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Pulmonary mycobacterial infection is associated with increased mortality in patients with acute respiratory distress syndrome

Jong Hwan Jeong, MD[a], Manbong Heo, MD[a], Sunmi Ju, MD[a], Seung Jun Lee, MD, PhD[a,b], Yu Ji Cho, MD, PhD[a,b], Yi Yeong Jeong, MD, PhD[a,b], Jong Deog Lee, MD, PhD[a,b], Jung-Wan Yoo, MD, PhD[a,*]

Abstract

Although pulmonary mycobacterial infection is associated with acute respiratory distress syndrome (ARDS) in critically ill patients, its clinical implication on patients with ARDS has not been clearly elucidated. The aim of study was to investigate the clinical significance of pulmonary mycobacterial infection in patients with ARDS.

Between January 2014 and April 2019, medical records of 229 patients with ARDS who met the Berlin criteria and received invasive mechanical ventilation in medical intensive care unit were reviewed. Clinical characteristics and the rate of mortality between patients with and without pulmonary mycobacterial infection were compared. Factors associated with a 28-day mortality were analyzed statistically.

Twenty two (9.6%) patients were infected with pulmonary mycobacteria (18 with tuberculosis and 4 with non-tuberculous mycobacteria). There were no differences in baseline characteristics, the severity of illness scores. Other than a higher rate of renal replacement therapy required in those without pulmonary mycobacterial infection, the use of adjunctive therapy did not differ between the groups. The 28- day mortality rate was significantly higher in patients with pulmonary mycobacterial infection (81.8% vs 58%, $P = .019$). Pulmonary mycobacterial infection was significantly associated with 28-day mortality (hazard ratio 1.852, 95% confidence interval 1.108–3.095, $P = .019$).

Pulmonary mycobacterial infection was associated with increased 28-day mortality in patients with ARDS.

Abbreviations: APACHE = acute physiology and chronic health evaluation, ARDS = acute respiratory distress syndrome, BMI = body mass index, ICU = intensive care unit, NTM = non-tuberculosis mycobacteria, SOFA = sequential organ failure assessment, TB = tuberculosis.

Keywords: acute respiratory distress syndrome, mortality, mycobacteria

1. Introduction

Acute respiratory distress syndrome (ARDS) is a common cause for admission in the intensive care unit (ICU) and has a high mortality rate.[1] The causes of ARDS are heterogeneous and it is important to recognize early and modify them.[2] Tuberculosis (TB) has been recognized as a global health concern[3] and pulmonary TB with acute respiratory failure has a high mortality rate ranging from 50% to 60%.[4–8] The incidence of non-tuberculosis mycobacteria (NTM) pulmonary infection has increased[9] and clinical outcomes are usually unfavorable.[10–12] Although patients with NTM pulmonary infection usually do not require intensive care, one study reported that NTM pulmonary infection was common and associated with higher mortality rate in medical ICUs.[13] The incidence of pulmonary TB is still high[14] and NTM pulmonary infection has risen in South Korea.[15,16] Some studies reported the characteristics of ARDS related to pulmonary tuberculosis,[6,7] but the frequency and clinical relevance of pulmonary mycobacterial infection in patients with ARDS is poorly elucidated.

The aim of this study was to evaluate the prevalence of pulmonary mycobacterial infections in patients with ARDS and, to compare the clinical outcomes between patients with and without pulmonary mycobacterial infection.

2. Materials and methods

2.1. Subjects

Medical records of patients with ARDS who received invasive mechanical ventilation in a medical ICU with 13 beds at a tertiary

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

[a] Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Korea, [b] Gyeongsang National University College of Medicine, Jinju, Korea.

[*] Correspondence: Jung-Wan Yoo, Department of Internal Medicine, Gyeongsang National University Hospital, 79 Gangnam-ro, Jinju 52727, Republic of Korea (e-mail: chareok@gmail.com).

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hospital between January 2014 and April 2019 were retrospectively reviewed. All patients met the Berlin definition criteria for ARDS.[17] This study was approved by the Institutional Review Board of Gyeongsang National University Hospital (IRB No. 2020–03–022). Due to the retrospective nature of the study, informed consent was waived. The study was performed in accordance with the ethical standards of institutional and/or national research committees and with the Helsinki Declaration and its later amendments or comparable ethical standards.

2.2. Definitions of pulmonary mycobacterial infection

Pulmonary TB was confirmed in case of positive culture or TB-PCR in respiratory samples obtained before or during ICU admission.[18] Pulmonary NTM infection was diagnosed according to 2007 ATS/ERS guidelines. [19]

2.3. Data collection

Baseline characteristics (age, gender, body mass index [BMI]), clinical characteristics including acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, septic shock, treatment modality well as laboratory test results (white blood cell count, hemoglobin, platelet, red cell distribution width, C-reactive protein level, total protein level, albumin level, etc.) were analyzed. Mortality rates and factors associated with mortality were also analyzed.

2.4. Statistical analysis

Continuous data were expressed as median with interquartile range and were compared using the Mann–Whitney *U* test. Non-continuous data were expressed as numbers and percentages and were analyzed using the chi-square test or Fisher exact test. Factors associated with 28-day mortality in patients with ARDS were analyzed using the Cox regression hazard model. Factors with P value $<.1$ during univariate analysis as well as age and gender were considered for multivariable analysis. Differences of $P<.05$ were considered statistically significant. All data were analyzed using the SPSS software version 18.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Characteristics of patient

During the study period, 229 patients with ARDS were admitted to the MICU. Twenty two patients had pulmonary mycobacterial infection (18 with pulmonary TB and 4 with NTM). Comparison of characteristics is shown in Table 1. Median age of patients was 72 years and 71% were males. There were no significant differences in age, gender, and comorbidities between the groups. BMI was significantly lower in patients with pulmonary mycobacterial infection than those without. The severity of illness scores and the percentage of patients who developed septic shock and acute kidney injury were not different between groups. The use of neuromuscular blocking agents, corticosteroids and extracorporeal oxygenation membrane also did not differ between groups. Laboratory parameters are shown in Table 2. Serum Albumin and C-reactive protein were significantly lower in patients with pulmonary mycobacterial infection.

3.2. Comparison of mortality rates between patients with pulmonary mycobacterial infection and those without

Table 3 shows the comparison of mortality rates between patients with and without pulmonary mycobacterial infection. 28-day, 60-day, ICU and in-hospital mortality rates were significantly higher in patients with pulmonary mycobacterial infection.

3.3. Factors associated with 28-day mortality

Table 4 shows the univariate and multivariate analyses of factors associated with 28-day mortality. After univariate analysis, APACHE II and SOFA scores, pulmonary mycobacterial infection, serum albumin, partial pressure of oxygen/fractioned inspired oxygen, the use of neuromuscular blocking agent were entered into the multivariate analysis. Pulmonary mycobacterial

Table 1

Comparison of baseline and clinical characteristics between patients with pulmonary mycobacterial infection and those without.

Variables	Total N = 229	Mycobacterial infection N=22	No mycobacterial infection N=207	*P* value
Age, yrs old	72 (59–79)	71.5 (56.8–78.8)	72 (59–79)	.862
Gender, male	163 (71.2)	16 (71.7)	147 (71)	.866
BMI, kg/m^2	21.8 (19.7–24.7)	19.7 (17.1–19.7)	22.2 (20–24.9)	.002
Diabetes mellitus	68 (29.7)	4 (18.2)	64 (30.9)	.214
Chronic kidney disease	16 (7)	1 (4.5)	15 (7.2)	1
Chronic liver disease	31 (13.5)	1 (4.5)	30 (14.5)	.325
Cerebrovascular disease	37 (16.2)	3 (13.6)	34 (16.4)	1
Active malignancy	22 (9.6)	1 (4.5)	21 (10.1)	.704
APACHE II score	26 (22–32)	27.5 (21.8–35)	26 (23–32)	.378
SOFA score	13 (10–15)	13.5 (10.8–14)	13 (10–15)	.862
Septic shock	163 (71.2)	16 (72.7)	147 (71)	.866
AKI	146 (63.8)	13 (59.1)	133 (64.3)	.632
RRT	66 (28.8)	3 (13.6)	63 (30.4)	.098
NM blockers	58 (25.3)	6 (27.3)	52 (25.1)	.825
Steroid	70 (30.6)	8 (36.4)	62 (30)	.535
ECMO	19 (8.3)	2 (9.1)	17 (8.2)	.702

AKI = acute kidney injury, APACHE = acute physiology and chronic health evaluation, BMI = body mass index, COPD = chronic obstructive pulmonary disease, ECMO = extracorporeal membrane oxygentation, RRT = renal replacement therapy, SOFA = sequential organ failure assessment.

Table 2

Comparison of laboratory parameters between patients with pulmonary mycobacterial infection and those without.

Variables	Total N = 229	Mycobacterial infection N = 22	No mycobacterial infection N = 207	*P* value
WBC, x10^3/mm^3	12.5 (5.5–18.5)	11 (2.6–16.5)	12.6 (5.6–18.6)	.285
Hb, g/dL	11.1 (9.5–12.7)	10.5 (8.3–12.3)	11.1 (9.5–12.8)	.078
Platelet, x 10^3/mm^3	181 (102–262)	173 (106.5–285.5)	183 (102–262)	.706
Albumin, g/dL	2.6 (2.3–3.1)	2.5 (2–2.7)	2.7 (2.3–3.1)	.008
CRP, mg/dL	17.9 (10.2–27.5)	12.9 (7.1–20.6)	18.5 (11.1–27.8)	.048
$PaCO_2$, mm Hg	39 (33–45)	38.5 (31.8–49.3)	39 (33–45)	.793
PaO_2/FiO_2 ratio	110 (81.6–146.3)	119.4 (84.3–159.5)	110 (81.3–146)	.437

CRP = C-reactive protein, Hb = hemoglobin, PaCO2 = partial pressure of carbon dioxide, PF = partial pressure of oxygen/fractioned inspired oxygen, WBC = white blood cell.

Table 3

Comparison of mortality between patients with pulmonary mycobacterial infection and those without.

Variables	Total N = 229	Mycobacterial infection N = 22	No Mycobacterial infection N = 207	*P* value
14-d mortality	112 (48.9)	15 (68.2)	97 (46.9)	.057
28-d mortality	138 (60.3)	18 (81.8)	120 (58)	.030
60-d mortality	158 (69)	20 (90.9)	138 (66.7)	.019
ICU mortality	140 (61.1)	18 (81.8)	122 (58.9)	.036
In hospital mortality	149 (65.1)	19 (86.4)	130 (62.8)	.028

ICU = intensive care unit.

Table 4

Univariate and multivariate analysis for factor associated with 28-day mortality.

	Univariate			Multivariate		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.012	1.000–1.025	.050	1.008	0.994–1.023	.275
Male gender	0.932	0.645–1.347	.709	0.917	0.627–1.343	.657
Pulmonary mycobacterial infection	1.945	1.183–3.196	.009	1.852	1.108–3.095	.019
APACHEII	1.108	1.078–1.138	<.001	1.071	1.034–1.108	<.001
SOFA	1.182	1.117–1.250	<.001	1.074	1.002–1.151	.045
Albumin	0.581	0.425–0.794	.001	0.692	0.512–0.936	.017
P/F ratio	0.993	0.989–0.996	<.001	0.995	0.991–1.000	.043
NM blocker	0.686	0.455–1.034	.072	0.590	0.378–0.921	.020

APACHE = acute physiology and chronic health evaluation, CI = confidence interval, HR = hazard ratio, NM = neuromuscular, PF = partial pressure of oxygen/fractioned inspired oxygen, SOFA = sequential organ failure assessment.

infection, higher APACHE II and SOFA score, lower serum albumin, lower partial pressure of oxygen/fractioned inspired oxygen ratio and the use of neuromuscular blocking agents were associated with 28-day mortality.

3.4. Characteristics of pulmonary mycobacterial infection

Table 5 presents the characteristics of pulmonary mycobacterial infection. Eighteen patients had pulmonary TB while 4 had NTM pulmonary infection. Pulmonary mycobacterial infection was identified in 72.7% (16/22) patients before or during ICU admission. Six patients (3 pulmonary TB and 3 NTM pulmonary infection) were identified after death. Positive acid-fast bacilli (AFB) on smear were seen in 63.6% patients. Cavity lesion was seen in 31.8% patients in their lung. NTM species could not be identified because all patients with pulmonary NTM infection died before NTM species tests were performed. Anti-mycobacterial treatment was administered to 63.6% patients and only 1 patient with NTM pulmonary infection received medication without identification of the NTM species. Mortality rate at 28-day was high (81.8%) and all patients with NTM pulmonary infection died.

4. Discussion

In the present study, pulmonary mycobacterial infection was seen in 9.6% patients with ARDS who were admitted to MICU required invasive mechanical ventilation. Pulmonary TB infection was seen in 7.9% (18/229) patients. Patients with pulmonary mycobacterial infection had a higher mortality than those without mycobacterial infection. Moreover, pulmonary mycobacterial infection was associated with higher 28-day mortality in patients with ARDS. Pulmonary mycobacterial infection was identified from the respiratory sample obtained in 6 patients who

Table 5

Characteristics of pulmonary mycobacterial infection.

	Total N = 22	TB N = 18	NTM N = 4
Timing of diagnosis of mycobacteria			
Before ICU admission	3 (13.6)	3 (16.7)	0
During ICU admission	13 (59.1)	12 (66.7)	1 (25)
After ICU discharge or death	6 (27.3)	3 (16.7)	3 (75)
Positive AFB smear	14 (63.6)	11 (61.1)	3 (75)
Cavity disease	7 (31.8)	5 (27.8)	2 (50)
Treatment of mycobacterial infection	14 (63.6)	13 (72.2)	1 (25)
Death at 28 d	18 (81.8)	14 (77.8)	4 (100)

AFB = acid-fast bacilli, ICU = intensive care unit, NTM = non-tuberculosis mycobacteria, TB = tuberculosis.

died later (3 with TB and 3 with NTM) during ICU admission. Patients with TB were treated with anti-mycobacterial agents while only 1 patient received anti-NTM medication empirically.

ARDS is a common condition to admit to ICU and accounts for a significant substantial mortality rate.[1,17] There are various causes of ARDS.[2] The early recognition and control of causative is the key modality although lung protective mechanical ventilation and adjunctive therapies has been advanced in ARDS.[2,20] Tuberculosis (TB) is a global concerned infectious disease and lung is the main organ involved.[3] Favorable outcomes have been reported in drug susceptible pulmonary TB; however, pulmonary TB with acute respiratory failure has a high mortality rates ranging from 50% to 60%.[4–6] Acute respiratory form of TB presents as ARDS associated with radiologically pneumonic consolidation or a military pattern.[6,7] The incidence of NTM pulmonary infection has been increasing and it is recognized as an emerging infectious disease.[9] Clinical and radiological features are usually similar between pulmonary TB and NTM infection. Microbiologic confirmation is needed to meet diagnostic criteria of pulmonary NTM infection.[19] At least more than 1 month is taken to microbiologic isolation and sequential identification of NTM species.

Few antibacterial agents are available for treating pulmonary NTM infection and clinical outcomes are generally not favorable.[10–12] The clinical significance of pulmonary NTM infection in critically ill patients remain unknown. One study conducted in Taiwan reported that 47 patients out of 2866 patients admitted to MICU had NTM pulmonary infection.[13] This study indicated that NTM pulmonary infection was associated with higher mortality rate in MICUs. In South Korea, the incidence of pulmonary TB is still high.[14] The incidence and prevalence of NTM infection have been increased annually.[15,16] Several studies reported that clinical outcomes of pulmonary TB with respiratory failure including ARDS were poor in South Korea.[5–7] The proportion of types of pulmonary mycobacterial infection (TB and NTM) and their association with mortality in patients presenting with ARDS has not been investigated. In the current study, pulmonary mycobacterial infection was seen in 9.6% patients who admitted to MICU for ARDS and requiring invasive mechanical ventilation. In baseline characteristics, BMI was significantly lower in patients with pulmonary mycobacterial infection than those without. Several studies showed that low BMI was associated with development, progression and clinical outcomes of pulmonary mycobacterial infection.[21–25]

Patients with pulmonary mycobacterial infection had a higher mortality than those without mycobacterial infection and pulmonary mycobacterial infection was associated with a higher 28-day mortality in patients with ARDS. The proportion of pulmonary TB infection was higher than pulmonary NTM infection. Pulmonary mycobacterial infection was identified from respiratory sample obtained in 6 patients later who died (3 with TB and 3 with NTM) during ICU admission. The species of NTM could not be identified because NTM isolation was reported after patients with pulmonary NTM infection died. 72.2% patients with TB received anti-TB medication during ICU admission. However, only 1 patient with pulmonary NTM infection started anti-NTM medication empirically in MICU before isolation of NTM culture and identification of the NTM species to meet diagnostic criteria and select appropriate agents. In the current study data, mortality rate was 100% in 4 patients with NTM pulmonary infection. In spite of small number of cases, higher APACHE II score, ARDS itself, positive AFB smear and cavity lesion at diagnosis of NTM pulmonary infection may have contributed to higher mortality noted in our analysis compared to Shu et al study reporting 26% ICU mortality in 43 patients with pulmonary NTM infection.[13] The present study suggests that prompt recognition of pulmonary mycobacterial infection and distinguishing between TB and NTM for optimal medical treatment in patients who present with ARDS is essential in the high pulmonary TB and NTM infection burden countries.

There are several limitations in this study. Retrospective design and small number of pulmonary mycobacterial patients with ARDS in a single center does not exclude selection bias. Our conclusion cannot be generalized to other centers. Second, NTM species was not identified because all patients with NTM died although repeated NTM isolation was identified. Third, pulmonary mycobacterial infection was associated with mortality in patients with ARDS; however, other confounding factors might exist. A prospective study is necessary to support our data.

In conclusion, pulmonary mycobacterial infection was not uncommon and associated with increased mortality in patients presenting with ARDS and admitted to the ICU. Early recognition and discernment of pulmonary TB and NTM infection might be important to optimize medical treatment and improve survival rates.

Author contributions

Conceptualization: Jong Hwan Jeong, Manbong Heo, Jung-Wan Yoo.

Data curation: Sunmi Ju, Seung Jun Lee, Yu Ji Cho, Yi Yeong Jeong, Jong Deog Lee.

Methodology: Sunmi Ju, Seung Jun Lee, Yu Ji Cho, Yi Yeong Jeong, Jong Deog Lee.
Writing – original draft: Jong Hwan Jeong, Manbong Heo, Jung-Wan Yoo.
Writing – review & editing: Jung-Wan Yoo.

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