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Predictors of Influenza PCR Positivity in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Purpose: Influenza infection is an important cause of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Clinical features predicting influenza PCR positivity are unknown. We aim to identify predictors of influenza PCR positivity in AECOPD.

Patients and Methods: A retrospective study of AECOPD cases admitted between 1st January 2016 to 30 June 2017 with combined nasal/throat swabs sent for influenza PCR (Xpert Xpress Flu/RSV) within 24 hours of admission was performed. Clinical parameters and investigations within 24 hours of admission were retrieved from electronic medical records.

Results: Influenza PCR were sent for 925 AECOPD cases (mean age 75 years, 87.9% male). There were 90 PCR positive cases (68 Influenza A, 22 Influenza B). Influenza PCR positive cases had higher temperatures, higher heart rates, lower white cell and lower eosinophil counts. Age, gender, COPD severity, comorbidities and smoking status were similar in both groups. There were no differences in blood pressure, oxygen status, neutrophil or lymphocyte counts, C reactive protein, procalcitonin or chest X-ray consolidation between groups. Higher temperature, higher heart rate, white cell count in the lowest quartile ($Q1 < 8.1 \times 10^9/L$) and non-eosinophilic exacerbations predicted influenza PCR positivity on univariate logistic regression and these factors remained significant after multivariate adjustment (temperature adjusted odds ratio [adj OR] 1.324 [1.009–1.737], $p = 0.043$; heart rate adj OR 1.017 [1.004–1.030], $p = 0.011$; white cell count $Q1$ adj OR 3.330 [1.690–6.562], $p = 0.001$; eosinophilic exacerbations adj OR 0.390 [0.202–0.756], $p = 0.005$).

Conclusion: Higher temperature, higher heart rate, low white cell count (especially when $< 8.1 \times 10^9/L$) and non-eosinophilic exacerbations are independent predictors of influenza PCR positivity in AECOPD cases.

Keywords: chronic obstructive pulmonary disease, exacerbation, influenza, eosinophil

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) refers to the acute worsening of respiratory symptoms, such as increase in dyspnea, cough, sputum production and sputum purulence, that results in additional therapy.¹ AECOPD is strongly associated with mortality, morbidity, disease progression, Emergency Department visits and hospitalizations.² Viral infections such as rhinovirus, influenza and respiratory syncytial virus are often implicated in AECOPD.^{3,4} Recent data based on more sensitive and specific diagnostic methods such as polymerase chain reaction (PCR) reveal higher viral detection rates in AECOPD, suggesting that the role of viruses in AECOPD is more

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significant than previously reported.⁵ Furthermore, viral associated AECOPD are more severe⁶ and frequently associated with complications such as secondary bacterial infections.⁷ As such, predictors of viral etiology in AECOPD are of clinical importance, especially since they may guide early initiation of antiviral agents such as oseltamivir, which have been shown to reduce disease duration, disease severity and respiratory complications in COPD patients,^{8,9} especially if started within 12 hours of symptom onset.¹⁰ Current guidelines, such as the 2021 GOLD Report,¹¹ 2017 European Respiratory Society (ERS)/American Thoracic Society (ATS) Guideline¹² and the 2018 NICE Guideline,¹³ do not provide recommendations on when or in whom to perform influenza PCR in the setting of AECOPD. Despite the potential benefits, indiscriminate influenza PCR testing of all patients presenting with AECOPD is of questionable yield and may not be cost effective. Given the uncertainty of influenza PCR testing in AECOPD, we performed this study with the aim of identifying predictors of influenza PCR positivity in AECOPD patients.

Materials and Methods

Patient Population

This is a retrospective study conducted at Tan Tock Seng Hospital, Singapore, a 1700-bed acute general hospital, between 1st January 2016 to 30 June 2017. Patients admitted for AECOPD with an influenza multiplex real-time, reverse transcriptase PCR (Xpert Xpress Flu/RSV, Cepheid Innovation, California, USA) obtained from combined nasal/throat swab within 24 hours of admission were included. All patients must have a diagnosis of COPD fulfilling the Global Initiatives for Chronic Obstructive Lung Disease (GOLD) criteria¹⁴ either in the past, or newly diagnosed based on spirometry performed during the index admission after clinical stabilization if they were not known to have COPD previously. This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval, including a waiver of need for written informed consent, was obtained from the Domain Specific Review Board (DSRB) of the National Healthcare Group (IRB 2018/00237). The data accessed complied with all relevant data protection and privacy regulations.

Clinical Variables and Data Collection

Clinical parameters and investigations within 24 hours of admission were retrieved from medical records, analyzed, and stratified by influenza PCR positivity. Baseline characteristics such as age, sex, GOLD staging for COPD severity,

smoking status, comorbidities (specifically diabetes mellitus, hypertension, and hyperlipidemia) and vital signs were recorded. Blood analyses including a full blood count, C reactive protein (CRP) and procalcitonin (PCT) were performed. We defined eosinophilic exacerbation as blood eosinophil count ≥ 300 cells/ μL , which was shown to be a reliable marker for sputum eosinophilia¹⁵ and used by other studies on COPD exacerbation.¹⁶ The presence of pulmonary consolidation on chest radiography performed within 24 hours of admission were determined from review of finalized radiology reports.

Statistical Analysis

All continuous variables were reported either as mean with standard deviation (SD) or median with interquartile range whenever appropriate. Between the influenza PCR positive and negative groups, differences of continuous variables were analyzed with a *t*-test or Mann–Whitney *U*-test, while a chi-squared test or Fisher's exact test was used for comparing differences of categorical variables. Predictors of influenza PCR positivity were identified by performing univariate and multivariate binary logistic regression, with results expressed as the odds ratio (OR) accompanied by the 95% confidence interval (95% CI). Multicollinearity of the model was assessed using the variance-independent factor (VIF). Statistical analysis was performed with the SPSS Statistics software (SPSS 26, SPSS Inc, Chicago, IL, USA) where $P < 0.05$ was considered significant.

Results

Participants and Baseline Characteristics

There were 925 AECOPD cases included in this study. The baseline characteristics, COPD severity, comorbidities, vital signs on presentation, and investigation results stratified by influenza PCR positivity are shown in Table 1. The included patients were predominantly male (87.9%) with a mean age of 75 years. Most patients were in GOLD Stage II or III.

Influenza PCR Positivity

There were 90 (9.7%) Influenza PCR positive cases, of which 68 were Influenza A and 22 were Influenza B. The influenza PCR positive and negative groups had similar baseline characteristics, COPD severity and comorbidities. There were also no differences in blood pressure, oxygen status, neutrophil or lymphocyte counts, CRP, PCT or chest X-ray consolidation. The influenza PCR positive group had higher temperatures (37.8 [37.1–38.4] vs 37.0 [36.6–37.5] °C, $p < 0.001$), higher

Table I Comparison of Clinical Variables in AECOPD Patients by Influenza PCR Positivity

	All n = 925	Influenza PCR Positive n = 90	Influenza PCR Negative n = 835	P
Age	74.7 (10.2)	75.3 (9.7)	74.6 (10.3)	0.564
Male, n (%)	813 (87.9)	80 (88.9)	733 (87.8)	0.760
COPD Severity, n (%)				0.213
Unknown	79 (8.5)	10 (11.1)	69 (8.3)	
GOLD I	41 (4.4)	6 (6.7)	35 (4.2)	
GOLD II	119 (24.8)	26 (28.9)	203 (24.3)	
GOLD III	375 (40.5)	36 (40.0)	339 (40.6)	
GOLD IV	201 (21.7)	12 (13.3)	189 (22.6)	
Comorbidities, n (%)				
Hypertension	569 (61.5)	62 (68.9)	507 (60.7)	0.130
Hyperlipidemia	562 (60.8)	58 (64.4)	504 (60.4)	0.451
Diabetes Mellitus	266 (28.8)	24 (26.7)	242 (29.0)	0.645
Smoking status, n (%)				0.846
Non-smoker	29 (3.1)	2 (2.2)	27 (3.2)	
Current smoker	376 (40.6)	38 (42.2)	338 (40.5)	
Ex-smoker	520 (56.2)	50 (55.6)	470 (56.3)	
Vital signs on admission				
HR (bpm)	101 (19)	107 (19)	101 (18)	0.004
SBP (mmHg)	135 (24)	138 (25.5)	135 (24)	0.244
Temperature (°C)	37.0 (36.6–37.5)	37.8 (37.1–38.4)	37.0 (36.6–37.5)	<0.001
SpO ₂ (%)	96 (94–98)	95 (94–98)	96 (94–98)	0.970
FiO ₂ (%)	21 (21–21)	21 (21–25)	21 (21–21)	0.168
SpO ₂ /FiO ₂ ratio	4.52 (4.29–4.62)	4.48 (3.93–4.57)	4.52 (4.29–4.62)	0.075
Serum investigations				
White cell count (×10 ⁹ /L)	10.5 (8.1–13.8)	9.45 (7.35–11.8)	10.6 (8.2–13.9)	0.007
Neutrophil (%)	72.8 (13.7)	74.1 (12.0)	72.7 (13.8)	0.355
Lymphocyte (%)	16.4 (10.3)	15.2 (9.7)	16.5 (10.3)	0.247
Eosinophil (cells/μL)	120 (30–320)	40 (20–113)	140 (30–350)	<0.001
Eosinophilic exacerbation, n (%)	251 (27.1)	11 (12.2)	240 (28.7)	<0.001
CRP (mg/L)	17.5 (4.3–54.3)	20.7 (12.1–43.2)	21.7 (5.3–59.7)	0.054
PCT (μg/L)	0.09 (0.06–0.18)	0.10 (0.07–0.19)	0.09 (0.06–0.18)	0.213
CXR consolidation, n (%)	277 (30.0)	28 (31.1)	249 (29.9)	0.805

Notes: Quantitative variables are expressed as mean (SD) or median (interquartile range) where appropriate. Categorical variables are expressed as numbers (percentage). Eosinophilic exacerbation is defined as blood eosinophil count ≥ 300 cells/ μ L.

Abbreviations: GOLD, Global Initiative for Obstructive Lung disease; HR, heart rate; SBP, systolic blood pressure; SpO₂, oxygen saturation; FiO₂, Fraction of inspired oxygen; CRP, C reactive protein; procalcitonin, PCT; CXR, chest X-ray.

heart rates (107 [19] vs 101 [18] bpm, $p = 0.004$) and lower white cell counts (9.45 [7.35–11.8] vs 10.6 [8.2–13.9] $\times 10^9/L$, $p = 0.007$). There were also fewer patients with eosinophilic exacerbation in the influenza PCR positive group (11 [12.2%] vs 240 [28.7%], $p < 0.001$). Table 2 shows the univariate and multivariate analysis of clinical variables associated with influenza PCR positivity. We further divided the total white cell counts (WCC) into quartiles (Q), with the cutoff values as $Q_1 < 8.1$, $Q_2 = 8.1–10.4$, $Q_3 = 10.5–13.7$ and $Q_4 > 13.7$ ($\times 10^9/L$) for

the purpose of binary logistic regression analysis. Higher temperature, higher heart rate, white cell count in the lowest quartile ($Q_1 < 8.1 \times 10^9/L$) and non-eosinophilic exacerbations predicted influenza PCR positivity on univariate logistic regression and these factors remained significant after multivariate adjustment (temperature adjusted odds ratio [adj OR] 1.324 [1.009–1.737], $p = 0.043$; heart rate adj OR 1.017 [1.004–1.030], $p = 0.011$; white cell count Q_1 adj OR 3.330 [1.690–6.562], $p = 0.001$; eosinophilic exacerbations adj OR

Table 2 Predictors of Influenza PCR Positivity in AECOPD Patients Based on Multivariate Logistic Regression Analysis

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.006 (0.985–1.028)	0.569		
Male	1.113 (0.559–2.218)	0.760		
COPD Severity				
Unknown	Ref			
GOLD I	1.218 (0.408–3.630)	0.724		
GOLD II	0.884 (0.406–1.926)	0.756		
GOLD III	0.731 (0.346–1.542)	0.410		
GOLD IV	0.438 (0.181–1.060)	0.067		
Hypertension	1.425 (0.893–2.275)	0.137		
Hyperlipidemia	1.190 (0.756–1.873)	0.451		
Diabetes Mellitus	0.891 (0.546–1.455)	0.645		
Smoking status				
Non-smoker	Ref			
Current smoker	1.518 (0.347–6.634)	0.579		
Ex-smoker	1.436 (0.332–6.219)	0.628		
HR	1.017 (1.005–1.029)	0.004	1.017 (1.004–1.030)	0.011
SBP	1.005 (0.996–1.014)	0.247		
Temperature	1.440 (1.129–1.838)	0.003	1.324 (1.009–1.737)	0.043
SpO ₂	1.033 (0.964–1.105)	0.357		
FiO ₂	1.005 (0.982–1.028)	0.669		
SpO ₂ /FiO ₂ ratio	0.894 (0.645–1.239)	0.500		
WCC Quartile				
Q1	2.216 (1.166–4.212)	0.015	3.330 (1.690–6.562)	0.001
Q2	1.577 (0.801–3.107)	0.188	2.198 (1.090–4.433)	0.028
Q3	1.405 (0.700–2.819)	0.338	1.677 (0.825–3.409)	0.153
Q4	Ref		Ref	
Neutrophil%	1.008 (0.991–1.024)	0.370		
Lymphocyte%	0.987 (0.965–1.009)	0.252		
Eosinophilic exacerbation	0.345 (0.181–0.660)	0.001	0.390 (0.202–0.756)	0.005
CRP	0.999 (0.995–1.003)	0.524		
PCT	0.903 (0.614–1.330)	0.606		
Consolidation on CXR	1.063 (0.664–1.701)	0.800		

Notes: Multivariate model is adjusted for heart rate, temperature, white cell count quartile and eosinophilic exacerbation. White cell count quartiles are defined as Q1 < 8.1 × 10⁹/L, Q2 = 8.1–10.4 × 10⁹/L, Q3 = 10.5–13.7 × 10⁹/L and Q4 > 13.7 × 10⁹/L.

Abbreviations: GOLD, Global Initiative for Obstructive Lung disease; HR, heart rate; SBP, systolic blood pressure; SpO₂, oxygen saturation; FiO₂, Fraction of inspired oxygen; WCC, white cell count; Q, quartile; CRP, C reactive protein; procalcitonin, PCT; CXR, chest X-ray; OR, odds ratio; CI, confidence interval.

0.390 [0.202–0.756], p = 0.005). There was low multicollinearity among the predictors (temperature VIF = 1.067, heart rate VIF = 1.120, white cell count quartile VIF = 1.082, eosinophilic exacerbation VIF = 1.015).

Discussion

Respiratory tract infections, particularly of viral origin, are very important causes of AECOPD.¹¹ A meta-analysis of 28 studies by Jafarnejad et al showed that influenza is

the second most prevalent respiratory virus identified during AECOPD¹⁷ although some reports have identified it as the most common virus isolated in certain settings.¹⁸ In our study, influenza PCR positivity was seen in 9.7% of AECOPD patients with influenza PCR sent within 24 hours of hospital presentation, a figure consistent with other Asian studies.^{19–21}

Although many studies have demonstrated the link between higher temperatures and viral associated AECOPD in general,⁴ very few studies have assessed this relationship specifically in influenza associated AECOPD. Neuzil et al reported that fever was associated with influenza infection in a cohort of vaccinated COPD patients.²² The link between fever and influenza infection in AECOPD is likely related to an exaggerated airway inflammatory response triggered by influenza through a variety of cytokine pathways.²³

Similarly, sympathetic nervous system activation, resulting in modulation of proinflammatory cytokines and severe systemic and myocardial inflammation,^{24,25} has been implicated as the cause of an abnormal cardiovascular response to influenza infection. These effects range from abnormal electrocardiogram findings such as tachycardia,²⁶ atrial fibrillation,^{24,27} or even life threatening ventricular arrhythmias²⁵ and adverse cardiac events.²⁸ Taken in combination, these findings may explain why tachycardia can be a predictor of influenza infection. Of note, one study reported that during influenza infection, electrocardiogram confirmed tachycardia resolves by Day 2 of infection,²⁶ hence limiting the use of this marker to early presentations only.

Lower white cell counts predicted influenza PCR detection in AECOPD patients. Influenza, being a viral infection, is known to cause leukopenia and lymphopenia.^{29,30} Patients with influenza infection or undergoing vaccination with a live attenuated virus experience T-cell depression prior to the onset of clinical illness.³¹ Of note, the T cell depression persisted during the course of the illness but returns to normal with recovery, again highlighting the importance of correlating the white cell count values to the timing of illness.

There is much interest in blood eosinophil count as a biomarker in COPD, particularly in its ability to predict risk of severe exacerbation,³² clinical response to inhaled corticosteroid (ICS) therapy or other anti-eosinophilic therapy,^{33–35} and outcomes.^{36–38} However, the role of blood eosinophil count in predicting a specific etiology in AECOPD is not well studied. Jang et al reported that low eosinophil count in the setting of AECOPD suggests

viral infection in general.¹⁹ Blood eosinophil count of <50 cells/ μ L was also shown to be associated with infectious AECOPD as defined by viral PCR positivity or CRP levels.³⁹ On the contrary, an eosinophilic COPD exacerbation is characteristic of non-infectious inflammation and responds better to steroid therapy.⁴⁰ Although the exact mechanism for this association is unknown, it has been recently reported that eosinophils exert an immunomodulatory function in the airway epithelium against influenza A.⁴¹ It is therefore possible that patients with eosinophilic exacerbations are able to mount a stronger protective response against influenza, and hence be PCR negative for influenza. The results of our study add on to existing literature demonstrating an inverse relationship between eosinophils and influenza PCR positivity, although further research is needed to better study this association.

Despite systemic inflammation being a likely contributor to our findings, CRP and PCT did not emerge as significant predictors of influenza PCR positivity. This is consistent with many prior studies demonstrating CRP and PCT as poor predictors of virus detection in AECOPD.^{18,42} While viruses are known to generate an intense host inflammatory response in AECOPD patients which serum biomarkers such as CRP are indicative of,⁴³ CRP can also be raised in stable COPD patients,^{44,45} which may confound any associations drawn.

Identification of influenza in AECOPD patients is of clinical relevance given the availability of effective antiviral therapy. In practice however, clinical features alone do not reliably identify influenza-infected AECOPD patients as symptoms poorly distinguish influenza from non-influenza illness amongst patients with chronic lung diseases.²² Major societal guidelines currently do not offer definite recommendations on when or in whom to perform influenza PCR testing. Routine and indiscriminate PCR testing of all AECOPD cases is likely to be of low yield and poor cost effectiveness given an influenza PCR positivity rate of under 10% in our cohort. We identified higher temperature, higher heart rate, lower white cell count, and non-eosinophilic exacerbation (<300 cells/ μ L) as independent predictors of influenza PCR positivity in AECOPD. Although several of these factors may be seen in general respiratory viral infections, our study is one of the few in the literature to establish an independent relationship between them and influenza specifically. These predictors, especially in combination, may have a role in guiding the clinician in identifying AECOPD patients in whom influenza PCR testing is appropriate. This will ideally enable early diagnosis and treatment

with antivirals, which has been shown to reduce the severity and duration of AECOPD^{8,9} and potentially improve health-related quality of life.⁴⁶ In addition, these predictors are of interest in infection control as they can potentially be used to identify AECOPD patients with suspected influenza infection for initial isolation and air-borne precautions to prevent in-hospital spread⁴⁷ while awaiting PCR confirmation.

This study has several limitations. Despite being one of the largest studies specifically assessing influenza PCR positivity in AECOPD patients, our single center study in a predominantly Asian population may not be generalizable to other patient populations. Unlike temperate countries, tropical Singapore lacks a defined influenza season, but local epidemiological data has shown a bimodal increase in influenza incidence observed between April to July and between November to January.⁴⁸ To overcome this seasonal variation, our study period spanned 1.5 years in order to include as many patients possible from the periods with high influenza incidence. The retrospective nature of the study meant that it was highly reliant on accurate and comprehensive electronic medical records. As such, we did not have reliable data on prior influenza vaccination as many patients could have had influenza vaccinations administered at primary care settings or other institutions which we did not have medical records for. We could not control for variables such as time between onset of clinical illness and hospital presentation, or the exact timing of the influenza PCR and other investigations performed upon hospital admission. Finally, in the absence of a reliable alternative marker, we assumed that the presence of influenza PCR positivity indicated active influenza infection, although it has been shown that PCR may detect minute quantities of viral DNA or RNA which may not indicate the presence of live virus.⁴⁹

Conclusion

While influenza is an important cause of AECOPD, it is not commonly detected amongst AECOPD patients in our cohort. Clinical features of higher temperature, higher heart rate, a lower total white cell count and non-eosinophilic exacerbation are predictors of influenza PCR positivity. These may guide appropriate influenza PCR testing and early treatment in AECOPD patients for better outcomes.

Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval; CRP, C reactive protein; CXR, chest X-ray; DSRB, Domain Specific Review Board; FiO₂, Fraction of inspired oxygen;

GOLD, Global Initiatives for Chronic Obstructive Lung Disease; HR, heart rate; OR, odds ratio; PCR, polymerase chain reaction; PCT, Procalcitonin; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; SpO₂, oxygen saturation; VIF, variable inflation factor.

Data Sharing Statement

The data analyzed is available upon reasonable request.

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Disclosure

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