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Serum inflammatory biomarkers and clinical outcomes of COPD exacerbation caused by different pathogens

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Background and objective: COPD exacerbation is characterized by worsening of symptoms, warranting change in treatment. Systemic and airway inflammation play roles in the pathogenesis of COPD exacerbation. We hypothesized whether increased serum inflammatory biomarkers are associated with the clinical outcomes of COPD exacerbation caused by different infectious pathogens.

Methods: COPD patients with exacerbation were recruited from a hospital emergency department during 2014–2015. Serum procalcitonin (PCT) and C-reactive protein (CRP) were measured. Dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation (DECAF) score was calculated for predicting mortality. Multiplex polymerase chain reaction was carried out for respiratory viral assay from nasopharyngeal swabs, and sputum bacterial culture was also performed. Hospital mortality, invasive mechanical ventilation requirement, and length of hospital stay (LOS) were evaluated, and their associations with clinical characteristics, DECAF score, and serum biomarkers were examined.

Results: A total of 62 COPD patients were enrolled. These patients were classified as Global Initiative for Obstructive Lung Disease (GOLD) stage 2, 3, and 4 in 12.9%, 6.4%, and 80.7% of cases, respectively. Isolated bacterial exacerbation was recovered in 30.6% of exacerbation episodes: *Klebsiella pneumoniae* was the most commonly identified bacteria. Viral pathogens and coinfections were noted in 9.6% and 16.1% of exacerbated patients, respectively. Influenza was the most commonly detected viral pathogen. Serum biomarkers and DECAF score for viruses, bacteria, coinfection, and noninfectious causes of exacerbations were similar. Neither DECAF score nor serum biomarkers were able to differentiate patients with and without mortality or requiring mechanical ventilation. Increased serum PCT was noted in patients with LOS ≥7 days when compared with those with LOS <7 days (0.38 ng/mL vs 0.1 ng/mL; P=0.035).

Conclusion: Increased serum PCT is associated with longer LOS in COPD exacerbation. However, CRP and DECAF score play limited roles in predicting clinical outcome and lack an association with causes of exacerbation.

Keywords: biomarkers, inflammation, viruses, bacteria, COPD exacerbation, outcome

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Introduction

COPD is the fourth leading cause of death worldwide, a public health challenge that is preventable and treatable.[1] Exacerbation episodes are a hallmark of this disease. COPD exacerbation is characterized by a change in the patient's baseline dyspnea, cough, and/or sputum beyond day-to-day variability sufficient to lead to a change in medication. Exacerbation is associated with not only disease progression but also increased mortality.[2] Infectious causes (bacteria, viruses, and atypical pathogens)

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and non-infectious causes (environmental exposure and poor compliance with medications) have been described.[3,4] Antibiotics have been shown to reduce mortality and treatment failure.[5] Therefore, COPD guidelines of the Global Initiative for Obstructive Lung Disease (GOLD) recommend antibiotics for the treatment of exacerbations in the presence of purulent sputum.[1,6,7] However, clinical findings and laboratory investigations cannot distinguish viral from bacterial exacerbation or pneumonia.[4,8] Over-utilization of antibiotics in the absence of bacterial infection can cause serious drug resistance problems, while under-treatment is related to poor outcomes. The dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation (DECAF) score was developed and further validated for predicting mortality in COPD exacerbation.[9] DECAF aids clinicians in accurate prognosis, allows triage of patients to an appropriate level of care, and improves clinical outcomes.[10]

Apart from the clinical score, inflammatory biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) are promising tools for differentiating bacterial from non-bacterial respiratory infection in adults and children.[11] PCT has shown potential for predicting outcome in lower respiratory tract infections and minimizing unnecessary antibiotic use.[12–16] Increased PCT was reported in patients hospitalized with COPD exacerbation or pneumonia with proven bacterial infection.[17] In addition, CRP and copeptin have been evaluated for identifying causes and predicting exacerbation outcomes.[18] However, the roles of biomarkers for differentiating viral infections from bacterial infections causing COPD exacerbation are limited. We hypothesized whether increased serum inflammatory biomarkers are able to discriminate bacterial infection from viral or noninfectious causes of COPD exacerbation in an emergency room setting.

Methods

A cross-sectional study was conducted at Ramathibodi Hospital, Mahidol University, Thailand, between August 2014 and December 2015. Patients with COPD exacerbation at the emergency department were enrolled. All patients provided written, informed consent prior to participation in the study. COPD was diagnosed according to GOLD criteria with the presence of symptoms, history of risk factor exposure, and irreversible airflow limitation (post-bronchodilator forced expiratory volume in 1 second/forced vital capacity [FEV_1/FVC] less than 0.7).[1] Risk stratification was performed according to Anthonisen criteria: increased degree of dyspnea, increased sputum volume, and presence of sputum purulence.[6]

All patients underwent investigations to identify infectious causative pathogens. Nasopharyngeal swabs were taken for detecting different strains of respiratory viruses by analyzing 18S ribosomal RNA. This viral detection method used an xTAG® RVP Fast v2 assay (Luminex Cooperation, Austin, TX, USA) for multiplex reverse transcription-polymerase chain reactions (RT-PCRs). Bacterial lower respiratory tract infections were determined by aerobic bacterial culture of expectorated sputum using a fluorescent technology system (Bactec™; Becton Dickinson, Franklin Lakes, NJ, USA). PCT and CRP were measured simultaneously at the emergency department within 48 h after the diagnosis of COPD exacerbation: serum PCT by electrochemiluminescence immunoassay on a Cobas e601 analyzer (Roche, Switzerland) and serum CRP on a Cobas c501 system. Arterial blood samples were obtained. Chest radiography was performed for detecting pulmonary opacity, and the results were reported by an experienced radiologist. Complete blood count was performed after whole blood assay. Total eosinophil count was obtained with hemocytometer. Electrocardiography was performed using standard leads, and any signs of cardiac arrhythmia were reported. Functional status was classified using a modified Medical Research Council dyspnea scale. The previously mentioned parameters were integrated to obtain the DECAF score. Clinical outcomes were reviewed in all patients, including hospital mortality, invasive mechanical ventilation requirement, and total length of hospital stay (LOS). The study was approved by Ethics Committee of Human Study, Ramathibodi Hospital, Mahidol University.

Statistical analysis

Continuous data were expressed as mean and standard deviation (SD) or median as appropriate. Comparisons of continuous variables between two and more independent groups were made by *t*-test and analysis of variance or non-parametric statistics (Mann–Whitney test and Kruskal–Wallis test) according to the distribution. The association between two categorical variables was examined using chi-square or Fisher's exact test. Statistical analysis was performed using PASW Statistics 18; a *P*-value of <0.05 was considered to be statistically significant.

Results

A total of 62 COPD patients were enrolled. According to GOLD guideline, these patients were classified as stage 2, 3, and 4 (12.9%, 6.4%, and 80.7%, respectively). The demographics, baseline pharmacologic treatments, and clinical findings of exacerbated COPD are shown in Table 1.

Table 1 Clinical characteristics of COPD exacerbation during emergency room visit (n=62)

Characteristics	Mean ± SD or n (%)
Mean age (years)	79.16±5.0
Male gender	55 (88.7%)
Post-bronchodilator FEV_1 (% predicted)	37.01±12.5
White blood cell count at ER (cells/mm^3)	12,675±5,732
P_aCO_2 at ER (mmHg)	43.3±13.7
Number of underlying medical diseases	2.8 (range 0–8)
Patients with ICS/LABA or ICS treatment	52 (83.8%)
Patients with influenza vaccination in the past year	2 (3.2%)

Abbreviations: SD, standard deviation; FEV_1, forced expiratory volume in 1 second; ER, emergency room; P_aCO_2, partial pressure of arterial carbon dioxide; ICS, inhaled corticosteroid; LABA, long acting β2 agonist.

Influenza was the most commonly detected virus (9 of 16 cases, 56.25%) from PCR. *Klebsiella pneumoniae* was the most commonly isolated pathogenic bacteria from sputum culture. The identified bacterial and viral pathogens are summarized in Table 2.

The prevalence rates of isolated viral exacerbation, isolated bacterial exacerbations, and coinfection of viruses and bacteria in COPD patients were 9.6%, 30.6%, and 16.1%, respectively. Hence, 43.6% of exacerbated patients were classified as noninfectious etiology. The clinical characteristics including DECAF score and serum biomarker are summarized in Table 3.

Table 2 Bacterial pathogens obtained using sputum aerobic bacterial culture and viral pathogens obtained using multiplex reverse transcription-polymerase chain reaction (RT-PCR)

Bacterial pathogen	Number of samples*	Viral pathogen	Number of samples*
Gram-negative bacteria			
Klebsiella pneumoniae	9	Influenza A/B	9
Pseudomonas aeruginosa	5	Rhinovirus	4
Escherichia coli	4	Coronavirus	2
Haemophilus influenzae	3	Human metapneumovirus	2
Acinetobacter baumannii	3	Enterovirus	1
Stenotrophomonas maltophilia	2	Parainfluenza	1
Proteus mirabilis	1	Respiratory syncytial virus	1
Neisseria spp.	1		
Gram-positive bacteria			
Streptococcus viridans	16		
Staphylococcus aureus	4		
Coagulase-negative *Staphylococci*	5		
Enterobacter cloacae	3		
Corynebacterium spp.	3		
Group D *Streptococci*	2		
Enterococcus spp.	1		

Note: *More than one pathogen was identified in exacerbated patient respiratory samples.

There was no difference in terms of invasive mechanical ventilation (P=0.137), LOS >7 days (P=0.302), and hospital death (P=0.151) among exacerbated patients with isolated viral infection, isolated bacterial infection, coinfection, or noninfectious group. However, culture-proven bacterial lower respiratory tract infection was noted in 19 of 25 hospitalizations. Hence, bacterial infection was associated with hospitalization (P=0.007). The higher median serum PCT in exacerbated patients with positive sputum bacterial culture was 0.22 ng/mL (0.04–19.29) compared to those with negative bacterial culture 0.11 ng/mL (0.03–18.48). However, the difference did not reach statistical significance. Regarding exacerbation outcomes, serum biomarkers and DECAF score were similar for COPD-exacerbated patients who survived versus those who died and who were intubated versus those who were not. The results are shown in Table 4.

The increased PCT was noted in COPD-exacerbated patients with LOS ≥7 days when compared with LOS <7 days (0.38 ng/mL vs 0.1 ng/mL, P=0.035). Results are shown in Table 5. In terms of clinical characteristics and laboratory investigations, low serum albumin (<30 g/L) was associated with longer hospitalization for COPD exacerbation (P=0.028). In addition, the higher serum PCT (≥0.25 ng/mL) was associated with the longer LOS ≥7 days when compared with PCT <0.25 ng/mL (P=0.015). Most of exacerbated patients who were treated without invasive mechanical ventilator had LOS <7 days. Hence, invasive ventilation was associated with LOS ≥7 days (P<0.004).

Discussion

The prevalence of viral exacerbation ranged from 25% to 48% according to the detection methods in several previous reports.[4,19,20] Adenovirus was the most commonly identified respiratory virus causing exacerbation in a study by Sethi and Murphy.[4] A systematic review has shown conflicting results for viral etiologies identified using PCR.[3] However, influenza was the most prevalent virus in this study, since coverage by influenza vaccination in our cohort was very low. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are common bacterial causes of exacerbation.[8] Enteric gram-negative bacteria are more common in severe COPD in Thailand. In this study, *K. pneumoniae* was a common bacterial pathogen. This is similar to a previous Asian multicenter study which included Thailand.[21] Our study included COPD with severe airflow limitation, which may increase lower airway bacterial colonization.[22] Coinfection

Table 3 Clinical characteristics including DECAF score and serum inflammatory biomarkers of COPD patients with exacerbation according to etiologies

Clinical features	Virus n=6 (9.6%)	Bacteria n=19 (30.6%)	Coinfection n=10 (16.1%)	Noninfectious n=27 (43.6)	*P*-value
Mean age (years)*	81.30 (6.9)	79.00 (7.9)	79.90 (4.8)	77.95 (7.5)	0.73
Comorbid ≥2 disease, n (%)	3 (50.0%)	9 (47.3%)	5 (50.0%)	6 (22.2%)	0.60
ICS + LABA or ICS, n (%)	5 (83.3%)	16 (84.2%)	10 (100%)	22 (81.4%)	0.58
LAMA, n (%)	3 (50.0%)	10 (52.6%)	5 (50%)	14 (51.8%)	0.39
Oral long acting xanthine, n (%)	4 (66.7%)	9 (47.3%)	2 (20%)	15 (55%)	0.66
P_aCO_2 at ER (mmHg)#	34.2 (9.0)	41.1 (15.9)	45.7 (9.9)	47.3 (15.1)	0.24
Serum albumin (g/L)#	29.1 (8.8)	30.9 (8.0)	25.0 (11.2)	28.3 (6.7)	0.38
WBC count (cells/mm^3)*	11,930 (7,920–14,210)	15,950 (6,500–40,480)	11,725 (6,950–22,240)	10,331 (5,099–20,000)	0.25
Eosinophil count (cells/mm^3)*	82 (0–399)	216 (0–1,584)	326 (0–1,024)	112 (0–1,601)	0.76
DECAF*	2.5 (2–5)	3.0 (2–5)	2.0 (1–4)	2.0 (1–4)	0.46
PCT (ng/mL)*	0.26 (0.07–18.48)	0.30 (0.04–17.6)	0.31 (0.05–1.63)	0.09 (0.03–19.29)	0.35
CRP (mg/L)*	37.46 (23.69–700.0)	41.62 (4.16–274.8)	34.24 (9.03–67.56)	15.56 (1.0–238.5)	0.45

Notes: #Data were presented as mean (SD) and *data were presented as median (range).
Abbreviations: DECAF, dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation; ICS, inhaled corticosteroid; LABA, long acting β2 agonist; LAMA, long acting muscarinic antagonist; P_aCO_2, partial pressure of arterial carbon dioxide; ER, emergency room; WBC, white blood cells; PCT, procalcitonin; CRP, C-reactive protein; SD, standard deviation.

with bacteria and viruses in COPD exacerbation was not uncommon in our cohort similar to a previous report.[19] Initial viral infection followed by subsequent bacterial infection is associated with mechanical ventilation requirement and longer hospitalization.[19,23] However, there was no difference in clinical outcomes between coinfection and isolated infection in terms of mortality in our study.

COPD exacerbation is characterized by increased inflammatory mediators and airway inflammation.[19] Increased biomarker levels are related to disease severity.[24] For example, PCT level is associated with exacerbation severity, LOS, and hospital mortality.[17,25,26] Elevated serum CRP in COPD exacerbation has also been reported;[27] however, it was not correlated with LOS or disease severity.[26] Similarly, in our study, increased serum PCT, but not CRP, was associated with longer LOS (≥7 days). Although the DECAF score is used for evaluating exacerbation severity and predicting mortality, this score could not differentiate between patients with and without poor outcome mortality and invasive ventilation requirement in our study.[10] Because lower numbers

Table 4 Comparison of serum biomarkers and DECAF score of exacerbated patients: survived versus dead patients and non-intubated versus intubated patients

Parameter	Survived patients (n=60)	Patients who died (n=2)	*P*-value
PCT (ng/mL)	0.11 (0.03–19.29)	1.175 (0.47–1.88)	0.121
CRP (mg/L)	25.37 (1–700)	76.53 (67–85)	0.233
DECAF score	2 (1–5)	2 (2–2)	0.401
Parameter	**Non-intubated patients (n=57)**	**Intubated patients (n=5)**	***P*-value**
PCT (ng/mL)	0.11 (0.03–19.29)	0.38 (0.06–0.47)	0.373
CRP (mg/L)	26.79 (1–700)	37.46 (10–67)	0.867
DECAF score	2 (1–5)	2 (2–4)	0.822

Note: Data were presented as median (range).
Abbreviations: DECAF, dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation; PCT, procalcitonin; CRP, C-reactive protein.

Table 5 Comparison of clinical presentation and biomarkers of exacerbated patients with LOS <7 days and ≥7 days

Parameter	LOS <7 days (n=42)	LOS ≥7 days (n=20)	*P*-value
PCT (ng/mL)*	0.10 (0.03–19.6)	0.38 (0.05–18.48)	0.03
CRP (mg/L)*	27 (1–274)	37 (4–700)	0.31
DECAF score*	2 (1–5)	3 (2–4)	0.05
Number of comorbidities*	3 (0–5)	3 (1–6)	0.92
Age (years)#	78.74 (8.0)	80.59 (6.2)	0.40
Serum albumin (mg/dL)#	31.41 (8.1)	25.2 (6.8)	0.01
P_aCO_2 at ER#	42.63 (14.34)	45.85 (12.78)	0.44
WBC count (cells/mm^3)*	12,264 (5,270–24,390)	14,397 (5,360–40,480)	0.23
Invasive mechanical ventilation, n (%)	37 (88.1%)	6 (30.0%)	0.004

Notes: *Data were presented as median (range) and #data were presented as mean (SD).
Abbreviations: LOS, length of hospital stay; PCT, procalcitonin; CRP, C-reactive protein; DECAF, dyspnea, eosinopenia, consolidation, acidemia, and atrial fibrillation; P_aCO_2, partial pressure of arterial carbon dioxide; ER, emergency room; WBC, white blood cells.

of patients were enrolled in this study with few exacerbated patients reporting mortality.

Confounders that are associated with length of COPD hospitalization, such as age, severity of COPD, hypoalbuminemia, hypercapnia, leukocytosis, comorbidities, and ventilator support, must be taken into account.[28,29] Our findings showed that the serum albumin <30 g/L (P=0.01) and invasive ventilator support (<0.05) were associated with hospitalization ≥7 days similar to the previous study.[28] After adjusting for the effect of confounders, elevated serum PCT (≥0.25 ng/mL) was associated with prolonged LOS in this study in accordance with a previous report.[14] The use of 0.25 ng/mL of PCT is generally recommended as a cutoff level for antibiotic therapy. This biomarker approach differentiates between bacterial and viral respiratory infections and minimizes unnecessary antibiotic use.[30]

Serum biomarkers did not differ significantly between exacerbated patients with or without bacterial infection in our study. Despite that the finding of our study is similar to that of the previous report.[31] This is possibly due to a lack of statistical power because of the small sample size enrolled. Despite that using serum PCT and CRP did not discriminate virus-associated exacerbations from others.[32] However, IL-6 is a promising serum biomarker, which has been studied. Higher serum IL-6 was noted in viral than nonviral exacerbation.[33] In addition, coinfection of rhinovirus and *H. influenzae* in COPD exacerbation is associated with higher serum IL-6 compared to those without both pathogens.[34]

Nevertheless, the results of these serum biomarkers for differentiating COPD exacerbating causes are inconclusive from previous studies and systematic review.[35,36] In addition, identifying other serum biomarkers may improve the ability to predict COPD exacerbation outcome. Furthermore, integrating biomarkers into clinical findings or composite score is a promising approach. However, the role of inflammatory biomarkers in stratifying COPD exacerbation has to be further evaluated.

Conclusion

Bacterial and viral infections are the common causes of COPD exacerbation. There was no difference in mortality in exacerbated COPD for different etiologies. Serum PCT is capable of predicting longer hospital stay regardless of the etiology of exacerbation. The role of DECAF score in predicting exacerbation outcomes was limited in this study.

Disclosure

The authors report no conflicts of interest in this work.

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