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Health Sciences: Research Article

Bacterial pathogens causing community–acquired pneumonia in hospitalized adult patients with and without chronic obstructive pulmonary disease

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ABSTRACT

Background: Community-acquired pneumonia (CAP) is a common infection that often occurs in older adults who may have chronic obstructive pulmonary disease (COPD), a common respiratory condition characterized by airflow limitation. Chronic obstructive pulmonary disease and community-acquired pneumonia usually cause the same symptoms as respiratory tract infections, but they have potential differences in microbial etiology. This study aimed to assess the potential of bacterial pathogens in hospitalized CAP patients with and without COPD as well as bacterial combinations and to examine different rates of bacterial pathogens causing CAP between patients with and without COPD. **Methods:** This is a multicenter study conducted on hospitalized adult patients with community-acquired pneumonia with and without chronic obstructive pulmonary disease at the Respiratory Department of Nguyen Tri Phuong Hospital, Nhan Dan Gia Dinh Hospital and University Medical Center from 04/2021 to 03/2023. Collected sputum samples that were assessed as reliable (according to the Bartlett scale) were included in the study. The sputum samples were transported to Nam Khoa Company's laboratory to carry out multiplex real-time PCR with King Fisher FLEX as the nucleic acid extraction instrument and CFX 96^{TM} of Bio-Rad as the real-time PCR system. For statistical analysis, data collection was solved by SPSS 20.0 software and Microsoft Excel 2020. **Results:** Among 341 CAP patients, there were 91 patients (26.7%) with COPD, in which 89 patients were detected with a bacterial infection. The positive rates were 97.8% in CAP patients with COPD and 54.0% in CAP patients without COPD (p<0.001). Bacterial pathogens that caused CAP in patients with and without COPD extended to gram-negative bacilli. The top 5 bacterial pathogens in CAP patients with and without COPD were *Acinetobacter baumannii* (25.3% & 14.4%), *Haemophilus influenzae* (23.1% & 10.8%), *Klebsiella pneumoniae* (22.0% & 17.2%), *Streptococcus pneumoniae* (20.9% & 14.8%) and *Escherichia coli* (13.2% & 8.4%), in which the different percentages of *Acinetobacter baumannii* and *Haemophilus influenzae* were statistically significant (p < 0.05). *Pseudomonas aeruginosa* was found at a low frequency (1.1% & 5.6%). Atypical bacteria were detected for only *Mycoplasma* at low frequencies (4.4% & 6.8%) and often occurred as a combined bacterium. *Klebsiella pneumoniae* and *Escherichia coli* in CAP with COPD and *Acinetobacter baumannii* and *Escherichia coli* in CAP without COPD were not often defined as the primary bacteria alone. More than one bacterial pathogen was commonly found in the sputum of CAP patients with and without COPD. **Conclusions:** CAP patients with COPD occur at a rate of 26.7%. Bacterial pathogens were detected in 97.8% of CAP patients with COPD and 54.0% of CAP patients without COPD (p < 0.001), and they extended to gram-negative bacilli. The top 5 bacterial pathogens in the two groups were the same with different rates, in which the different rates of *Acinetobacter baumannii* and *Haemophilus influenzae* were statistically significant (p < 0.05). *Pseudomonas aeruginosa* is found less commonly, although it is important because of its critical antibiotic resistance and mortality. Atypical bacteria are detected for only *Mycoplasma* in low frequency, and it often occurs as a combined bacterium. *Klebsiella pneumoniae* and *Escherichia coli* in CAP with and without COPD are rarely or not defined as the primary bacteria alone. More than one bacterial pathogen is commonly found in the sputum of CAP patients with and without COPD.

Key words: Hospitalized community-acquired pneumonia, chronic obstructive pulmonary disease, bacterial pathogens, combined bacteria

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INTRODUCTION

Community-acquired pneumonia (CAP) is a common infection that occurs in any individual at any age, especially in older adults, who may have chronic obstructive pulmonary disease (COPD), a common respiratory condition characterized by abnormalities of the airways [1]. Chronic obstructive pulmonary disease is also one of the leading causes of morbidity

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and mortality worldwide. Recent projections predict that by 2030, it will be the fourth main cause of death and the seventh cause of the global burden of infectious disease [2]. Chronic obstructive pulmonary disease and community-acquired pneumonia usually cause the same symptoms as respiratory tract infections, but they have potential differences in microbial etiology [1,3]. Otherwise, as a consequence of its chronicity, chronic obstructive pulmonary disease causes high resource utilization with clinician office visits and frequent hospitalization due to acute exacerbation for treatment, especially with antibiotics for microbial infection [4–6]. Hospitalized community-acquired pneumonia, with or without chronic obstructive pulmonary disease, is hard to identify the pathogenic bacteria since the primary specimen is often taken from patients' sputum, which is at high risk of contamination when passing through the oropharynx. Therefore, traditional cultural techniques are limited due to many difficulties [7]: most patients have taken antibiotics, and the bacteria could still be alive in the alveola or bronchial epithelia fluid but could have already perished in the sputum. In addition, several subjective reasons from the laboratory could reduce the ability to successfully culture pathogens, such as a lack of adequate environment to isolate the primary pathogens while they are often difficult to culture, samples that cannot be cultured as quickly as possible to increase the chance of detecting pathogens, inexperienced technicians hence unable to choose the right pathogen colonies on the isolating agar plates, or the sample was not assessed for its reliability to remove nonsputum fluid such as viscous mucus in the oropharynx prior to the isolation procedure. To overcome such difficulties, multiplex real-time PCR was used as the optimal technique, which has also proven its high sensitivity and specificity. Multiplex real-time PCR can not only simultaneously detect the specific nucleic acid sequence of the bacteria but also calculate the number of copies to allow the identification of bacterial agents as pathogens. The aims of this study were (1) to assess the potential of bacterial pathogens in hospitalized patients with community-acquired pneumonia with and without chronic obstructive pulmonary disease as well as bacterial combinations. (2) To examine different rates of bacterial pathogens that caused community-acquired pneumonia between patients with and without chronic obstructive pulmonary disease.

METHODS

This is a multicenter study conducted on hospitalized adult patients with community-acquired pneumonia with and without chronic obstructive pulmonary disease at the Respiratory Department of Nguyen Tri Phuong Hospital, Nhan Dan Gia Dinh Hospital and University Medical Center from 04/2021 to 03/2023. Collected sputum samples that were assessed as reliable (according to the Bartlett scale) were included in the study. The samples were transported to Nam Khoa Company's laboratory to carry out multiplex real-time PCR in which DNARNAprep-MAGBEAD (from Nam Khoa Co.) and King Fisher FLEX (from Thermo) were used for the nucleic acid extraction step; multiplex real-time PCR mixes specific for bacterial pathogens causing pneumonia (Nam Khoa Co.) and the CFX 96^{TM} real-time PCR machine (from Bio-Rad) were used for the amplification step to detect and quantify the target nucleic acid by real-time PCR. Bacterial agents were identified as pathogens when their quantitative measurement was $\geq$ 100.000 copies. For atypical bacteria, the detected bacteria were identified as pathogenic agents regardless of their quantity. Bacteria with the highest quantity were considered primary pathogens, and others with lower quantities were considered combined agents [7,8]. For statistical analysis, data collection was performed using SPSS 20.0 and Microsoft Excel 2020 software.

For ethical considerations, we only practiced in the laboratory to detect bacterial pathogens causing community-acquired pneumonia due to the requirement of clinical doctors. The researcher had no contact with patients or clinical doctors for requirements. Our research was approved by the Independent Ethical Committee (IEC) of the University of Medicine and Pharmacy HCMC at Decision No 330/DHYD-HDDD, issue: June 14th, 2019.

RESULTS

There were 341 sputum samples from hospitalized adult patients with community-acquired pneumonia that matched the inclusion criteria of this study. The demographic data and the results of bacterial detection by multiplex real-time PCR are shown in Table 1. Table 1 shows that the incidence of community-acquired pneumonia patients with COPD was only 26.7% among the 341 CAP patients. Male sex accounted for 90.1% of patients with COPD and 52.4% of patients without COPD, and the rates of bacterial pathogens detected in patients with COPD and without COPD were 97.8% and 54.0%, respectively. This difference was statistically significant (p<0.001).

In 91 CAP patients with COPD, 89 patients were detected with bacterial pathogens. The positive rate was 97.8%. The bacterial pathogens causing CAP in 91

Table 1: Demographic data and bacterial detection by MPL-rPCR

Characteristics	Patients with COPD (91) n (%)	Patients without COPD (250) n (%)	p value
Gender Female Male	9 (9.9) 82 (90.1)	119 (47.6) 131 (52.4)	p < 0.001
Age 16 - 60 years > 60 years	20 (22.0) 71 (78.0)	72 (28.8) 178 (71.2)	p = 0.209
CAP patients	91 (26.7)	250 (73.3)	p < 0.001
Positive rate	89 (97.8)	135 (54.0)	p < 0.001

Table 2: The proportion of bacterial pathogens in CAP patients with COPD

Pathogens			N	%*
gram-positive (38)		*Streptococcus pneumoniae*	19	20.9
		Streptococcus agalactiae	2	2.2
		Staphylococcus aureus (MRSA)	1	1.1
		Staphylococcus epidermidis (MRSE)	11	12.1
		Coagulase negative staphylococcus	2	2.2
		Enterococcus faecalis	2	2.2
		Enterococcus faecium	1	1.1
gram-negative (98)	Enterobacteriaceae (37)	*Escherichia coli*	12	13.2
		Klebsiella pneumoniae	20	22.0
		Morganella morganii	3	3.3
		Providencia sp.	2	2.2
	Others (61)	*Acinetobacter baumannii*	23	25.3
		Burkholderia cepacia	3	3.3
		Pseudomonas aeruginosa	1	1.1
		Moraxella catarrhalis	3	3.3
		Haemophilus influenzae	21	23.1
		Haemophilus influenzae type B	1	1.1
		Stenotrophomonas maltophilia	9	9.9
Atypical bacteria (4)		*Mycoplasma sp.*	4	4.4

* The percentage among 91 sputum samples collected from CAP patients with COPD

patients with COPD detected by multiplex real-time PCR are shown in Table 2.

The data from Table 2 show that bacterial pathogens that caused CAP in patients with COPD extended to gram-negative bacilli, in which *Acinetobacter baumannii* was at the highest rate (25.3%), followed by *Haemophilus influenzae* (23.1%) and *Klebsiella pneumoniae* (22.0%). *Pseudomonas aeruginosa* was found to be less common (1.1%). *Mycoplasma*, an atypical bacterium, was isolated in 4.4%. In many cases, more than one bacterial pathogen was isolated from the sputum of CAP patients with COPD.

Among 250 CAP patients without COPD, 135 patients were detected with bacterial pathogens. The positive rate was 54.0%. The bacterial pathogens detected by multiplex real-time PCR of the sputum samples collected from 250 CAP patients without COPD are shown in Table 3.

According to Table 3, the list of bacterial pathogens that caused CAP in patients without COPD extended to gram-negative patients, in which *Klebsiella pneumoniae* was at the highest rate (17.2%), followed by *Streptococcus pneumoniae* (14.8%) and *Acinetobacter baumannii* (14.4%). *Mycoplasma*, an atypical bacterium, was found at a rate of 6.8%. In many cases, more than one bacterial pathogen was isolated from the sputum samples of CAP patients without COPD.

From the list of bacterial pathogens that caused CAP in patients with and without COPD, we selected the top 5 bacterial pathogens, which are shown in Table 4.

Data from Table 4 show that the top 5 bacterial pathogens detected in CAP with and without COPD were the same however, their percentages in CAP with COPD were higher than those in CAP without COPD, in which the different percentages of *Acinetobacter baumannii* and *Haemophilus influenzae* were statistically significant ($p < 0.05$). Based on the copy number of the bacterial pathogens detected by multiplex real-time PCR, we defined the causative bacteria as the primary bacterial pathogen (the one with the highest copy number) and the combined bacterial pathogens (the one with the lowest copy number).Table 5 shows the combination of the top 5 bacterial pathogens detected by multiplex real-time PCR in 91 CAP patients with COPD and 250 CAP patients without COPD.

The data from Table 5 show that *Escherichia coli* occurred as the only combined bacteria in CAP patients with COPD, whereas *Streptococcus pneumoniae* and *Haemophilus influenzae* were detected commonly as primary bacteria alone in CAP patients without COPD.

DISCUSSION

In our study, the rate of CAP patients with COPD aged over 60 years was 78.0%, and the rate of male sex was 90.1%. These rates were similar to the reports by previous authors: Julio A., Ramirez and Rodrigo Cavallazzi (74.0% and 90.5%) [9], Xue-Jun Li MD (75.3% and 71.0%) [10], Joan Gómez-Junyent (79.9% and 90.5%) [11], Dang Quynh Giao Vu, Le Thuong Vu (87.6% and 88.5%) [12]. There has been a significant increase in the age of CAP patients with and without COPD over the past decade, probably because of the increasing age of the population [13]. Community-acquired pneumonia patients with COPD had a prevalence rate of 26.7% (91/341), similar to the reports by Sogaard M (33.3%) [14], Amir Sharafkhaneh (32.7%) [15], Joan Gómez-Junyent (23.9%) [11] and Pascual-Guardia (21%) [16].

Although COPD was only 26.7% in total CAP patients, the proportion of bacterial pathogens (positive rate) was 97.8%, while in CAP patients without COPD, the proportion was 54.0%. There was a statistically significant difference in the pathogen detection rate between these two groups of patients ($p < 0.001$). The pathogen detection rate in CAP patients with COPD by Ly Khanh Van and Pham Hung Van was 69.0% [17], lower than that in our research (97.8%). The pathogen detection rates in CAP patients without COPD were 53% by Xue-Jun Li MD [10] and 53.8% by Dao Thi My Ha [18], similar to our study (54.0%). Some previous reports indicated that the microbial etiology of CAP in patients with COPD may differ from that of CAP patients without COPD, and more than one bacterial pathogen was found in the sputum of CAP patients with and without COPD [11,13,19–21].

In CAP patients with COPD, *Acinetobacter baumannii* was the most prevalent at 25.3%, while *Streptococcus pneumoniae* was only at 20.9% (Table 4). In contrast, some previous reports indicated that in CAP patients with COPD, *Streptococcus pneumoniae* was the most prevalent at 39.4% [11], 45.7% [22], 32.6% [23] and 28.8% [24]. Other previous studies reported that *Streptococcus pneumoniae* occurred less frequently than gram-negative bacilli in recent days, but it still plays a role in causing CAP in adult patients [3,11,13,21,22,25,26].

In our study, bacterial pathogens causing CAP in patients with and without COPD extended to gram-negative bacteria more than gram-positive bacteria (Tables 2 and 3), similar to reports by previous authors [9,12,14,21,27]. Perhaps gram-negative bacilli, especially *Acinetobacter baumannii* and *Klebsiella pneumoniae* , have increased in CAP patients with COPD as well as without COPD in recent days.

Table 3: The proportion of bacterial pathogens in CAP patients without COPD

Pathogens			N	%*
gram-positive (70)		*Streptococcus pneumoniae*	37	14.8
		Staphylococcus aureus (MRSA)	7	2.8
		Staphylococcus aureus (MSSA)	1	0.4
		Coagulase negative staphylococcus	2	0.8
		Staphylococcus epidermidis (MRSE)	10	4.0
		Enterococcus faecalis	5	2.0
		Enterococcus faecium	8	3.2
gram-negative (192)	Enterobacteriaceae (88)	*Escherichia coli*	21	8.4
		Klebsiella pneumoniae	43	17.2
		Enterobacter cloaceae	1	0.4
		Morganella morganii	9	3.6
		Providencia sp.	9	3.6
		Proteus mirabilis	5	2.0
	Others (104)	*Acinetobacter baumannii*	36	14.4
		Burkholderia cepacia	6	2.4
		Pseudomonas aeruginosa	14	5.6
		Moraxella catarrhalis	1	0.4
		Haemophilus influenzae	27	10.8
		Stenotrophomonas maltophilia	20	8.0
Atypical bacteria (17)		*Mycoplasma sp.*	17	6.8

* The percentage among 250 sputum samples collected from CAP patients without COPD

Table 4: The top 5 bacterial pathogens causing CAP with or without COPD

CAP with COPD		CAP without COPD		p - value
Pathogens	**n (%)**	**Pathogens**	**n (%)**	
Acinetobacter baumannii	23 (25.3)	*Acinetobacter baumannii*	36 (14.4)	0.018
Haemophilus influenzae	21 (23.1)	*Haemophilus influenzae*	27 (10.8)	0.003
Klebsiellla pneumoniae	20 (22.0)	*Klebsiellla pneumoniae*	43 (17.2)	0.314
Streptococcus pneumoniae	19 (20.9)	*Streptococcus pneumoniae*	37 (14.8)	0.180
Escherichia coli	12 (13.2)	*Escherichia coli*	21 (8.4)	0.186

Table 5: The combination of the top 5 bacterial pathogens causing CAP with and without COPD

Pathogen *	Primary alone	Primary in combination	Combined only	Combined bacteria mainly common
CAP with COPD				
A. baumannii (23)	5	5	13	*E. coli* *H. influenzae* *K. pneumoniae*
H. influenzae (21)	6	5	10	*S. pneumoniae* *A. baumannii*
K. pneumoniae (20)	1	4	15	*E. coli* *S. maltophilia*
S. pneumoniae (19)	3	6	10	*K. pneumoniae* *H. influenzae*
E. coli (12)	0	4	8	*M. morganii* *Providencia sp.*
CAP without COPD				
K. pneumoniae (43)	8	12	23	*A. baumannii* *P. aeruginosa* *E. coli*
S. pneumoniae (37)	14	12	11	*K. pneumoniae* *H. influenzae* *M. catarrhalis*
A. baumannii (36)	5	8	23	*K. pneumoniae* *S. pneumoniae* *E. faecalis* *E. faecium*
H. influenzae (27)	13	5	9	*S. pneumoniae* *A. baumannii* *Mycoplasma sp.*
E. coli (21)	2	4	15	*A. baumannii* *M. catarrhalis*

(*) Bacterial pathogens can play a role as primary bacteria alone or as a primary bacterium in combination or as only combined bacteria.

In our study, the top 5 bacterial pathogens in CAP with and without COPD were the same as *Acinetobacter baumannii*, *Haemophilus influenzae, Klebsiella pneumoniae, Streptococcus pneumoniae*, and *Escherichia coli* but at different prevalence rates, in which the different percentages of *Acinetobacter baumannii* and *Haemophilus influenzae* were statistically significant ($p < 0.005$), similar to the report by previous authors [3,10,11,23].

In this study, *Pseudomonas aeruginosa* causing CAP in patients with and without COPD was counted at rates of 1.1% and 5.6%, respectively (Tables 2, 3). Although *Pseudomonas aeruginosa* was counted at a low rate, it was important because of risk factors such as antibiotic resistance, mortality and outcomes [10,13,17,27–31]. Furthermore, previous studies have reported that *Pseudomonas aeruginos*a played an important role in CAP patients with severe COPD who were elderly and associated with regular oral corticosteroid therapy [31–33].

Atypical bacteria were detected for only *Mycobacteria* at low frequency in CAP patients with COPD (4.4%) and without COPD (6.8%), similar to a previous report by De-Shun Liu (6.5%) [3]. Some recent studies have suggested that atypical bacteria in CAP patients are rare and often occur as combined bacteria, along with typical bacterial pathogens [34–36].

In the bacterial combination, our study showed that *K. pneumoniae*, *A. baumannii*, *H. influenzae*, *S. pneumoniae* and *E. coli* can play a role as primary bacterial

pathogens as well as combined bacterial pathogens in which *K. pneumoniae* and *E. coli* were rarely or not found as the primary bacteria alone in CAP with and without COPD.

CONCLUSIONS

Among 341 CAP patients, 91 patients had COPD (26.7%), 97.8% had bacterial pathogens detected by multiplex real-time PCR, and the positive rate in CAP patients without COPD was 54.0% ($p < 0.001$). Bacterial pathogens causing CAP in patients with and without COPD extend to gram-negative bacilli. The top 5 bacterial pathogens in the two groups were the same with different rates, in which the different rates of *Acinetobacter baumannii* and *Haemophilus influenzae* were statistically significant ($p < 0.05$). *Pseudomonas aeruginosa* is less common, although it is important because of its critical antibiotic resistance and mortality. Atypical bacteria are detected for only *Mycoplasma* at low frequency and often occur as a combined bacterium. *Klebsiella pneumoniae* and *Escherichia coli* in CAP with and without COPD are rarely or not defined as the primary bacteria alone. More than one bacterial pathogen is commonly found in the sputum of CAP patients with and without COPD.

ABBREVIATIONS

CAP: Community-acquired pneumonia
CMV: Cytomegalo virus
COPD: Chronic Obstructive Pulmonary Disease
EBV: Epstein-Barr virus
IEC: Independent Ethics Committee
MRSA: Methicillin-Resistant *Staphylococcus aureus*
MRSE: Methicillin-resistant *Staphylococcus epidermidis*
MSSA: Methicillin-susceptible *Staphylococcus aureus*

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Conceptualization, writing original protocol: L.K.V and L.V.X.; investigation writing – original draft, and collecting data: L.K.V.; protocol review: L.V.X.; formal analysis: L.K.V; writing – review and editing: L.K.V, L.V.X and P.H.V; All authors, including L.K.V, L.V.X and P.H.V revised the manuscript and agreed to the final version before submission.

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