ORIGINAL RESEARCH

The Relationship Between Comorbidities and Microbiologic Findings in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Purpose: Data regarding the relationship between microbiologic features and comorbidities in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) are limited. The aim of this study was to correlate microbiologic findings with comorbidities in patients with moderate to severe AECOPD.

Patients and Methods: This multicenter observational study included patients with AECOPD seen at 28 hospitals in South Korea between January 2015 and December 2018, and the data were retrospectively collected. Pathogens were examined in patients with either pulmonary or extrapulmonary comorbidities, and compared to those of patients without comorbidities. The relationship between pathogen type and the number of comorbidities was also evaluated.

Results: Bacterial infections (178 [37.2%] vs 203 [28.7%], p = 0.002) and co-infections with bacteria and viruses (65 [13.6%] vs 57 [8.1%], p = 0.002) were more prevalent in patients with pulmonary comorbidities. Bacterial pathogens (280 [34.7%] vs 101 [26.7%], p=0.006) were detected at a higher rate in patients with extrapulmonary comorbidities. Previous pulmonary tuberculosis (PTB), bronchiectasis, and diabetes mellitus were risk factors for bacterial infection, and congestive heart failure was a risk factor for bacterial and viral co-infection. As the number of comorbidities increased, the risk of bacterial infection increased considerably. *Pseudomonas aeruginosa* was more frequently identified in patients with previous PTB (57 [15.3%] vs 59 [7.4%], p < 0.001) and bronchiectasis (33 [19.6%] vs 83 [8.3%], p < 0.001).

Conclusion: AECOPD patients with comorbidities were more likely to experience infection-related exacerbations compared to those without comorbidities. As the overall number of comorbidities increased, the risk of bacterial infection increased significantly.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, comorbidity, bacteria, virus

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease with acute exacerbations throughout its course. Acute exacerbation of COPD (AECOPD) is defined as an acute worsening of respiratory symptoms that require additional treatment.[1] An AECOPD is associated with increased risks of hospitalization and mortality, and higher healthcare costs.[2–5]

Many patients with COPD have comorbidities that significantly influence their prognosis.[6] The presence of comorbidities in patients with COPD has been related to longer hospitalization, higher short-term mortality, and increased healthcare costs associated with hospitalization during an AECOPD.[7,8] Spece et al reported that patients with comorbidities were less likely to receive corticosteroid and antibiotic treatment during an AECOPD.[9] This may be due to the increased complexity of the overall treatment and concerns related to treatment-related adverse events.

COPD exacerbations can be triggered by several factors, including respiratory infections, air pollution, and other environmental conditions.[10] Of these, bacterial and viral infections are the major causes of AECOPD.[10–12] Therefore, appropriate antimicrobial treatment is important for managing AECOPD. Investigating the relationship between patient comorbidities and microbiologic features would help the selection of appropriate antimicrobial agents, thus aiding the management of AECOPD. However, data regarding this relationship are limited. The aim of this study was to explore the relationship between the microbiology and comorbidities of patients with moderate to severe AECOPD.

Materials and Methods

Study Design and Population

This multicenter observational study included patients that experienced an AECOPD between January 2015 and December 2018. Demographic, clinical, and microbiologic data were extracted from electronic medical records held by 28 hospitals in South Korea. Inclusion criteria included: aged > 40 years; COPD diagnosis confirmed by a pulmonary function test (post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity < 0.7) performed within 6 months before the onset of AECOPD; diagnosed with moderate to severe exacerbation, defined as acute worsening of respiratory symptoms that required antibiotics or systemic corticosteroid treatment or hospitalization; and patients who underwent both culture of lower respiratory tract samples, including sputum, tracheal aspirate, and bronchial washing fluid, and PCR test for viruses.

The positivity rate for bacterial or viral pathogens was investigated in patients with AECOPD who had pulmonary or extrapulmonary comorbidities. This was compared to the rate in patients without comorbidities. The association between the number of comorbidities and identity of the pathogen was also evaluated, in addition to the relationship between individual comorbidities and pathogen species. This study was approved by the Institutional Review Board of Kyungpook National University Hospital (KNHU IRB No. 2020-01-019). All the patients in the current study provided written informed consent for participation. This study was conducted in accordance with the guidelines of the 2013 Declaration of Helsinki.

Data Collection

Demographic data, including age, sex, smoking history, and body mass index, were collected. The presence and number of comorbidities in each patient were reviewed. Pulmonary comorbidities included previous pulmonary tuberculosis (PTB), bronchiectasis, and interstitial lung disease. Extrapulmonary comorbidities included diabetes mellitus, hypertension, liver cirrhosis, congestive heart failure (CHF), chronic kidney disease, cerebrovascular disease, and advanced cancer. Lung function according to FEV_1 and symptom severity according to the Modified Medical Research Council (mMRC) dyspnea scale were also reviewed. In addition, moderate or severe exacerbations in the previous year and treatments of COPD were recorded.

Microbiological Data

Microbiological data were collected from bacterial and viral pathogen test results. Pathogens were deemed as the causative agent of AECOPD if any of the following criteria were met: a culture of bacteria from a lower respiratory tract sample collected within 2 days of hospitalization plus a compatible Gram-stain finding; positivity for a respiratory virus (adenovirus, influenza [types A and B], parainfluenza virus [types 1, 2 and 3], rhinovirus, respiratory syncytial virus, bocavirus, metapneumovirus, coronavirus [229E and OC43] or enterovirus) in a throat or nasopharyngeal swab as determined by multiplex reverse transcriptase (RT)-PCR test (Real-Q RV Detection kit, BioSewoom, Korea; Anyplex II RV16, Seegene, Korea; AdvanSure RV, LG Life Sciences, Korea); identification of influenza A or B antigen in a throat or

nasopharyngeal swab (SD BIOLINE Influenza Antigen test, Standard Diagnostics, Yongin, Korea; BD Veritor System for Rapid Detection of FluA+B, BD Diagnostics, Sparks, MD, USA); presence of *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, or *Legionella pneumophila* in sputum, as confirmed by polymerase chain reaction (PCR) tests (Seeplex® PneumoBacter ACE Detection, Seegene, Korea; AmpliSens *Mycoplasma pneumoniae/Chlamydophila pneumoniae*-FEP PCR, Central Research Institute for Epidemiology, Moscow, Russia); *M. pneumoniae and C. pneumoniae* were identified based on a positive immunoglobulin M result in blood.

Statistical Analysis

Data are expressed as means with standard deviations for continuous variables, and as numbers with percentages for categorical variables. Student's *t*-test was used to compare continuous variables between groups and the chi-square test was used to compare categorical variables. Multiple logistic regression analysis was conducted to investigate the relationship between comorbidities and positive respiratory pathogen results. Age, gender, and ICS use were included as confounding variables when performing multiple logistic regression analyses. To assess the goodness-of-fit of the logistic regression models, the Hosmer–Lemeshow test was used. SPSS Statistics software (version 25.0; IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corp., Redmond, WA, USA) was used for the statistical analysis. A p-value < 0.05 was considered statistically significant.

Results

Enrolled Patients

Overall, 1186 patients with AECOPD were included in the study. The mean age of the enrolled patients was 73.78 ± 9.22 years and 979 (82.5%) were male (Table 1). Of the patients, 844 (73%) had a history of smoking, with a mean average of 38.74 ± 26.03 packs/year; 966 (81.5%) patients had at least one comorbidity, with pulmonary and extrapulmonary comorbidities being present in 478 (40.3%) and 808 (68.1%) patients, respectively. Of the pulmonary comorbidities, previous PTB (31.8%) was the most common, followed by bronchiectasis (14.2%) and interstitial lung disease (2.3%). The most common extrapulmonary comorbidities were hypertension (49.2%), diabetes mellitus (26.8%), and CHF (14.0%). The mean FEV_1 was 49.5% predicted, and the mean mMRC score was 2.25. Moderate and severe exacerbations in the previous year were 0.59 and 0.97, respectively. Nearly half of the patients received inhaled corticosteroid therapy.

Identification of Respiratory Pathogens

Causative pathogens were identified in 55.1% of the patients with AECOPD (Figure 1). Bacteria and viruses were detected in 32.1% and 33.2% of the patients, respectively. Bacterial and viral co-infections were identified in 10.3% of patients. Bacterial infections (178 [37.2%] vs 203 [28.7%], p = 0.002) and bacterial/viral co-infection (65 [13.6%] vs 57 [8.1%], p = 0.002) were more prevalent in patients with pulmonary comorbidities compared to those without pulmonary comorbidities. In patients with extrapulmonary comorbidities, all causative pathogens (463 [57.3%] vs 190 [50.3%], p = 0.023) and bacteria (280 [34.7%] vs 101 [26.7%], p=0.006) were more commonly detected than in those without extrapulmonary comorbidities.

To evaluate the relationship between individual comorbidities and the presence of respiratory pathogens, multiple logistic regression analysis was performed (Table 2). Previous PTB [odds ratio (OR) 1.426, 95% confidence interval (CI) 1.096–1.857, p=0.008], bronchiectasis (OR 1.437, 95% CI 1.020–2.024, p=0.038), and diabetes mellitus (OR 1.318, 95% CI 1.003–1.733, p=0.048) were associated with an increased likelihood of detecting bacteria (Hosmer–Lemeshow test, p= 0.625). Having CHF (OR 1.701, 95% CI 1.047–2.763, p=0.032) was a risk factor for bacterial and viral co-infection (Hosmer–Lemeshow test, p=0.953). No comorbidities showed statistically significant associations with all causative pathogens and viruses (Table S1).

The association between the number of comorbidities and likelihood of detecting a causative pathogen was also examined (Table 3). A multiple logistic regression analysis that included the number of comorbidities, age, sex, and use of inhaled corticosteroids was performed. The risk of bacterial infection increased significantly as the number of comorbidities increased. Compared to patients without comorbidities, the OR for bacterial infection was 1.430

Table 1 Baseline Characteristics of Patients with Acute Exacerbation of COPD (n=1186)

Characteristics	
Age, years	73.78 ± 9.22
Male sex	979 (82.5)
Smoking	
Never smoker	313 (27.1)
Current smoker	156 (13.5)
Ex-smoker	688 (59.5)
Pack-years	38.74 ± 26.03
BMI (kg/m2)	21.53 ± 3.98
Comorbidities	
Pulmonary comorbidities	
Previous pulmonary tuberculosis	377 (31.8)
Bronchiectasis	169 (14.2)
Interstitial lung disease	27 (2.3)
Extrapulmonary 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)
Lung function	
FEV_1, L	1.19 ± 0.54
FEV_1, %	49.46 ± 21.08
Modified medical research council	2.25 ± 0.88
Moderate exacerbations in the previous year	0.59 ± 1.27
Severe exacerbations in the previous year	0.97 ± 1.29
COPD treatment	
Inhaled treatment	
LABA	41 (3.5)
LAMA	172 (14.5)
LMMA/LABA	193 (16.3)
ICS-containing regimens	565 (47.6)

(*Continued*)

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Table 1 (Continued).

Characteristics	
ICS	36 (3.0)
ICS/LABA	185 (15.6)
ICS/LAMA/LABA	355 (29.9)
Xanthine derivative	365 (30.9)

Note: Data are presented as mean ±standard deviation or n (%).
Abbreviations: BMI, body mass index; FEV$_1$, forced expiratory volume in one second; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid.

(95% CI 1.008–2.027. p=0.045) in patients with one or two comorbidities and 2.101 (95% CI 1.409–3.132, p<0.001) in patients with three or more comorbidities (Hosmer–Lemeshow test, p=0.690).

Microbiologic Analysis of Patients with Pulmonary Comorbidities

Among all patients with AECOPD, the most frequently detected bacteria were *Pseudomonas aeruginosa* (9.9%), *M. pneumoniae* (8.2%), *Streptococcus pneumoniae* (5.0%), and *Klebsiella pneumoniae* (4.4%) (Table 4). The most frequently detected viruses were influenza A virus (10.9%), rhinovirus (10.4%), and respiratory syncytial virus (RSV) (4.3%).

The causative microorganisms in patients with and without pulmonary comorbidities were compared. Of the bacterial pathogens, *P. aeruginosa* was more commonly detected in patients with previous PTB (57 [15.3%] vs 59 [7.4%], p < 0.001) and bronchiectasis (33 [19.6%] vs 83 [8.3%], p < 0.001) than in those with no history of those conditions. *Escherichia coli* was more frequently identified in patients with bronchiectasis (11 [6.5%] vs 17 [1.7%], p < 0.001) and interstitial lung disease (4 [15.4%] vs 50 [4.4%], p = 0.003) than in those without those conditions. Of the viral pathogens, rhinovirus was less frequently
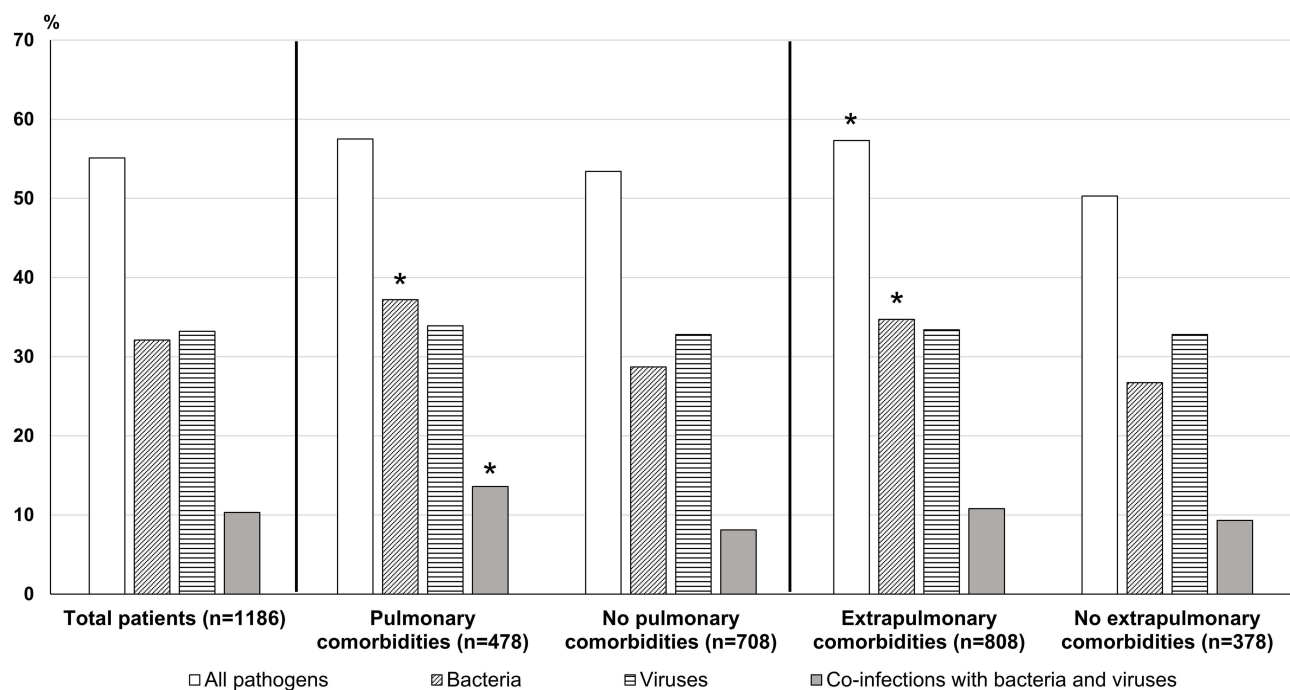

Figure 1 Identification of respiratory pathogens according to comorbidities in patients with acute exacerbation of chronic obstructive pulmonary disease. Asterisks (*) indicate a p-value < 0.05 in comparisons between patients with and without pulmonary comorbidities, and between patients with and without extrapulmonary comorbidities.

Table 2 Multiple Logistic Regression Analysis of Comorbidities for Identification of Bacteria and Co-Infection with Bacteria and Viruses

	Bacteria		Bacterial and Viral Co-Infection	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age	1.007 (0.993–1.022)	0.316	1.006 (0.985–1.028)	0.582
Male sex	0.764 (0.549–1.063)	0.111	0.920 (0.561–1.508)	0.740
Use of ICS	1.479 (1.155–1.894)	0.002	1.168 (0.798–1.711)	0.424
Pulmonary comorbidities				
Previous pulmonary tuberculosis	1.426 (1.096–1.857)	0.008	1.455 (0.984–2.151)	0.060
Bronchiectasis	1.437 (1.020–2.024)	0.038	1.481 (0.884–2.480)	0.136
Interstitial lung disease	1.378 (0.613–3.099)	0.437	1.172 (0.341–4.024)	0.801
Extrapulmonary comorbidities				
Diabetes mellitus	1.318 (1.003–1.733)	0.048	0.937 (0.604–1.454)	0.772
Hypertension	1.115 (0.860–1.445)	0.412	1.059 (0.710–1.579)	0.779
Liver cirrhosis	0.968 (0.398–2.356)	0.944	0.000	0.998
Congestive heart failure	1.256 (0.879–1.794)	0.211	1.701 (1.047–2.763)	0.032
Chronic kidney disease	1.075 (0.646–1.787)	0.781	1.731 (0.892–3.361)	0.105
Cerebrovascular disease	1.029 (0.603–1.756)	0.916	1.310 (0.621–2.761)	0.478
Advanced cancer	1.443 (0.991–2.101)	0.056	0.794 (0.412–1.528)	0.489

Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid.

detected in patients with previous PTB (23 [7.5%] vs 80 [11.7%], p = 0.047), while adenovirus was more frequently detected in patients with bronchiectasis (5 [3.7%] vs 8 [0.9%], p = 0.023), compared to those without those conditions.

Microbiologic Analysis of Patients with Extrapulmonary Comorbidities

The causative microorganisms in patients with and without extrapulmonary comorbidities were compared (Table 5 and Table S2). Of the bacterial pathogens, *E. coli* was more frequently detected in patients with diabetes mellitus than in those without diabetes mellitus (14 [4.5%] vs 14 [1.6%], p = 0.005). *M. pneumoniae* was more frequently detected in patients with CHF (22 [16.5%] vs 51 [6.7%], p < 0.001) and advanced cancer (15 [15.0%] vs 58 [7.3%], p = 0.008) than in those without those conditions. Of the viruses, RSV was more commonly detected in patients with CHF than in those without it (12 [8.3%] vs 30 [3.6%], p = 0.009). Adenovirus was more common in patients with chronic kidney disease than in those without the disease (3 [4.6%] vs 10 [1.1%], p = 0.048), and metapneumovirus was more frequently detected in patients with cerebrovascular disease than in those without (6 [9.0%] vs 30 [3.3%], p = 0.030).

Discussion

This study demonstrated that among patients with AECOPD, bacterial infections and viral/bacterial co-infections were more prevalent in those with than without pulmonary comorbidities. Bacterial pathogens were detected at higher rates in patients with extrapulmonary comorbidities. Previous PTB, bronchiectasis, and diabetes mellitus increased the risk of having a bacterial infection, while CHF increased the risk of experiencing a bacterial and viral co-infection. As the number of comorbidities increased, the risk of experiencing a bacterial infection increased considerably. Moreover, there was a correlation between pathogen species and the type of comorbidity. *P. aeruginosa* was more frequently detected in

Table 3 The Multivariate Adjusted Odds Ratios for Identification of Respiratory Pathogens According to the Number of Comorbidities

	All Pathogens		Bacteria		Viruses		Bacterial and Viral Co-Infection	
	Odds Ratio (95% CI)	**P-value**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Age	1.008 (0.995–1.021)	0.216	1.004 (0.991–1.018)	0.558	1.006 (0.993–1.020)	0.371	1.003 (0.982–1.024)	0.795
Male sex	0.693 (0.508–0.945)	0.020	0.757 (0.552–1.038)	0.084	0.809 (0.591–1.109)	0.188	0.824 (0.515–1.320)	0.421
Use of ICS	1.240 (0.984–1.562)	0.068	1.484 (1.159–1.900)	0.002	0.901 (0.706–1.149)	0.400	1.102 (0.756–1.606)	0.612
Number of comorbidities								
0	Reference		Reference		Reference		Reference	
1–2	1.456 (1.073–1.975)	0.016	1.430 (1.008–2.027)	0.045	1.461 (1.049–2.035)	0.025	2.239 (1.197–4.189)	0.012
≥ 3	1.514 (1.052–2.177)	0.025	2.101 (1.409–3.132)	<0.001	1.025 (0.688–1.527)	0.904	2.195 (1.092–4.413)	0.027

Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid.

Table 4 Microbiologic Analysis of AECOPD Patients with Pulmonary Comorbidities

	Total	Previous PTB			Bronchiectasis			Interstitial Lung Disease		
	n=1186	(+) (n=377)	(-) (n=809)	p-value	(+) (n=169)	(-) (n=1017)	p-value	(+) (n=27)	(-) (n=1159)	p-value
Bacteria										
Mycoplasma pneumoniae	73 (8.2)	23 (8.2)	50 (8.1)	0.954	11 (8.1)	62 (8.2)	0.994	1 (5.0)	72 (8.2)	>0.999
Chlamydia pneumoniae	18 (2.3)	5 (2.0)	13 (2.4)	0.740	4 (3.4)	14 (2.1)	0.317	0 (0.0)	18 (2.3)	>0.999
Legionella pneumophila	5 (0.8)	2 (1.1)	3 (0.7)	0.653	0 (0.0)	5 (1.0)	>0.999	1 (5.9)	4 (0.7)	0.134
Haemophilus influenzae	22 (1.9)	7 (1.9)	15 (1.9)	>0.999	2 (1.2)	20 (2.0)	0.758	0 (0.0)	2 (0.4)	>0.999
Streptococcus pneumoniae	59 (5.0)	20 (5.4)	39 (4.9)	0.725	10 (6.0)	49 (4.9)	0.562	2 (7.7)	22 (1.9)	0.381
Moraxella catarrhalis	10 (0.9)	2 (0.5)	8 (1.0)	0.517	1 (0.6)	9 (0.9)	>0.999	1 (3.8)	57 (5.0)	0.202
Pseudomonas aeruginosa	116 (9.9)	57 (15.3)	59 (7.4)	<0.001	33 (19.6)	83 (8.3)	<0.001	3 (11.5)	9 (0.8)	0.738
Klebsiella pneumoniae	51 (4.4)	17 (4.6)	34 (4.3)	0.813	4 (2.4)	47 (4.7)	0.174	1 (3.8)	113 (9.9)	>0.999
Escherichia coli	28 (2.4)	10 (2.7)	18 (2.3)	0.654	11 (6.5)	17 (1.7)	0.001	4 (15.4)	50 (4.4)	0.003
Staphylococcus aureus										
Methicillin-susceptible	5 (0.4)	2 (0.5)	3 (0.4)	0.656	1 (0.6)	4 (0.4)	0.540	0 (0.0)	5 (0.4)	>0.999
Methicillin-resistant	27 (2.3)	9 (2.4)	18 (2.3)	0.865	3 (1.8)	24 (2.4)	0.786	0 (0.0)	27 (2.4)	>0.999
Stenotrophomonas maltophilia	4 (0.3)	1 (0.3)	3 (0.4)	>0.999	1 (0.6)	3 (0.3)	0.463	0 (0.0)	4 (0.3)	>0.999
Virus										
Rhinovirus	103 (10.4)	23 (7.5)	80 (11.7)	0.047	15 (11.1)	88 (10.3)	0.769	1 (4.5)	102 (10.5)	0.719
Adenovirus	13 (1.3)	3 (1.0)	10 (1.5)	0.764	5 (3.7)	8 (0.9)	0.023	0 (0.0)	13 (1.3)	>0.999
Influenza A	124 (10.9)	43 (11.7)	81 (10.4)	0.507	19 (11.4)	105 (10.8)	0.792	4 (16.0)	120 (10.7)	0.339
Influenza B	39 (3.4)	18 (4.9)	21 (2.7)	0.055	4 (2.4)	35 (3.6)	0.440	0 (0.0)	39 (3.5)	>0.999
Respiratory syncytial virus	42 (4.3)	14 (4.6)	28 (4.1)	0.705	4 (3.0)	38 (4.5)	0.423	1 (4.5)	41 (4.2)	>0.999
Parainfluenza	38 (3.8)	11 (3.6)	27 (3.9)	0.790	6 (4.4)	32 (3.7)	0.693	1 (4.5)	37 (3.8)	0.581
Coronavirus	38 (3.8)	14 (4.6)	24 (3.5)	0.420	6 (4.4)	32 (3.7)	0.693	0 (0.0)	38 (3.9)	>0.999
Metapneumovirus	36 (3.6)	13 (4.3)	23 (3.4)	0.485	2 (1.5)	34 (4.0)	0.214	0 (0.0)	36 (3.7)	>0.999

Note: Data are presented as n (%). PTB, pulmonary tuberculosis.

Table 5 Microbiologic Analysis of AECOPD Patients with Diabetes Mellitus, Congestive Heart Failure, and Chronic Kidney Disease

	Diabetes Mellitus			Congestive Heart Failure			Chronic Kidney Disease		
	(+) (n=318)	(−) (n=868)	p-value	(+) (n=166)	(−) (n=1020)	p-value	(+) (n=76)	(−) (n=1110)	p-value
Bacteria									
Mycoplasma pneumoniae	26 (10.2)	47 (7.4)	0.169	22 (16.5)	51 (6.7)	<0.001	8 (12.1)	65 (7.9)	0.223
Chlamydia pneumoniae	6 (2.7)	12 (2.1)	0.627	2 (1.7)	16 (2.4)	>0.999	1 (1.8)	17 (2.3)	>0.999
Legionella pneumophila	2 (1.1)	3 (0.7)	0.639	2 (1.9)	3 (0.6)	0.205	1 (2.0)	4 (0.7)	0.348
Haemophilus influenzae	3 (1.0)	19 (2.2)	0.160	1 (0.6)	21 (2.1)	0.348	1 (1.3)	21 (1.9)	>0.999
Streptococcus pneumoniae	19 (6.1)	40 (4.7)	0.334	9 (5.5)	50 (5.0)	0.796	4 (5.3)	55 (5.0)	0.787
Moraxella catarrhalis	5 (1.6)	5 (0.6)	0.143	2 (1.2)	8 (0.8)	0.640	1 (1.3)	9 (0.8)	0.486
Pseudomonas aeruginosa	31 (9.9)	85 (9.9)	0.990	17 (10.3)	99 (9.9)	0.860	7 (9.3)	109 (10.0)	0.860
Klebsiella pneumoniae	16 (5.1)	35 (4.1)	0.448	8 (4.8)	43 (4.3)	0.742	3 (4.0)	48 (4.4)	>0.999
Escherichia coli	14 (4.5)	14 (1.6)	0.005	2 (1.2)	26 (2.6)	0.412	2 (2.7)	26 (2.4)	0.699
Staphylococcus aureus									
Methicillin-susceptible	1 (0.3)	4 (0.5)	>0.999	1 (0.6)	4 (0.4)	0.533	0 (0.0)	5 (0.5)	>0.999
Methicillin-resistant	8 (2.6)	19 (2.2)	0.735	5 (3.0)	22 (2.2)	0.572	4 (5.3)	23 (2.1)	0.089
Stenotrophomonas maltophilia	0 (0.0)	4 (0.5)	0.579	0 (0.0)	4 (0.4)	>0.999	0 (0.0)	4 (0.4)	>0.999
Virus									
Rhinovirus	27 (10.2)	76 (10.5)	0.918	14 (9.6)	89 (10.5)	0.730	9 (13.8)	94 (10.2)	0.345
Adenovirus	5 (1.9)	8 (1.1)	0.348	2 (1.4)	11 (1.3)	>0.999	3 (4.6)	10 (1.1)	0.048
Influenza A	40 (12.9)	84 (10.1)	0.175	14 (8.5)	110 (11.3)	0.289	9 (12.2)	115 (10.8)	0.709
Influenza B	10 (3.2)	29 (3.5)	0.830	2 (1.2)	37 (3.8)	0.092	5 (6.8)	34 (3.2)	0.102
Respiratory syncytial virus	6 (2.3)	36 (5.0)	0.062	12 (8.3)	30 (3.6)	0.009	3 (4.6)	39 (4.2)	0.753
Parainfluenza	11 (4.2)	27 (3.7)	0.735	9 (6.2)	29 (3.4)	0.113	3 (4.6)	35 (3.8)	0.733
Coronavirus	9 (3.4)	29 (4.0)	0.672	8 (5.5)	30 (3.6)	0.255	5 (7.7)	33 (3.6)	0.097
Metapneumovirus	11 (4.2)	25 (3.4)	0.594	5 (3.4)	31 (3.7)	0.894	2 (3.1)	34 (3.7)	>0.999

Note: Data are presented as n (%).

patients with previous PTB and bronchiectasis, while *E. coli* was more commonly detected in patients with bronchiectasis, interstitial lung disease, and diabetes mellitus.

In previous studies, the most commonly isolated bacteria in patients with AECOPD were *Haemophilus influenzae, S. pneumoniae, Moraxella catarrhalis*, and *P. aeruginosa*.[11] However, *H. influenzae* and *M. catarrhalis* were not commonly identified in our study. According to a study conducted at a tertiary hospital in South Korea, *P. aeruginosa* was the most common cause of AECOPD, with *H. influenzae* accounting for 5.3% and *M. catarrhalis* accounting for 1.1%.[13] The prevalence of *H. influenzae* and *M. catarrhalis* in patients with community-acquired pneumonia in the Korean population were also lower than in other countries.[14] We assume that the low detection rate of these pathogens may be related to regional differences and laboratory environmental factors.

Many patients with COPD have comorbidities, and those with more advanced COPD are more likely to have comorbidities.[7] This is associated with an increased risk of experiencing acute exacerbation and mortality.[15,16] Moreover, many patients with COPD have more than one comorbidity.[17] According to a previous study, the overall number of comorbidities has been related to the frequency of experiencing acute exacerbation.[18] Previous studies have also demonstrated that comorbidities are highly prevalent among patients experiencing AECOPD,[19] which was associated with longer hospitalization and a higher likelihood of mortality.[6–9] Therefore, the presence of comorbidities must be recognized in the management of patients with AECOPD, which require more complex and individualized therapy.

The findings of this study suggested that respiratory infection was more likely to be a cause of exacerbation in patients with AECOPD who had comorbidities compared to those who did not. A previous study also demonstrated that infection-related exacerbations were more severe than exacerbations that were not related to infections.[12] Considering the high incidence of infection-related AECOPD in patients with comorbidities and the severity of infection related exacerbation, efforts to identify causative pathogens to guide the appropriate use of antimicrobial agents are required in AECOPD patients with comorbidities. In addition, exacerbations caused by bacterial and viral co-infection are more severe than infection caused by bacteria or viruses alone.[10,12] In this study, bacterial and viral co-infections occurred more often in patients with than without pulmonary comorbidities. In, addition, CHF was a risk factor for bacterial and viral co-infection. A recent study investigated the efficacy of a vaccine targeted at non-typeable *H. influenzae* and *M. catarrhalis* in preventing AECOPD.[20] Our study will aid in determining which subgroups require vaccination against a particular pathogen.

P. aeruginosa may be associated with an increased risk of exacerbation and death in patients with COPD.[21] Furthermore, *P. aeruginosa* in the sputum of patients hospitalized for AECOPD has been identified as an independent prognostic factor for 3-year mortality.[22] Therefore, in patients with AECOPD who have risk factors for *P. aeruginosa* infection, it is more crucial to use a sputum culture to identify the causative bacteria, and the use of antipseudomonal agents should be considered. In this study, *P. aeruginosa* as a causative pathogen, was more common in patients experiencing AECOPD who had bronchiectasis or previous PTB. In patients with bronchiectasis, *P. aeruginosa* is well known to be a common cause of respiratory infection.[23,24] Additionally, the presence of *P. aeruginosa* is associated with more severe disease and a higher risk of mortality.[25] It was previously reported that COPD patients with prior PTB were more likely to have a positive *P. aeruginosa* culture during an exacerbation, and showed a higher prevalence of bronchiectasis.[26] Previous PTB is a risk factor for bronchiectasis,[27,28] and coexisting bronchiectasis might be associated with a higher rate of detection of *P. aeruginosa* in patients with AECOPD and previous PTB.

E. coli is an uncommon respiratory pathogen, but can cause respiratory tract infections in the elderly and those with compromised immunity.[29] According to previous studies, *E. coli* pneumonia was associated with comorbidities such as diabetes mellitus, cerebrovascular disease, and chronic lung diseases.[29,30] In this study of patients with AECOPD, *E. coli* was not a common causative agent, but it was significantly more prevalent in patients with bronchiectasis, interstitial lung disease, and diabetes mellitus. Previous investigations of the relationship between bacteriologic etiology and lung function in patients with AECOPD demonstrated that *P. aeruginosa* and *Enterobacteriaceae* were predominant in patients with severely impaired lung function.[31,32] Since accompanying pulmonary diseases might contribute to decreased lung function in patients with COPD, the results of this study support those of the previous ones.

Viral infection is an important cause of exacerbation of COPD. Viruses have been identified in 20–40% of patients with AECOPD.[33] Atypical bacteria, such as *M. pneumoniae* and *C. pneumoniae*, also contribute to AECOPD.[10]

However, data regarding the relationship between comorbidities and infection with a virus or atypical bacteria are scarce. Further study based on the present one may yield additional useful information.

This study had several limitations. First, data regarding comorbidities were retrospectively obtained from electronic medical records. Therefore, the prevalence of comorbidities might be underestimated. Compared to other studies investigating patients with AECOPD, the prevalence rates of most comorbidities in this study were similar. However, the prevalence of heart failure was relatively lower, and the prevalence of advanced cancer was relatively higher.[9,19] In addition, chest computed tomography was not performed in all patients, so our ability to confirm the pulmonary comorbidities was limited. Second, the numbers of patients with AECOPD who had comorbidities such as liver cirrhosis and interstitial lung disease were too small to establish definitive conclusions. Third, serologic tests for atypical bacteria, and PCR tests for atypical bacteria and certain viruses, were not performed in all patients with AECOPD. Fourth, COPD severity, such as the GOLD group, was not included in the multiple logistic regression analyses for identification of pathogens.

Conclusion

In conclusion, patients with moderate to severe AECOPD who had comorbidities were more likely to have an infection-related exacerbation than those without comorbidities. Bacterial infection was associated with previous PTB, bronchiectasis, and diabetes mellitus. Bacterial and viral co-infection was associated with congestive heart failure. The risk of experiencing a bacterial infection increased significantly as the number of comorbidities increased. Of the causative pathogens, *P. aeruginosa* was more common in patients with previous PTB and bronchiectasis. Because infections are the major cause of AECOPD, pathogen identification and appropriate antimicrobial therapy are important in the management of AECOPD patients. Our findings suggest that in AECOPD patients with comorbidities, a more careful diagnostic evaluation for causative pathogens is required. In addition, our findings may help with the selection of empirical antimicrobial drugs in AECOPD patients with comorbidities.

Disclosure

The authors report no conflicts of interest in this work.

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