical analysis

Categorical variables were compared using the chi-square test or Fisher exact test. Descriptive variables were expressed as the mean ± standard deviation. All variables were tested for normal distributions by using the Kolmogorov–Smirnov test. The Student *t* test was used for comparing the means of continuous variables with a normal distribution and the Mann–Whitney *U* test was used for the remaining variables. The cumulative survival curves as a function of time were generated through the Kaplan–Meier approach and compared using the log-rank test. All the statistical tests were two tailed and $P < 0.05$ was considered statistically significant. The SPSS (SPSS for Windows, SPSS Inc, Chicago, Ill) statistical package was employed for all the statistical analyses.

RESULTS

A total of 902 adult ARDS patients met the Berlin definition and were enrolled in this study (Fig. 1). Of the risk factors of ARDS, pneumonia was the most common (n = 430), followed by sepsis (n = 247), aspiration (n = 159), and others (n = 66). Of the 430 pneumonia-related ARDS patients, 301 had received BAL for microbial examination after no definite microbial sample was identified from tracheal aspirate or sputum examination. After four patients in whom BAL was performed before ARDS development and 42 patients in whom ARDS development occurred in >7 days were excluded, a total of 255 pneumonia-related ARDS patients with BAL were included in this study. The median time between ARDS diagnosis and BAL examination was 3.5 ± 1.6 days. Of these patients, 142 (57.7%) were pathogen-positive and 113 (44.2%) were pathogen- negative.

The demographics, underlying conditions, clinical characteristics, and outcomes of the 255 included patients are reported in Table 1. The mean age was 65.4 ± 15.6 years and the mean peak airway pressure, PEEP, and PaO_2/FiO_2 were 30.5 ± 5.1 cm H_2O, 10.4 ± 2.21 cm H_2O, and 27.6 ± 70.7 mm Hg, respectively. Severe ARDS was observed in 45.9% of the patients, followed by moderate ARDS in 34.5% and mild ARDS in 19.6% of the patients. Of these 255 ARDS patients receiving BAL, 86 patients were immunosuppressed including 71 patients with malignancy and 15 patients without malignancy. Of the 71 patients with malignancy, head and neck cancer was the most common (n = 28), followed by hematologic malignancy (n = 14), lung cancer (n = 13), esophageal cancer (n = 8), liver cancer (n = 6), and breast cancer (n = 2). Of the 15 patients without malignancy, systemic lupus erythematous was the most common (n = 7), followed by rheumatoid arthritis (n = 3), human immunodeficiency virus infection (n = 3), and renal transplantation (n = 2). There were no significant differences in baseline characteristics, comorbidities, severity scores, the severity distribution of ARDS, or mechanical ventilation settings between the pathogen-positive and pathogen-negative patients, except for a significantly higher tidal volume in the pathogen-negative patients versus the pathogen-positive patients (8.5 ± 2.2 mL vs. 8.0 ± 2.1 mL; $P = 0.03$). The ICU and hospital mortality rates were numerically but not significantly higher in the pathogen-positive patients compared with the pathogen-negative patients (55.6% vs. 45.1% [$P = 0.09$] and 65.5% vs. 54.9% [$P = 0.08$], respectively).

Of the 142 pathogen-positive patients, 55 (39.8%) had bacterial, 88 (62%) had viral, and 81 (57%) had fungal pathogens (Table 2). A total of 55 bacterial pathogens were identified in 42 patients: two pathogens were identified in eight patients,

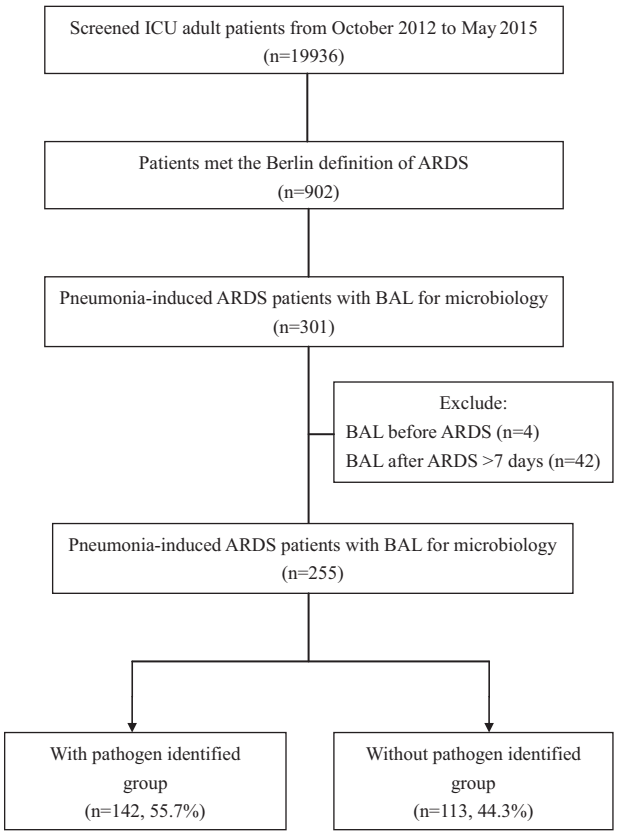

FIG. 1. **Flowchart of patient enrollment.** ARDS indicates acute respiratory distress syndrome; BAL, bronchoalveolar lavage; ICU, intensive care unit.

and three pathogens in two patients. Gram-negative bacteria were more common than gram-positive bacteria (n = 36 [26.5%] vs. n = 10 [7%]). The most common gram-negative and gram-positive bacteria were *P aeruginosa* and methicillin-resistant *S aureus*, respectively. A total of 88 viral pathogens were identified in 82 patients: two pathogens were identified in six patients. The most common virus was CMV, followed by influenza. A total of 81 fungal pathogens were identified in 77 patients: two pathogens were identified in four patients. The most common identified fungus was *P jirovecii.*

Patient characteristics, underlying conditions, and clinical outcomes were comparable among the virus-only, no virus, and coinfection groups (Table 3). Comparison among the three groups revealed no statistically significant differences regarding demographics characteristics, comorbidities, severity scores, mechanical ventilation settings, and the severity of ARDS. The hospital mortality rates were 53.7% in virus-only identified group, 63.3% in no virus identified group, and 80.5% in coinfection group. The coinfection group had significantly higher mortality than virus-only group (80.5% vs. 53.7%; $P = 0.01$). The ICU mortality rates had the same trend, but the differences were not significant (68.3%, 51.7%, and 43.9%, respectively; $P = 0.07$).

DISCUSSION

This study has some major findings. More than half (55.7%) of the patients with pneumonia-induced ARDS whose tracheal aspirate or sputum microbial samples were negative had microbial pathogens identified in BAL. Furthermore, the BAL pathogen-positive patients had higher mortality rate

TABLE 1. **Demographics and clinical characteristics of pneumonia-related ARDS patients receiving BAL for pathogen positive**

Characteristics	Total patients (n = 255)	Pathogen-positive group (n = 142)	Pathogen-negative group (n = 113)	*P*
Age (years)	62.4 ± 15.6	62.4 ± 16.4	62.3 ± 15.0	0.96
Gender (male/female)	175/80	95/47	80/33	0.50
BMI (kg/m^2)	23.7 ±	23.4 ± 4.0	24.1 ± 4.9	0.18
PBW (kg)	56.7 ± 9.2	56.4 ± 9.4	57.1 ± 9.1	0.55
Charlson comorbidity index	2.5 ± 2.1	2.6 ± 2.1	2.5 ± 2.1	0.68
APACHE II score	23.5 ± 7.1	23.2 ± 7.0	23.8 ± 7.3	0.54
SOFA score	9.4 ± 3.3	9.3 ± 3.2	9.6 ± 3.4	0.51
MOD score	8.4 ± 2.9	8.5 ± 2.9	8.4 ± 3.0	0.75
Lung injury score	3.0 ± 0.5	3.1 ± 0.5	3.0 ± 0.5	0.26
Tidal volume (mL/PBW)	8.2 ± 2.2	8.0 ± 2.1	8.5 ± 2.2	0.03*
Peak Paw (cm H_2O)	30.5 ± 5.1	30.3 ± 5.1	30.7 ± 5.2	0.57
PEEP (cm H_2O)	10.4 ± 2.2	10.3 ± 2.3	10.4 ± 2.0	0.83
PaO_2/FiO_2 (mm Hg)	127.6 ± 70.7	125.5 ± 71.3	130.3 ± 70.0	0.38
Severity (n, %)				0.85
Mild	50 (19.6%)	28 (19.7%)	22 (19.5%)	
Moderate	88 (34.5%)	47 (33.1%)	41 (36.3%)	
Severe	117 (45.9%)	67 (47.2%)	50 (44.2%)	
Duration of MV (days)	21.7 ± 17.1	22.4 ± 18.0	20.8 ± 16.1	0.45
ICU mortality (n, %)	130 (51%)	79 (55.6%)	51 (45.1%)	0.09
Hospital mortality (n, %)	155 (60.8%)	93 (65.5%)	62 (54.9%)	0.08

All values are expressed as the number of patients (percentage) or mean ± SD.
*$P < 0.05$: pathogen-positive group versus pathogen-negative group.
APACHE indicates acute physical and chronic health evaluation; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; BMI, body mass index; ICU, intensive care unit; MOD, multiple organ dysfunction; MV, mechanical ventilation; PaO_2/FiO_2, alveolar oxygen pressure/fraction of inspiratory oxygen; Paw, airway pressure; PBW, predicted body weight; PEEP, positive end expiratory pressure; SOFA, Sequential Organ Function Assessment.

TABLE 2. **Identified pathogens in ARDS patients receiving BAL for pathogen positive***

Pathogens	n = 142
Bacteria	55 (39.8%)
Gram (+)	10 (7.0%)
Staphylococcus aureus-methicillin resistant	5 (3.5%)
Streptococcus pneumoniae	4 (2.8%)
Enterococcus faecium	1 (0.7%)
Gram (−)	36 (26.5%)
Pseudomonas aeruginosa	10 (7.0%)
Acinetobacter baumannii	7 (4.9%)
Stenotrophomonas maltophilia	5 (3.5%)
Klebsiella pneumonia	4 (2.8%)
Corynebacterium spp.	3 (2.1%)
Enterobacter cloacae	2 (1.4%)
Escherichia coli	1 (0.7%)
Burkholderia cepacia	1 (0.7%)
Proteus mirabilis	1 (0.7%)
Peptostreptococcus spp.	1 (0.7%)
Veillonella parvula	1 (0.7%)
Mycobacteria	9 (6.3%)
Mycobacteria tuberculosis	8 (5.6%)
Mycobacteria intracelllura	1 (0.7%)
Virus	88 (62.0%)
Cytomegalovirus	51 (35.9%)
Influenza	18 (12.7%)
Herpes simplex virus-1	14 (9.9%)
Respiratory syncytial virus	2 (1.4%)
Parainfluenza	1 (0.7%)
Human metapneumovirus	1 (0.7%)
Enterovirus	1 (0.7%)
Fungus	81 (57.0%)
Pneumocystis jirovecii	67 (47.2%)
Candida albicans	7 (4.9%)
Candida tropicalis	4 (2.8%)
Candida glabrata	3 (2.1%)

Data are presented as the number (percentage) of patients.
*More than one pathogen was detected in some patients.
ARDS indicates acute respiratory distress syndrome; BAL, bronchoalveolar lavage.

compared with the pathogen-negative patients with pneumonia-related ARDS, but the difference was not significant. The hospital mortality rate was significantly higher in the coinfection group (virus and bacterium or virus and fungus) than in the virus-only group.

Pneumonia is the most common cause of sepsis-related ARDS (3–7). Sepsis-related ARDS was reported to have a lower extubation rate, longer ICU stay duration, and higher mortality rate than those of non-sepsis-related ARDS (18, 19). However, the 60-day mortality rates of pneumonia and non-pneumonia sepsis-related ARDS patients were not significantly different (36.9% vs. 38.4%; $P = 0.226$) (7). In the present study of pneumonia-related ARDS patients receiving BAL for pathogen surveys, the ICU mortality rates were higher in the pathogen-positive patients versus the pathogen-negative patients, although the difference was not significant (55.6% vs. 45.1%; $P = 0.09$). The impact of causal pathogens on the outcomes of pneumonia-related ARDS patients should be addressed because most pathogens are potentially treatable.

In a previous study, we observed that pneumonia was the most frequent cause of ARDS in different settings and that patients with community-acquired ARDS had a lower ICU mortality rate than those of hospital-acquired and ICU-acquired ARDS patients (37% vs. 61% and 37% vs. 52%; both $P < 0.05$) (20). Community-acquired pneumonia is the most frequent cause of ARDS and no specific bacterium has been identified to be solely responsible for pneumonia-induced ARDS (8). Although fungi are not the common cause of ARDS, some fungal pathogens such as *P jirovecii* and *Aspergillus fumigatus* may be responsible for ARDS in immunocompromised patients (21). In this study, the most common pathogen identified through BAL was *P jirovecii* (47.2%) and not a bacterium. This may be due to the patient-selection criteria and the methodological procedures used in this study. First, the indication for BAL in these pneumonia-related ARDS patients was a negative tracheal aspirate or sputum culture. Because the most common bacterial pathogens, such as *S pneumonia* and *Haemophilus influenza,* might be more readily identified from the tracheal aspirate or sputum culture of ARDS patients, they would have been excluded from this study according to the selection criteria. Second, *P jirovecii* was detected through BAL by using either PCR or conventional staining in this study. Studies have reported that PCR detection of *P jirovecii* DNA provides greater sensitivity for diagnosis compared with conventional staining (a sensitivity value of 98.3% [95% confidence interval: 91.3%–99.7%]) (22, 23). *P jirovecii* detection through BAL in ARDS patients has clinical implications and is worth further investigation; early identification and proper therapy can alter the patient outcome.

In previous studies of critically ill patients with severe pneumonia, coinfection seemed to have no considerable impact on the clinical outcome. In a study of 198 patients with severe pneumonia requiring ICU admission, bacterial–viral coinfection had a higher, but not significantly, mortality rate than those of bacterial and viral infection alone (33.3%, 25.5%, and 26.5%, respectively; $P = 0.82$) (11). In another study of 49 mechanically ventilated patients with severe community acquired pneumonia, a bacterial–viral group had a higher, but not significantly, ICU mortality rate than that of a bacterial-only group (21% vs. 10%; $P = 0.4$) (12). In the present study of pneumonia-related ARDS patients who received BAL for pathogen detection, the hospital mortality rate was significantly higher in the coinfection group (virus and bacterium or virus and fungus) than in the virus-only group (80.5% vs. 53.7%; $P = 0.01$). The poor outcome in the coinfection group might be partly explained by underlying disease with a higher Charlson comorbidity index compared with that of the virus-only group (2.6 ± 2.1 vs. 1.9 ± 1.7; $P = 0.03$). In future studies, the relationship between coinfection and poor outcomes in pneumonia-related ARDS patients and whether mixed pathogen detection through BAL is true infection or merely a presentation of severe underlying disease should be investigated.

ARDS might result from viral pneumonia, subsequent to initial viral lung infection-induced damage. Viral pneumonia can be roughly divided into two categories: community-acquired viral disease, with respiratory viruses such as influenza, rhinoviruses, parainfluenza, adenovirus, respiratory syncytial virus, coronaviruses, and human metapneumovirus; and nosocomial viral disease, with Herpesviridae such as CMV and HSV (24–27). However, isolation of a virus through BAL is not necessarily

TABLE 3. **Demographics and clinical characteristics of pneumonia-related ARDS patients receiving BAL for pathogen positive**

Characteristics	Virus-only identified group (n = 41)	No virus identified group (n = 60)	Coinfection group (n = 41)	*P*
Age (years)	62.5 ± 14.1	63.8 ± 16.1	60.0 ± 14.4	0.45
Gender (male/female)	28/13	45/15	22/19	0.08
BMI (kg/m^2)	22.2 ± 3.9	22.4 ± 3.2	22.9 ± 4.2	0.74
PBW (kg)	55.5 ± 8.0	58.4 ± 10.0	54.4 ± 9.3	0.09
Charlson comorbidity index	1.9 ± 1.7	3.1 ± 2.2	2.6 ± 2.1	0.02*
APACHE II score	21.3 ± 7.0	24.4 ± 6.7	23.4 ± 6.9	0.08
SOFA score	8.7 ± 3.0	9.9 ± 3.5	9.0 ± 3.0	0.16
MOD score	8.0 ± 2.7	9.0 ± 3.0	8.2 ± 2.7	0.20
Lung injury score	3.1 ± 0.5	3.1 ± 0.5	3.0 ± 0.5	0.69
Tidal volume (mL/PBW)	7.8 ± 1.9	7.8 ± 2.1	8.3 ± 2.2	0.54
Peak Paw (cm H_2O)	30.4 ± 5.1	29.9 ± 5.5	30.8 ± 4.4	0.63
PEEP (cm H_2O)	10.6 ± 2.3	10.2 ± 2.0	10.3 ± 2.6	0.72
PaO_2/FiO_2 (mm Hg)	117.8 ± 71.6	125.0 ± 69.4	132.4 ± 73.5	0.65
Severity (n, %)				0.43
Mild	6 (14.6%)	10 (16.7%)	12 (29.3%)	
Moderate	13 (31.7%)	22 (36.7%)	12 (29.3%)	
Severe	22 (53.7%)	28 (46.7%)	17 (41.5%)	
Duration of MV (days)	34.5 ± 21.0	20.1 ± 16.3	23.8 ± 17.0	0.45
ICU mortality (n, %)	18 (43.9%)	31 (51.7%)	28 (68.3%)	0.07
Hospital mortality (n, %)	22 (53.7%)	38 (63.3%)	33 (80.5%)	0.03†

All values are expressed as the number of patients (percentage) or mean ± SD.
*$P < 0.05$: virus-only group versus no virus group; virus-only group versus coinfection group.
†$P < 0.05$: virus-only group versus coinfection group; no virus group versus coinfection group.
APACHE indicates acute physical and chronic health evaluation; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; BMI, body mass index; ICU, intensive care unit; MOD, multiple organ dysfunction; MV, mechanical ventilation; PaO_2/FiO_2, alveolar oxygen pressure/fraction of inspiratory oxygen; Paw, airway pressure; PBW, predicted body weight; PEEP, positive end expiratory pressure; SOFA, sequential organ function assessment.

associated with viral infection of the lung. CMV identified in the lower respiratory tract might be a reactivation but not a true lung infection. In critically ill patients, CMV reactivation has been associated with prolonged duration of mechanical ventilation and length of stay in the ICU, as well as increased mortality (28–33). A recent study of 271 ARDS patients revealed that CMV reactivation was independently associated with ICU mortality (34). The fraction of ICU mortality attributable to CMV reactivation was 23% by day 30, which translates into an absolute increasing mortality of 4.4%. The CMV reactivation rate was 27% in these 271 ARDS patients. In the present study, CMV was the most common virus detected through BAL and was identified in 51 (35.9%) patients. The exact implication of CMV detection in the lower respiratory tract is still debated. In future studies, evaluating the efficacy of therapy directed against CMV in ARDS patients is crucial.

This study has some limitations. First, the study was performed at a single tertiary referral center, which may limit the generalization of the results. It is critical to recognize the variability of pathogenic pneumonia species among different ICUs within a hospital, different hospitals, and different areas and countries. Such local epidemiologic information helps us understand and select the appropriate antimicrobial treatment for the specific clinical setting. Second, our study included patients with pneumonia-related ARDS who had negative results on tracheal aspirate or sputum culture and then received BAL for pathogen surveys. Thus, we did not study patients who had positive sputum culture results. Although quantitative BAL has a higher diagnostic yield in pathogen identification, it entails potential risks and ethical concerns in severe hypoxemic patients. In practice, it is not possible to perform BAL in all patients with pneumonia-related ARDS. Third, all of the patients had received empiric antimicrobial agents before BAL; some patients might have had false-negative results regarding bacterial culture, and consequently, the percentage of patients infected by other pathogens might have been overestimated. Fourth, the sensitivity and specificity of the available diagnostic methods used in this study are concerning. Although we performed quantitative BAL to increase the diagnostic yield in pathogen identification, it is possible to have false-negative results; for example, we did not uniformly use multiplex RT-PCR and serology study to detect respiratory viruses and some bacteria. Finally, the moderately small sample size may have influenced the statistical analysis and cannot represent the entire pneumonia-related ARDS population. Despite the limited number of study patients, this is one of the largest studies with BAL sampling of pneumonia-related ARDS patients thus far reported.

CONCLUSIONS

Pneumonia is one of the leading risk factors of ARDS. Pneumonia-related ARDS can be caused by bacterial, viral, fungal, and others. Coinfection with a virus and another pathogen in pneumonia-related ARDS patients is not unusual and is associated with higher hospital mortality. These findings provide relevant microbiologic information about pneumonia-related ARDS patients and support the need for additional studies evaluating the impact of viral coinfection on outcomes in these patients.

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