Original Article

trd Tuberculosis & Respiratory Diseases

Clinical Significance of Various Pathogens Identified in Patients Experiencing Acute Exacerbations of COPD: A Multi-center Study in South Korea

https://doi.org/10.4046/trd.2024.0089
ISSN: 1738-3536(Print)/
2005-6184(Online)
Tuberc Respir Dis 2025;88:292-302

Hyun Woo Ji, M.D.[1]*, Soojoung Yu, M.D.[2], Yun Su Sim, M.D., Ph.D.[3], Hyewon Seo, M.D.[4], Jeong-Woong Park, M.D., Ph.D.[5], Kyung Hoon Min, M.D., Ph.D.[6], Deog Kyeom Kim, M.D., Ph.D.[7], Hyun Woo Lee, M.D.[7], Chin Kook Rhee, M.D., Ph.D.[8], Yong Bum Park, M.D., Ph.D.[9], Kyeong-Cheol Shin, M.D., Ph.D.[10], Kwang Ha Yoo, M.D., Ph.D.[11] and Ji Ye Jung, M.D., Ph.D.[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, [2]International Healthcare Center, Soonchunhyang University Seoul Hospital, Seoul, [3]Division of Pulmonary, Allergy and Critical Care Medicine, Hallym University Kangnam Sacred Heart Hospital, College of Medicine, Hallym University, Seoul, [4]Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University Hospital, Daegu, [5]Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, [6]Division of Pulmonology, Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, [7]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, [8]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [9]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, [10]Division of Pulmonology and Allergy, Department of Internal Medicine, Yeungnam University Medical Center, Yeungnam University College of Medicine, Daegu, [11]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea

Address for correspondence
Ji Ye Jung, M.D., Ph.D.
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea
Phone 82-2-2228-1980
Fax 82-2-2227-8294
E-mail stopyes@yuhs.ac
Address for correspondence
Kwang Ha Yoo, M.D., Ph.D.
Department of Internal Medicine, Konkuk University Hospital. Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Republic of Korea
Phone 82-2-2030-7522
Fax 82-2-2030-7458
E-mail khyou@kuh.ac.kr
Received Jul. 4, 2024
Revised Oct. 22, 2024
Accepted Dec. 16, 2024
Published online Dec. 30, 2024

*Current affiliation: Division of Pulmonology, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Republic of Korea

Abstract

Background: Respiratory infections play a major role in acute exacerbation of chronic obstructive pulmonary disease (AECOPD). This study assessed the prevalence of bacterial and viral pathogens and their clinical impact on patients with AECOPD.

Methods: This retrospective study included 1,186 patients diagnosed with AECOPD at 28 hospitals in South Korea between 2015 and 2018. We evaluated the identification rates of pathogens, basic patient characteristics, clinical features, and the factors associated with infections by potentially drug-resistant (PDR) pathogens using various microbiological tests.

Results: Bacteria, viruses, and both were detected in 262 (22.1%), 265 (22.5%), and 129 (10.9%) of patients, respectively. The most common pathogens included *Pseudomonas aeruginosa* (17.8%), *Mycoplasma pneumoniae* (11.2%), *Streptococcus pneumoniae* (9.0%), influenza A virus (19.0%), rhinovirus (15.8%), and respiratory syncytial virus (6.4%). Notably, a history of pulmonary tuberculosis (odds ratio [OR], 1.66; p=0.046), bronchiectasis (OR, 1.99; p=0.032), and the use of a triple inhaler regimen within the past 6 months (OR, 2.04; p=0.005) were identified as significant factors associated with infection by PDR pathogens. Moreover, patients infected with PDR pathogens exhibited extended hospital stays (15.9 days vs. 12.4 days, p=0.018) and higher intensive care unit admission rates (15.9% vs. 9.5%, p=0.030).

Conclusion: This study demonstrates that a variety of pathogens are involved in episodes of AECOPD. Nevertheless, additional research is required to confirm their role in the onset and progression of AECOPD.

Keywords: Chronic Obstructive Pulmonary Disease; Acute Exacerbation; Pathogen; Drug Resistance

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation that is not fully reversible[1]. As a major global cause of death, COPD incurs substantial socioeconomic costs[2,3]. Moreover, acute exacerbation of chronic obstructive pulmonary disease (AECOPD) lead to accelerated decline in lung function, reduced quality of life, increased mortality, and greater socioeconomic expenses. Consequently, the prevention and early management of AECOPD are crucial for improving patient outcomes[4].

Given that respiratory tract infections may trigger AECOPD, it is essential to consider epidemiological characteristics and antimicrobial resistance when managing treatment. To date, most studies on AECOPD have been conducted in Western countries, with limited research from Asia focused on single centers or countries[5]. A recent prospective epidemiological study in the Asia-Pacific region assessed the prevalence of bacterial and viral pathogens in AECOPD via sputum samples. However, due to an insufficient number of participants, the results may not accurately reflect the disease burden in each country[6]. Furthermore, the majority of AECOPD cases examined were mild, and the study failed to assess pathogens associated with moderate to severe AECOPD adequately. Additionally, a recent domestic multicenter observational study aimed to identify pathogens linked to AECOPD, and preliminary findings have been reported. Nevertheless, further research is required to determine their clinical relevance to improve management of these exacerbations[7].

As antibiotic resistance represents a significant public health challenge globally, cases of AECOPD are frequently attributed to microorganisms such as *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), or *Stenotrophomonas maltophilia* that exhibit resistance to standard antibiotic treatments[8].

Consequently, this study sought to determine the rates of bacterial and viral identification in Korean patients hospitalized for AECOPD, explore variations in clinical characteristics depending on the pathogen, and ascertain factors associated with infections by potentially drug-resistant (PDR) pathogens unresponsive to conventional antibiotics.

Materials and Methods

1. Data recruitment

This study retrospectively evaluated data sourced from 28 hospitals in South Korea, compiled by the COPD study group of the Korean Academy of Tuberculosis and Respiratory Disease. According to the retrospective chart review, a total of 1,186 patients diagnosed with AECOPD from January 2015 to December 2018 were consecutively enrolled in our study[7]. The inclusion criteria for the study were as follows: (1) age over 40 years, (2) a history of COPD confirmed by relevant lung function tests, (3) diagnosis of moderate-to-severe AECOPD, and (4) assessment using all standard tests for pathogen detection. The exclusion criteria included: (1) antibiotic use within the previous 4 weeks for conditions other than AECOPD treatment, and (2) less than 30 days elapsed since the last acute exacerbation. COPD was diagnosed following the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] employing spirometry, with a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity of less than 0.70 after bronchodilator application indicative of persistent airflow limitation. The attending physician confirmed the diagnosis of moderate-to-severe AECOPD based on the GOLD guidelines, defined by a significant worsening of respiratory symptoms such as cough, dyspnea, wheezing, and chest discomfort, necessitating treatment with antibiotics, systemic glucocorticoids, or hospitalization. Pulmonary function and COPD assessment test (CAT) scores in a stable state were documented within 6 months prior to an AECOPD event.

The study protocol received approval from the Institutional Review Board of Severance Hospital (approval number: 4-2019-1316) and was conducted adhering to the ethical standards established in the 1964 Declaration of Helsinki and subsequent amendments. Due to the retrospective nature of the study and the employment of anonymized clinical data, the requirement for informed consent was waived.

2. Microbiological evaluation

All microbiological assessments were conducted within 48 hours following the diagnosis of AECOPD, utilizing blood and lower respiratory tract specimens such as sputum, bronchial washing fluid, endotracheal aspirate, or nasopharyngeal swabs at the discretion of the treating physicians.

Sputum samples were cultured semi-quantitatively, and an etiological diagnosis was established when a predominant microorganism was isolated from group 4 or 5 sputum according to Murray and Washington's grading system[9,10]. To confirm the presence of atypical bacterial pathogens, polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) were

employed. To identify viral pathogens, PCR and rapid antigen testing (RAT) were used on nasopharyngeal swab specimens. Details of each microbiological evaluation are described in Supplementary Table S1.

3. Definition of terms

The bacterial pathogen group is characterized by the detection of organisms typically linked to respiratory tract infections, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *P. aeruginosa*, *Klebsiella pneumoniae*, *S. aureus*, and *Stenotrophonomas maltophilia*, identified through culture methods, or atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophilia*, confirmed using PCR or RAT. The viral pathogen group is delineated by the identification of viruses commonly associated with respiratory tract infections, including rhinovirus, adenovirus, influenza A/B, respiratory syncytial virus (RSV), and parainfluenza, confirmed via PCR or RAT. Co-infection is identified by the simultaneous presence of both bacterial and viral pathogens associated with respiratory infections. The PDR pathogen group is defined as comprising *P. aeruginosa*, MRSA, and *S. maltophilia*.

4. Statistical analyses

Data were analyzed using SPSS version 26.0 software for Windows (IBM Corp., Armonk, NY, USA). Categorical variables are presented as absolute numbers and percentages. Continuous variables are expressed as mean±standard deviation. The chi-square test and Fisher's exact test were utilized to compare proportions between groups, whereas the Student's t-test and one-way analysis of variance were applied to continuous variables. Logistic regression analysis was conducted to identify factors associated with PDR pathogens. Variables included in the multivariable analysis were those commonly known to influence AECOPD or those statistically significant in the univariable analysis. All tests were two-tailed, and p-values <0.05 were considered statistically significant.

Results

1. Baseline characteristics

This study included a total of 1,186 patients, with 82.5% being male. The average age of the participants was 78.8 years. The mean duration since diagnosis with COPD was 7.6 years, the average percentage of predicted FEV_1 was 49.5%, and the mean CAT score was 22.5. Predominant underlying lung diseases included pulmonary tuberculosis (31.8%), bronchiectasis

Table 1. Baseline characteristics of patients

Characteristic	Total (n=1,186)
Age, yr	78.8±9.2
Male sex	979 (82.5)
Duration of COPD, yr	7.6±6.6
Smoking history	
Never smoked	313 (27.1)
Current smoker	156 (13.5)
Former smoker	688 (59.5)
Pack year	38.7±26.0
Underlying respiratory disease	
Tuberculosis	377 (31.8)
Bronchiectasis	169 (14.2)
Interstitial lung disease	27 (2.3)
Comorbidities	
Diabetes mellitus	318 (26.8)
Hypertension	584 (49.2)
Liver cirrhosis	23 (1.9)
Congestive heart failure	166 (14.0)
Chronic kidney disease	76 (6.4)
Cerebrovascular disease	70 (5.9)
Advanced cancer	138 (11.6)
FEV_1, %	49.5±21.1
CAT score	22.5±9.8
mMRC	2.3±0.9
During AECOPD	
ICU administration	112 (9.5)
Hospital length of stay, day	12.6±13.7
Antibiotics use	
Unused	47 (4.2)
Monotherapy	282 (25.5)
Beta-lactam	163 (57.8)
Quinolone	107 (37.9)
Macrolide	5 (1.8)
Others	7 (2.5)
Dual combination	651 (58.8)
Beta-lactam+Quinolone	280 (43.0)
Beta-lactam+Macrolide	236 (36.3)
Beta-lactam+Others	31 (4.8)
Quinolone+Others	27 (4.1)
Macrolide+Others	19 (2.9)
Triple combination	128 (11.5)
Levels of healthcare system	
Secondary	396 (33.5)
Tertiary	709 (66.5)

Values are presented as mean±standard deviation or number (%).
COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; CAT: COPD assessment test; mMRC: modified Medical Research Council Dyspnea Scale; AECOPD: acute exacerbation of chronic obstructive pulmonary disease; ICU: intensive care unit.

(14.2%), and interstitial lung disease (2.3%). During episodes of acute exacerbation, the rate of admission to the intensive care unit (ICU) was 9.5%. The average length of hospital stay amounted to 12.6 days, and a majority of patients (95.8%) received antibiotic therapy during their hospitalization (Table 1).

2. Identified pathogens

The distribution of patients infected with bacterial, viral, and both bacterial and viral pathogens included 262 (22.1%), 265 (22.5%), and 129 (10.9%) individuals, respectively. Predominant bacterial pathogens identified were *P. aeruginosa* (17.8%), *M. pneumoniae* (11.2%), *S. pneumoniae* (9.0%), and *K. pneumonia* (7.8%). The most frequently identified viral pathogens included influenza A (19.0%), rhinovirus (15.8%), RSV (6.4%), and influenza B (6.0%) (Figure 1).

3. Comparison between the clinical features based on PDR pathogen identification

Table 2 shows the clinical features of patients during AECOPD according to PDR pathogen identification. The PDR pathogen group exhibited a lower body mass index (20.7 kg/m^2 vs. 21.6 kg/m^2, p=0.017), a lower percentage of predicted FEV_1 (44.6% vs. 50.5%, p=0.021), more frequent acute exacerbation events over the past year (2.2 times vs. 1.5 times, p=0.001), and higher CAT scores (25.3 vs. 21.5, p=0.044) compared to

Figure 1. Types and proportions of pathogens identified. (A) Distribution of bacterial infection. (B) Distribution of viral infection. MRSA: methicillin-resistant *Staphylococcus aureus*; PDR: potentially drug-resistant; RSV: respiratory syncytial virus.

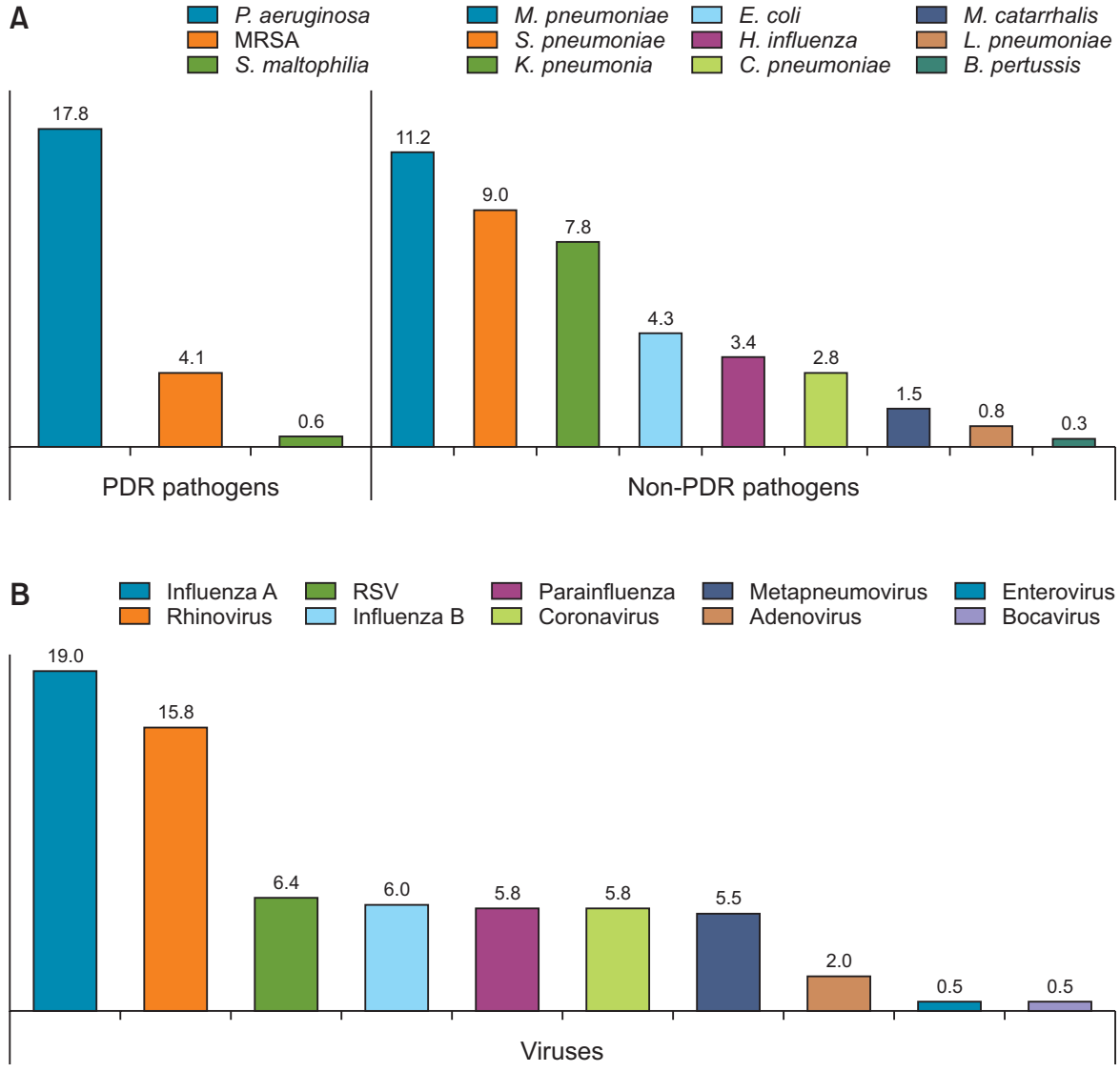

Table 2. Baseline characteristics and clinical features of patients during AECOPD according to PDR pathogen identification

Characteristic	Non-PDR pathogens (n=511)	PDR pathogens (n=142)	p-value
Baseline characteristics			
Male sex	417 (81.6)	106 (74.6)	0.066
BMI, kg/m^2	21.6±3.8	20.7±3.6	0.017
Pack-yr	36.6±23.3	40.6±32.3	0.270
FEV_1, %	50.0±21.2	44.6±19.1	0.021
Exacerbation frequency	1.5±2.0	2.2±2.1	0.001
CAT score	21.4±11.0	25.3±6.9	0.044
Comorbidities			
Diabetes mellitus	150 (29.4)	38 (26.8)	0.546
Hypertension	259 (50.7)	75 (52.8)	0.653
Liver cirrhosis	10 (2.0)	2 (1.4_	0.667
Congestive heart failure	74 (14.5)	20 (14.1)	0.905
Chronic kidney disease	30 (5.9)	10 (7.0)	0.607
Cardiovascular disease	36 (7.0)	5 (3.5)	0.126
Cancer	70 (13.7)	11 (7.7)	0.057
Tuberculosis	149 (29.2)	65 (45.8)	0.001
Bronchiectasis	65 (12.7)	36 (25.4)	0.001
Interstitial lung disease	11 (2.2)	3 (2.1)	0.977
Previous inhaled treatment administration			
None	118 (23.1)	25 (17.6)	0.210
ICS	10 (1.9)	3 (2.1)	0.680
LABA	9 (1.8)	3(2.1)	0.751
LAMA	55 (10.8)	14 (9.9)	0.210
LAMA+LABA	80 (15.6)	22 (15.5)	0.962
ICS+LABA	73 (14.3)	13 (9.1)	0.050
ICS+LAMA+LABA	166 (32.5)	62 (43.7)	0.001
Any treatment combined with ICS	249 (48.7)	78 (54.9)	0.191
Systemic steroids	102 (20.0)	46 (32.4)	0.002
Clinical features			
Symptom			
Dyspnea	463 (90.6)	127 (89.4)	0.676
Cough	398 (77.9)	101 (71.1)	0.093
Sputum	406 (79.5)	109 (76.8)	0.487
Fever	165 (32.3)	41 (28.9)	0.438
Symptom duration, day			
Dyspnea	5.2±5.7	6.6±8.0	0.054
Cough	5.2±5.7	6.2±7.9	0.196
Sputum	5.4±6.0	6.6±7.7	0.138
Length of hospitalization, day	12.4±14.7	15.9±17.3	0.018
Length of exacerbation, day	12.2±7.9	13.3±9.8	0.185
ICU admission	47 (9.5)	22 (15.9)	0.030
Duration of steroid use, day	12.8±14.9	19.7±44.2	0.107

Table 2. Continued

Characteristic	Non-PDR pathogens (n=511)	PDR pathogens (n=142)	p-value
Antibiotic use			
Monotherapy			
Beta-lactam	383 (80.0)	112 (81.8)	0.641
Quinolone	220 (45.9)	70 (51.1)	0.285
Macrolide	150 (31.3)	29 (21.2)	0.021
Other	23 (4.8)	17 (12.4)	0.001
Dual combination			
Beta-lactam+Quinolone	117 (24.4)	36 (26.3)	0.658
Beta-lactam+Macrolide	122 (25.5)	24 (17.5)	0.054
Triple combination	52 (10.9)	21 (15.3)	0.153

Values are presented as number (%) or mean±standard deviation.
AECOPD: acute exacerbation of chronic obstructive pulmonary disease; PDR: potentially drug-resistant; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; CAT: COPD assessment test; ICS: inhaled corticosteroid; LABA: long-acting beta agonists; LAMA: long-acting muscarinic antagonists; ICU: intensive care unit.

the non-PDR pathogen group. Additionally, this group had higher rates of pulmonary tuberculosis (45.8% vs. 29.2%, p=0.001) and bronchiectasis (25.4% vs. 12.7%, p=0.001), as well as more frequent use of triple inhalers (42.3% vs. 28.8%, p=0.001) and systemic steroids (32.4% vs. 20.0%, p=0.002) within the last 6 months compared to the non-PDR pathogen group.

During an acute exacerbation event, patients in the PDR pathogen group required a longer hospital stay (15.9 days vs. 12.9 days, p=0.018) and had a higher ICU admission rate (15.9% vs. 9.5%, p=0.030) compared to those in the non-PDR pathogen group. No significant differences in the frequency and duration of symptoms between the two groups were found.

When patients were categorized based on pathogen type, those in the bacterial pathogen group required a longer hospital stay (p=0.044), a higher ICU admission rate (p=0.007), and a longer period of systemic steroid administration (p=0.013) compared to those in the other groups. Similarly, patients in the viral pathogen group exhibited higher rates of cough, sputum, and fever (p=0.001) compared to those in the other groups (Supplementary Table S2).

4. Factors associated with infection by PDR pathogens

In multivariate logistic regression analyses including ICS use within six months as a covariate, a history of pulmonary tuberculosis (odds ratio [OR], 1.66; p=0.046) and bronchiectasis (OR, 1.99; p=0.032) were identified as factors associated with infection by PDR pathogens. Additionally, ICS use within 6 months (OR, 1.62; p=0.066) was observed to potentially increase the risk of infection with PDR pathogens (Table 3, ICS model). In subsequent analyses involving triple inhaler use within the same timeframe as a covariate, bronchiectasis (OR, 1.94; p=0.043) and triple inhaler use within 6 months (OR, 2.04; p=0.005) were also linked to infection by PDR pathogens (Table 3, triple inhaler model).

Discussion

This extensive, retrospective, multi-center study explored the variety of pathogens identified in patients with AECOPD in South Korea, delineated differences in clinical features among pathogen groups, and detailed the factors associated with PDR pathogen identification. Of the patients, 22.1% were infected with bacterial, 22.5% with viral, and 10.9% with both bacterial and viral pathogens. The predominant bacteria identified were *P. aeruginosa, M. pneumoniae*, and *S. pneumoniae*. Factors such as a history of pulmonary tuberculosis, bronchiectasis, and recent triple inhaler use were linked to PDR pathogen infections. Additionally, hospital stay length and ICU admission rates significantly increased when PDR pathogens were identified.

Respiratory infection is a principal cause of AECOPD. Prior studies have determined that the identification rates of bacteria and viruses are 40%–60% and 20%–40% in patients with AECOPD, respectively[11,12]. Aligned with these results, our study recorded bacterial and viral identification rates of 33.0% and 33.2%, respec-

Table 3. Multivariate logistic analysis of the associated factors for infection with PDR pathogens during AECOPD

Associated factors	ICS model		Triple inhaler model	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, yr	1.01 (0.98–1.03)	0.638	1.01 (0.98–1.04)	0.573
Male sex	1.41 (0.78–2.55)	0.261	1.50 (0.82–2.74)	0.189
BMI, kg/m^2	0.97 (0.91–1.04)	0.405	0.97 (0.91–1.04)	0.355
FEV_1 >60%	0.74 (0.41–1.34)	0.319	0.79 (0.44–1.43)	0.435
Comorbidities				
Tuberculosis	1.66 (1.01–2.75)	0.046	1.64 (0.99–2.72)	0.054
Bronchiectasis	1.99 (1.06–3.75)	0.032	1.94 (1.02–3.67)	0.043
Treatment status				
Systemic steroids	1.47 (0.85–2.57)	0.172	1.45 (0.84–2.53)	0.186
ICS	1.62 (0.97–2.71)	0.066	NA	NA
Triple therapy	NA	NA	2.04 (1.24–3.35)	0.005

PDR: potentially drug-resistant; AECOPD: acute exacerbation of chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; OR: odds ratio; CI: confidence interval; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; NA: not applicable.

tively. Environmental factors and racial demographics can influence the strains of pathogens identified. Previous research conducted in South Korea revealed that *H. influenzae*, *S. pneumoniae*, and *P. aeruginosa* were the predominant bacterial pathogens linked to AECOPD[13,14]. In our investigation, *P. aeruginosa* (9.8%), *M. pneumoniae* (6.2%), and *S. pneumoniae* (5.0%) were the most frequently identified bacteria. Typically, *P. aeruginosa* is commonly found in patients with severe airflow limitation and underlying structural lung diseases, such as bronchiectasis[15-17]. Our study reported a high proportion of these patients and may have identified *P. aeruginosa* at a more elevated rate compared to previous studies. Similarly, *M. pneumoniae* was identified at a greater rate than in earlier research, which can be attributed to the employment of both PCR and antibody detection testing in this analysis. In contrast, *H. influenzae* exhibited a lower identification rate in this investigation compared to previous reports, due to the absence of PCR testing for this bacterium. Regarding viruses, previous research in South Korea has identified the influenza A virus and the rhinovirus as the predominant viral pathogens[14]. Consistently, our findings confirm these results, with the influenza A virus (13.7%) and rhinovirus (8.7%) being the most frequently detected among patients.

Numerous clinical studies have substantiated that administering empirical antibiotics during AECOPD significantly reduces the incidence of treatment failure and decreases short-term mortality[18,19]. Nonetheless, it is crucial to consider factors associated with antibiotic-resistant strain infections when determining appropriate antibiotic therapy. Prior research indicates that the prevalence of antibiotic-resistant strains is elevated in patients with severe lung function impairment or structural lung disease during AECOPD[7,20]. In this study, significant predictors of PDR pathogen infection included a history of bronchiectasis (OR, 1.97), tuberculosis (OR, 1.69), and triple inhaler use within the previous 6 months (OR, 2.04).

Diminished mucociliary clearance, compromised innate immunity, and reduced alveolar macrophage activity lead to microbial colonization in COPD, which promotes chronic inflammation and subsequent infection or AECOPD[21]. When complicated by bronchiectasis, COPD leads to exacerbated airway inflammation, evidenced by elevated sputum levels of interleukin 6 (IL-6) and IL-8. A high incidence of bronchiectasis in COPD correlates with extensive pathogen colonization in the lower airway, increased rates of *P. aeruginosa* isolation, elevated airway inflammatory markers, and prolonged symptom recovery time post-exacerbation[22,23]. Previously, the incidence of post-infectious bronchiectasis was reported as 15% to 50%, with prior tuberculosis infection being the primary known cause of bronchiectasis among various factors[24].

The utilization of triple inhalers is indicative of severe COPD, characterized by frequent exacerbations and diminished pulmonary function as per the guidelines established by the Korean COPD Association[25]. A systematic review noted that patients with COPD, who have poor lung function, previous antibiotic exposure,

and hospitalizations, exhibited higher incidences of infections caused by antimicrobial-resistant pathogens[26].

In the current study, patients who tested positive for pathogens were more likely to have received systemic corticosteroids previously when compared with those who tested negative, and this was particularly noted in the PDR pathogen group as opposed to the non-PDR pathogen group. However, upon adjusting for various factors, there was no increased risk of infection with PDR pathogens. Among patients with severe AECOPD requiring intubation and mechanical ventilation, previous long-term use of corticosteroids did not elevate the risk of infection with multidrug-resistant pathogens, corroborating findings from earlier studies[27]. However, ICSs tended to enhance the risk of infection with PDR pathogens in this study. It is well documented that ICS increases the incidence of pneumonia in COPD patients. Prolonged ICS therapy has demonstrated an increase in bacterial load during COPD exacerbations, particularly in patients with low eosinophil counts in blood and/or sputum[28]. Use of ICSs has also been linked to a significant dose-related risk of acquiring *P. aeruginosa* infection in COPD patients[29,30]. Patients with chronic respiratory diseases predominantly managed with ICSs also face an independently elevated risk of infection with potentially antibiotic-resistant pathogens, leading to community-acquired pneumonia[31,32]. After inhalation, corticosteroids are deposited as small particles on the surface of the airway mucosa and gradually dissolve in the mucosal lining fluid before being absorbed into the airway/lung tissue. Consequently, ICSs remaining in the mucosal lining fluid may contribute more to colonization with pathogenic bacteria than systemic corticosteroids do[33].

This study exhibited several strengths. Conducted in multiple centers, our results accurately represent the local potentially pathogenic microorganisms (PPMs) in patients with AECOPD necessitating hospitalization. Additionally, data were amassed from tertiary or referral hospitals equipped with PCR capabilities for the detection of viral and atypical pathogens. Over 80% of the patients underwent viral PCR testing and more than 50% underwent PCR or antigen testing for atypical bacteria, thereby providing a comprehensive approach to identifying PPMs during AECOPD episodes.

However, the current study had multiple limitations. First, the microbiological evaluation was not uniformly carried out across all patients. Although traditional bacterial culture and viral PCR were performed in nearly all cases of AECOPD, atypical pathogen testing was employed at the discretion of the clinician when deemed necessary. Second, it was challenging to ascertain whether the identified pathogens were causative of respiratory infection or mere colonization. Prior microbiology test results from the same patients could assist in making this distinction; however, such data were not accessible in this study. Third, sputum was the primary respiratory specimen used in identifying pathogens during microbiological examinations. Although some previous studies have demonstrated higher pathogen identification rates using lower respiratory tract specimens compared to sputum, only 47 out of 1,186 patients in this study underwent microbiological testing using lower respiratory tract specimens[34]. Nevertheless, sputum tests remain critical as invasive testing poses challenges in most clinical settings. Lastly, the results of this study should be interpreted with caution when extrapolating to patients with mild or moderate COPD since our cohort predominantly included patients with moderate-to-severe AECOPD.

In conclusion, respiratory infections have been identified as a significant cause of AECOPD. In South Korea, the most prevalent bacterial pathogens are *P. aeruginosa*, *M. pneumoniae*, and *S. pneumoniae*, while principal viral pathogens include influenza and rhinovirus. We determined that factors associated with infection by PDR pathogens include a history of pulmonary tuberculosis, bronchiectasis, and/or triple inhaler use. Nonetheless, further research is required to ascertain whether these pathogens contribute to the development and progression of AECOPD.

Authors' Contributions

Conceptualization: Yoo KH, Jung JY. Methodology: Ji HW, Yu S, Yoo KH, Jung JY. Formal analysis: Kim DK, Lee HW. Data curation: all authors. Funding acquisition: Yoo KH, Jung JY. Project administration: Kim DK, Yoo KH. Visualization: Ji HW. Investigation: Ji HW, Yu S. Writing - original draft preparation: Ji HW, Yu S. Writing - review and editing: Yoo KH, Jung JY. Approval of final manuscript: all authors.

Conflicts of Interest

Kyung Hoon Min, Deog Kyeom Kim, Hyun Woo Lee, Ji Ye Jung are editors and Chin Kook Rhee a deputy editor of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Acknowledgments

All members of the Korean COPD Study Group contributed to the recruitment of patients with COPD and to the collection of data: Jae Ha Lee, M.D., Ph.D. (Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan), Byung-Keun Kim, M.D., Ph.D. (Division of Pulmonology, Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul), Myung Goo Lee, M.D., Ph.D. (Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon), Yeon-Mok Oh, M.D., Ph.D. (Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul), Seung Won Ra, M.D., Ph.D. (Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan), Tae-Hyung Kim, M.D., Ph.D. (Division of Pulmonary and Critical Care Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri), Yong Il Hwang, M.D., Ph.D. (Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang), Hyonsoo Joo, M.D., Ph.D. (Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul), Eung Gu Lee, M.D. (Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon), Jin Hwa Lee, M.D., Ph.D. (Department of Internal Medicine, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul), Hye Yun Park, M.D., Ph.D. (Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul), Woo Jin Kim, M.D., Ph.D. (Department of Internal Medicine and Environmental Health Center, Kangwon National University College of Medicine, Chuncheon), Soo-Jung Um, M.D., Ph.D. (Department of Internal Medicine, Dong-A University College of Medicine, Busan), Joon Young Choi, M.D., Ph.D. (Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul), Chang-Hoon Lee, M.D., Ph.D. (Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul), Tai Joon An, M.D. (Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul), Yeonhee Park, M.D. (Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul), Young-Soon Yoon, M.D. (Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang), and Joo Hun Park, M.D., Ph.D. (Department of Pulmonary and Critical Care Medicine, Ajou University School of Medicine, Suwon).

Funding

This work was supported by the Korean Academy of Tuberculosis and Respiratory Diseases (grant number KATRD-S-2019-1) and the Korea Environmental Industry & Technology Institute through the Digital Infrastructure Building Project for Monitoring, Surveying and Evaluating Environmental Health, sponsored by the Korean Ministry of Environment (grant number 2021003340002).

Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. The proportions of each specimen type and microbiological evaluation method.

Supplementary Table S2. Baseline characteristics and clinical features according to pathogen type.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report) [Internet]. Deer Park: GOLD; 2023 [cited 2025 Feb 10]. Available from: https://goldcopd.org/2023-gold-report-2/.
2. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117-71.
3. National Institutes of Health National Heart, Lung, and Blood Institute. Morbidity and mortality: chartbook on cardiovascular, lung and blood diseases. Bethesda: NHLBI; 2012.
4. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exac-

erbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;169:1298-303.
5. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 2006;173:1114-21.
6. Taddei L, Malvisi L, Hui DS, Malvaux L, Samoro RZ, Lee SH, et al. Airway pathogens detected in stable and exacerbated COPD in patients in Asia-Pacific. ERJ Open Res 2022;8:00057-2022.
7. Lee HW, Sim YS, Jung JY, Seo H, Park JW, Min KH, et al. A multicenter study to identify the respiratory pathogens associated with exacerbation of chronic obstructive pulmonary disease in Korea. Tuberc Respir Dis (Seoul) 2022;85:37-46.
8. Estirado C, Ceccato A, Guerrero M, Huerta A, Cilloniz C, Vilaro O, et al. Microorganisms resistant to conventional antimicrobials in acute exacerbations of chronic obstructive pulmonary disease. Respir Res 2018;19:119.
9. Jung JY, Park MS, Kim YS, Park BH, Kim SK, Chang J, et al. Healthcare-associated pneumonia among hospitalized patients in a Korean tertiary hospital. BMC Infect Dis 2011;11:61.
10. Murray PR, Washington JA. Microscopic and baceriologic analysis of expectorated sputum. Mayo Clin Proc 1975;50:339-44.
11. Mohan A, Chandra S, Agarwal D, Guleria R, Broor S, Gaur B, et al. Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review. Respirology 2010;15:536-42.
12. Sethi S, Murphy TF. Bacterial infection in chronic obstructive pulmonary disease in 2000: a state-of-the-art review. Clin Microbiol Rev 2001;14:336-63.
13. Ra SW, Kwon YS, Yoon SH, Jung CY, Kim J, Choi HS, et al. Sputum bacteriology and clinical response to antibiotics in moderate exacerbation of chronic obstructive pulmonary disease. Clin Respir J 2018;12:1424-32.
14. Choi J, Oh JY, Lee YS, Hur GY, Lee SY, Shim JJ, et al. Bacterial and viral identification rate in acute exacerbation of chronic obstructive pulmonary disease in Korea. Yonsei Med J 2019;60:216-22.
15. Adams SG, Melo J, Luther M, Anzueto A. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. Chest 2000;117:1345-52.
16. Miravitlles M, Espinosa C, Fernandez-Laso E, Martos JA, Maldonado JA, Gallego M. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD. Chest 1999;116:40-6.
17. Gallego M, Pomares X, Espasa M, Castaner E, Sole M, Suarez D, et al. Pseudomonas aeruginosa isolates in severe chronic obstructive pulmonary disease: characterization and risk factors. BMC Pulm Med 2014;14:103.
18. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006;2:CD004403.
19. Wilson R, Anzueto A, Miravitlles M, Arvis P, Alder J, Haverstock D, et al. Moxifloxacin versus amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: MAESTRAL results. Eur Respir J 2012;40:17-27.
20. Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med 2013;188:985-95.
21. Leung JM, Tiew PY, Mac Aogain M, Budden KF, Yong VF, Thomas SS, et al. The role of acute and chronic respiratory colonization and infections in the pathogenesis of COPD. Respirology 2017;22:634-50.
22. Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2015;10:1465-75.
23. Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;170:400-7.
24. Dhar R, Singh S, Talwar D, Mohan M, Tripathi SK, Swarnakar R, et al. Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry. Lancet Glob Health 2019;7:e1269-79.
25. Park YB, Rhee CK, Yoon HK, Oh YM, Lim SY, Lee JH, et al. Revised (2018) COPD clinical practice guideline of the Korean Academy of Tuberculosis and Respiratory Disease: a summary. Tuberc Respir Dis (Seoul) 2018;81:261-73.
26. Smith D, Gill A, Hall L, Turner AM. Prevalence, pattern, risks factors and consequences of antibiotic resistance in COPD: a systematic review. COPD 2021;18:672-82.
27. Nseir S, Di Pompeo C, Cavestri B, Jozefowicz E, Nyunga M, Soubrier S, et al. Multiple-drug-resistant bacteria in patients with severe acute exacerbation of chronic obstructive pulmonary disease: prevalence, risk factors, and outcome. Crit Care Med 2006;34:2959-66.
28. Contoli M, Pauletti A, Rossi MR, Spanevello A, Casolari P, Marcellini A, et al. Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. Eur Respir J 2017;50:1700451.
29. Eklof J, Ingebrigtsen TS, Sorensen R, Saeed MI, Alispahic IA, Sivapalan P, et al. Use of inhaled corticosteroids and risk of acquiring Pseudomonas aeruginosa in patients

with chronic obstructive pulmonary disease. Thorax 2022;77:573-80.
30. Shafiek H, Verdu J, Iglesias A, Ramon-Clar L, Toledo-Pons N, Lopez-Causape C, et al. Inhaled corticosteroid dose is associated with Pseudomonas aeruginosa infection in severe COPD. BMJ Open Respir Res 2021;8:e001067.
31. Prina E, Ranzani OT, Polverino E, Cilloniz C, Ferrer M, Fernandez L, et al. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. Ann Am Thorac Soc 2015;12:153-60.
32. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. Arch Intern Med 2009;169:219-29.
33. Janson C, Stratelis G, Miller-Larsson A, Harrison TW, Larsson K. Scientific rationale for the possible inhaled corticosteroid intraclass difference in the risk of pneumonia in COPD. Int J Chron Obstruct Pulmon Dis 2017;12:3055-64.
34. Soler N, Agusti C, Angrill J, Puig De la Bellacasa J, Torres A. Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. Thorax 2007;62:29-35.