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Neutrophil CD64 Expression as a Diagnostic Marker in Patients Hospitalized with Exacerbations of COPD: A Prospective Observational Study

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Abstract
Purpose The expression of the neutrophil high-affinity Fc-gamma receptor (CD64) can be used as a diagnostic marker for bacterial infection and sepsis. The aims of this study were to determine the diagnostic accuracy of CD64 compared to C-reactive protein (CRP) and white blood cell count (WBC) in patients hospitalized with acute exacerbations of COPD (AECOPD) and to investigate the kinetics of CD64 expression.
Methods The present study is a prospective, single-centre observation study. Blood samples were collected from patients hospitalized with AECOPD at admission and after 6, 24 and 48 h. Retrospective reviews on the patients' medical records were performed blinded to the CD64 results. The CD64 was measured using the Leuko64 kit from Trillium Diagnostics, LLC (Maine, USA) with the CELL-DYN Sapphire Haematology System (Abbott Laboratories, Illinois, USA). Diagnostic accuracy of the CD64, CRP and WBC was compared using a receiver operating characteristic (ROC) curve analysis.
Results A total of 113 patients were included. Thirty-six patients (32 %) had pulmonary infiltrate on chest X-ray at admission (PI). The CD64 was higher in samples from patients with AECOPD and PI than those without PI at admission (median 1.25 vs. 0.60, $p = 0.002$) and during 48 h of follow-up. The area under the ROC curve of CD64, CRP and WBC was 0.69, 0.73 and 0.64, respectively, ($p = 0.42$ for the test of difference).
Conclusion Neutrophil CD64 expression has about the same diagnostic accuracy as CRP in diagnosing pneumonia in patients hospitalized with AECOPD, but does not add to the diagnostic accuracy of CRP and WBC count.

Keywords COPD exacerbation · Infection · Biomarkers · Neutrophil CD64 expression · Diagnostic accuracy

Abbreviations

CD64	Neutrophil high-affinity Fc-gamma receptor expression
COPD	Chronic obstructive pulmonary disease
AECOPD	Acute exacerbations of COPD
CRP	C-reactive protein
WBC	White blood cell
PI	Pulmonary infiltrate on chest X-ray at admission
p-AECOPD	AECOPD with PI
np-AECOPD	AECOPD without PI
ROC	Receiver operating characteristic
DTM	Department of Thoracic Medicine

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TUH	Trondheim University Hospital
FEV_1	Forced expired volume (litres) in one second
FEV_1%	FEV_1 percent of predicted value
FVC	Forced vital capacity (litres)
FVC%	FVC percent of predicted value
FEV_1/FVC	FEV1 expressed as a proportion of FVC
ICS	Inhaled corticosteroids
LABA	Long-acting beta-adrenoceptor agonist

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. COPD is a leading cause of morbidity and mortality worldwide, and represent an economic and social burden that is both substantial and increasing [1].

Exacerbations of COPD (AECOPD), episodes of an acute increase in respiratory symptoms, are associated with increased airway and systemic inflammation [2, 3]. AECOPD are associated with significant morbidity and an impaired quality of life, and are the primary drivers of hospital admissions [4, 5].

About half of the AECOPD are triggered by bacterial and viral infections, but pollution can also contribute to the beginning of an exacerbation [6–9]. AECOPD are heterogeneous events, and there are no specific biomarkers to determine their causation [10].

Physicians' decisions would be more precise if they could be guided by the results of accurate biomarkers, which might not only differentiate stable diseases from exacerbations, but also predict the severity of such events [11]. After the first publications from Davis and colleagues in 1995, about the diagnostic potential of neutrophil CD64 [12] and from Bakke and colleagues, who for the first time reported statistical measures for the performance of CD64 as a diagnostic test in 2001 [13], a number of publications in the field have shown that the neutrophil CD64 expression (CD64) could be a useful diagnostic cell-based parameter of systemic bacterial infection particularly in relation to sepsis [14–19]. The test performed well in distinguishing infection from flare-ups in autoimmune disease [20–22], illustrating usefulness in the early detection of bacterial infection after surgery [23]. However, in patients with proven or suspected viral infection, neutrophil CD64 was also increased, though this increase was significantly lower than in patients with proven bacterial infections [24–26]. In spite of the substantial research in recent years, there is no general view on the usability of neutrophil CD64 in clinical infection diagnostics [27–29]. Specifically, the diagnostic accuracy of CD64 in patients with AECOPD has not yet been studied.

The primary aim of this study was to determine the diagnostic accuracy of CD64 compared to the C-reactive protein (CRP) and white blood cell (WBC) count in identifying patients with pneumonia among hospitalized patients with AECOPD. Secondarily, we wanted to investigate the kinetics of CD64 expression during the first 48 h after admissions for AECOPD.

Methods

Study Design

The present study is a prospective, single-centre observation study.

Participants

Participants were prospectively recruited among patients hospitalized at the Department of Thoracic Medicine (DTM) of Trondheim University Hospital (TUH). The initial investigation of the patients was performed in the emergency department, and they were invited to participate in the study if the following criteria were met: (1) a clinical diagnosis of AECOPD; (2) an established diagnosis of COPD confirmed by spirometry results in the patients' medical charts; (3) the ability to give informed consent. The exclusion criteria were (1) a malignant disease; (2) bronchiectasis; (3) chronic bacterial colonization of the airways with Pseudomonas aeruginosa; (4) long-term immunosuppressive treatment; (5) long-term antibiotics treatment.

Patients admitted repeatedly were only included at their first admission. Pneumonia was defined as a new pulmonary infiltrate on chest X-ray at admission (PI). Patients who had not undergone chest X-ray at admission were not included in the analysis. Based on the findings of chest X-ray at admission, the patients were characterized into two groups: patients with evidence of AECOPD and PI (p-AECOPD) and those who had evidence of AECOPD without PI (np-AECOPD). When the authors retrospectively reviewed the patients' medical charts, they were blinded to the CD64 results. The medical charts were reviewed for length of illness, symptoms, treatment with antibiotic or steroids within 48 h before admission and during the stay at the DTM, clinical parameters of the patients, CRP, WBC values and microbiological results as well as information about regular medication, unhealthy habits and pulmonary function results in a stable phase of COPD.

Informed Consent

Informed consent was obtained from all participants included in the study.

Sample Collection

CRP and WBC counts were routinely analysed for all patients in the study, while additional blood samples (EDTA blood) for CD64 analysis were obtained at admission and 6, 24 and 48 h after admission. The standard hospital procedures for microbiological surveys were followed at blood sample collection and during the processing of biological materials (blood cultures and sputum).

Laboratory Measurements

CD64 expression was measured using the Leuko64 kit from Trillium Diagnostics, LLC (Maine, USA) with the CELL-DYN Sapphire Hematology System (Abbott Laboratories, Illinois, USA) and Leuko64TM QuantiCALC software from Trillium Diagnostics, LLC. The software calculated a CD64 index (CD64), which is supposed to be less than 1.00 in healthy individuals. Between-day coefficient of variation was 4.6 % at a level of 2.61.

WBC was measured on Sysmex XE-2100 (Sysmex, Kobe, Japan). The reference limits in adults were 3.7–10.0 $\times$ 10^9/L, whereas the between-day coefficient of variation was 2.3 % at 6.7 $\times$ 10^9/L.

CRP was measured using a Roche modular P system (Roche Diagnostics GmbH, Mannheim, Germany), with reagents from the manufacturer and from Diagnostic Systems GmbH, Holzheim, Germany. The reference limit was less than 5.0 mg/L, and the between-day coefficient of variation was 6.3 % at 19 mg/L.

All analyses were monitored using the appropriate internal and external (WBC and CRP) quality control systems.

All pulmonary function tests (spirometry) were performed using a MasterScreen PFT powered by SentrySuite™ from Jaeger (Erich Jaeger GmbH, Würzburg, Germany), and COPD was defined as a post-bronchodilator $FEV_1/FVC < 0.7$ according to the GOLD (2015) criteria.

The physicians who were in charge of the patients were responsible for the diagnostic procedures, laboratory analyses and all decisions regarding treatment and follow-up.

Statistical Analysis

The distribution of the continuous variables was studied using Q–Q plots, histograms, values of skewness and kurtosis, and normality was tested by the Kolmogorov–Smirnov test. The median value (interquartile range) was used to present non-normal distributed variables. The Mann–Whitney *U* test and Fishers exact test were used to compare quantitative and categorical data, respectively, in two groups. The Spearman rank correlation coefficient was used to study correlations. The Friedman test was used to examine differences between measurements repeated at several time points, while receiver operating characteristic (ROC) curve analysis was used to study the accuracy of the various diagnostic tests and logistic regression to find the best combination of diagnostic tests. *P* values < 0.05 were considered to be statistically significant. Statistical analyses were carried out through the use of computer IBM software SPSS 21 (Chicago, IL, USA) and StataCorp. 2011. Stata statistical software: Release 12. College Station, TX: StataCorp LP.

Results

From May 2011 to May 2013, a total of 159 patients were invited to participate in the study, with 113 patients meeting the inclusion criteria. A total of 36 (32 %) patients were classified as belonging to the p-AECOPD group, while 77 patients belonged to the np-AECOPD group. There were no significant differences in baseline characteristics between the patients in the two groups regarding age, lung function, proportion of current smokers, length of illness before admission or proportion of patients who received antibiotics and/or Prednisolone before admission. There was a higher proportion of males in the p-AECOPD group compared with the np-AECOPD group (67 versus 33 %, $p < 0.01$), and a larger proportion of patients were treated with antibiotics after admission in the p-AECOPD group compared with those in the np-AECOPD group (48 versus 92 %, $p < 0.01$), Table 1.

Data on the CD64, CRP and WBC values were complete at admission in 98 patients, 31 (86 %) in the p-AECOPD group versus 67 (87 %) in the np-AECOPD group. In the p-AECOPD group, the median values of CD64, CRP and WBC were statistically significantly higher than in the np-AECOPD: 1.25 versus 0.60 ($p < 0.01$), 81.5 versus 12.0 ($p < 0.01$) and 12.75 versus 9.6 ($p < 0.01$), respectively.

The diagnostic accuracy of the CD64, CRP and WBC in differentiating between the np-AECOPD and p-AECOPD was similar, with an area under the ROC curve of 0.69 (95 % CI 0.58–0.81) for CD64, 0.73 (95 % CI 0.62–0.84) for CRP and 0.64 (95 % CI 0.52–0.76) for WBC (Fig. 1). The differences were not statistically significant ($p = 0.42$). In a logistic regression model with CRP and WBC, CD64 did not reach statistical significance ($p = 0.48$). There was a strong positive correlation between CD64 and CRP, with rho = 0.64 ($p < 0.01$), i.e.

Table 1 Demographic characteristics and disease status of the study population by groups

Characteristics	Study population ($n = 113$)		p value p-AECOPD versus np-AECOPD
	p-AECOPD ($n = 36$)	np-AECOPD ($n = 77$)	
Age	68.0	71.0	0.4
Median (IQR)	(65.0, 76.0)	(65.0, 76.0)	
Sex male, *n* (%)	24 (67)	25 (33)	0.001
Current smokers, *n* (%)	9 (25.0)	31 (40.3)	0.1
FEV_1, median (IQR)	0.79 (0.56,1.19)	0.74 (0.52,0.93)	0.4
FEV_1%, median (IQR)	27 (20,41)	28 (22,43)	0.5
FVC, median (IQR)	1.92 (1.82, 2.43)	1.73 (1.73,2.10)	0.3
FVC %, median (IQR)	52 (50, 62)	55 (56, 65)	0.2
FEV_1/FVC, median (IQR)	0.42 (0.39, 0.50)	0.43 (0.41, 0.42)	0.7
Length of illness before hospitalization, days (*n*), median (IQR)	6 (3.0,7.8)	7 (1.5,12.0)	0.9
Treatment before admission, *n* (%)			
Antibiotics	10 (28)	18 (23)	0.6
Oral steroid	12 (33)	26 (34)	1.0
Treatment after admission, *n* (%)			
Antibiotics	33 (92)	37 (48)	0.001
Oral steroids	32 (89)	68 (88)	1.0
Regular medication, combination ICS with LABA	29 (81)	55 (71)	0.2
Blood parameters at admission, median (IQR)			
WBC	12.8 (8.9,16.2)	9.6 (7.8,12.4)	0.001
CRP	81.5 (18.3,163.5)	12.0 (5.0,50.0)	0.001
CD64	1.25 (0.70,1.95)	0.60 (0.5,1.0)	0.002

AECOPD acute exacerbations of chronic obstructive lung disease, *p-AECOPD* AECOPD with pulmonary infiltrate on chest X-ray at admission, *np-AECOPD* AECOPD without pulmonary infiltrate on chest X-ray at admission, *IQR* interquartile range, FEV_1 forced expiratory volume (litres) in one second, FEV_1% FEV_1 percent of predicted value, *FVC* forced vital capacity (litres), *FVC%* FVC percent of predicted value, FEV_1/*FVC* FEV_1 expressed as a proportion of FVC, *ICS* inhaled corticosteroids, *LABA* long-acting beta-adrenoceptor agonist, *WBC* white blood cell, *CRP* C-reactive protein, *CD64* neutrophil CD expression

high levels of CD64 were associated with high levels of CRP. Furthermore, there was no correlation between the CD64 and WBC values.

There was a complete data set on the CD64 at admission and 6, 24 and 48 h after admission in 25 patients in the p-AECOPD group and 49 patients in the np-AECOPD group (Table 2). At all test times, the CD64 values were higher in the patients with p-AECOPD than the patients with np-AECOPD, but only at admission did these differences reach statistical significance. In the p-AECOPD group, the CD64 values in blood samples taken at admission and 6 h after admission were statistically significantly higher than in samples taken 24 and 48 h after admission ($p < 0.05$). No such dependency on time was observed in np-AECOPD patients.

A blood culture sample was taken in 26 patients with np-AECOPD and in 17 patients with p-AECOPD, but bacteremia was not present in any of the samples.

At admission, sputum samples were taken in 51 patients with np-AECOPD and in 19 patients with p-AECOPD.

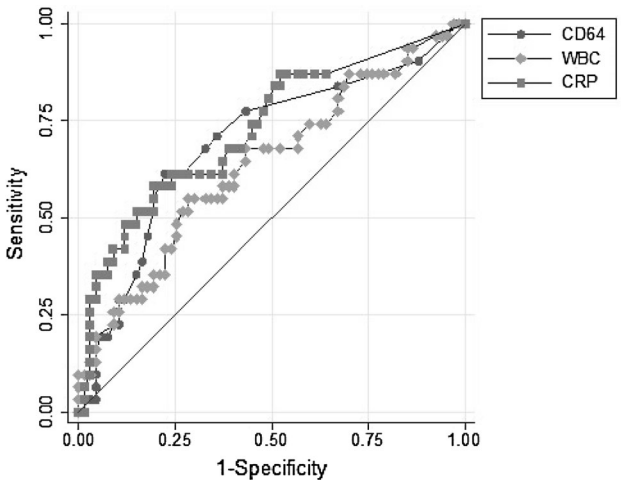

Fig. 1 Receiver operating characteristic (ROC) curves for CD64, WBC and CRP measured in samples taken at admission. The curves show how sensitivity (true positive fraction) varies with 1-specificity (false positive fraction) when the diagnostic cut-off limit is varied

Table 2 Median value of CD64 in blood samples taken at admission to the hospital, and 6, 24 and 48 h after admission, from patients with (p-AECOPD) and without (np-AECOPD) pulmonary infiltrate

Time of sampling in hours after admission	p-AECOPD ($n = 25$)	np-AECOPD ($n = 49$)	p value p-AECOPD versus np-AECOPD
0	1.30 (0.60, 2.05)[a]	0.60 (0.50, 1.10)	0.05
6	1.20 (0.50, 2.20)[a]	0.70 (0.50, 1.12)	0.07
24	0.90 (0.50, 2.25)	0.70 (0.50, 1.30)	0.20
48	1.00 (0.57, 1.55)	0.70 (0.50, 1.00)	0.09

AECOPD acute exacerbations of chronic obstructive lung disease, *p-AECOPD* AECOPD with pulmonary infiltrate on chest X-ray at admission, *np-AECOPD* AECOPD without pulmonary infiltrate on chest X-ray on admission

[a] Statistically significant higher values than measured in samples taken 24 and 48 h after admission. The numbers in parentheses are the corresponding interquartile ranges

Pathogens were found in 29 samples from the np-AECOPD group and in 10 samples from the p-AECOPD group. Individual CD64 values with corresponding findings in the sputum samples are shown in Table 3. *H. influenza* ($n = 11$), *M. catarrhalis* ($n = 5$), *S. pneumonia* ($n = 6$) and *S. aureus* ($n = 3$) were the agents most commonly found in the sputum samples. Mixed cultures, bacterial + bacterial ($n = 5$) and bacterial + viral ($n = 3$) were found exclusively in samples from patients with np-AECOPD. There was a great variability in the CD64 values between samples that were positive for the same pathogen.

Discussion

In the present study, we showed that the expression of CD64 on neutrophils is higher in patients with p-AECOPD than in patients with np-AECOPD, both at admission to the hospital and during the following 48 h.

To the best of our knowledge, this is the first report on the diagnostic accuracy of the CD64 in identifying those with pneumonia among patients with AECOPD applied in a real clinical setting in which acutely ill patients were being examined. Two previous studies have covered some aspects of the CD64 expression in patients with AECOPD. In the study by Zhang and colleagues [30], the CD64 expression in patients with AECOPD and healthy subjects was compared, and in the study by Mao and colleagues [31] the CD64 expression in patients with AECOPD, patients with stable COPD and healthy subject were compared. The CD64 expression was higher in those with AECOPD than in patients with stable COPD. There was no difference in the CD64 expression between patients with stable COPD and healthy subjects. However, none of these studies evaluated the diagnostic accuracy of the CD64 to distinguish between p-AECOPD and np-AECOPD. In the present study, the elevated CD64 values in patients with p-AECOPD declined between 6 and 24 h after admission. However, it should be noted that 92 % of the patients in the p-AECOPD group received antibiotics, and changes in CD64 expression may be related to the antibiotic treatment through restoration of the regulated immune response by such treatments. This finding may indicate that measuring the CD64 expression might be useful in monitoring the effects of antibiotic therapy implying that CD64 could be used as a prognostic marker. The kinetics of the CD64 expression found in this study is supported by the findings of other researchers [23, 32].

The diagnostic accuracy of CD64 in differentiating between p-AECOPD and np-AECOPD was about the same as that of CRP. Furthermore, CD64 did not add to the diagnostic accuracy of CRP and WBC counts when these laboratory tests were combined to discriminate between p-AECOPD and np-AECOPD. It must be considered that these findings are partly due to some limitations of the present study. First, the study population is rather small, and therefore the confidence intervals of the ROC areas are relatively wide. The differences between CD64, CRP and WBC counts might have been statistically significant in a larger population. Second, some patients included in the study were treated with systemic steroids and/or antibiotics before admission. If all patients were left untreated until admission, the diagnostic accuracy might have been better for all the laboratory tests. Third, the study was not designed with regard to microbiological diagnostics. In a small number of patients, blood culture samples were requested by the physician in charge, but bacteremia was not present in any of the samples. Advanced microbiological analysis of sputum was not performed routinely. Hence, we were not able to correlate the CD64 levels with bacteriological or viral findings. Our data are consistent with results from previous studies regarding the association of *H. influenzae, M. catarrhalis* and *S. pneumonia* with AECOPD [33–36]. An interesting question that ought to be addressed in future studies is whether CD64 has the potential as a useful biomarker in distinguishing between an acute airway infection or colonization of the airways with one or more bacteria.

Table 3 The individual values of neutrophil CD64 expression and positive culture findings

Recognized agents	Values of neutrophil CD64 expression	
	p-AECOPD ($n = 10$)	np-AECOPD ($n = 29$)
Haemophilus influenzae	1.8	3.9
	1.1[a]	2.6
	0.9[c]	0.5[c]
		1.6
		0.5
Haemophilus influenzae plus		
Klebsiella oxytoca		0.9[c]
Moraxella catarrhalis		0.7
Influenza A virus subtype H1N1		0.6
Moraxella catarrhalis	0.9	2.2
		0.9
Moraxella catarrhalis plus		
α-haemolytic streptococcus		0.6[b]
Stenotrophomonas maltophilia		2.8[a]
Klebsiella pneumoniae		1.0[a]
β-haemolytic Streptococcus group B		1.0
β-haemolytic Streptococcus group C plus Proteus species		0.6
Streptococcus pneumoniae	5.2	0.7
	3.3	0.7
	1.6	
	1.5[c]	
Staphylococcus aureus		1.4
		0.4[c]
Staphylococcus aureus plus		2.1[b]
Stenotrophomonas maltophilia		
Coagulase-negative staphylococci		0.6[c]
Stenotrophomonas maltophilia		0.5[b]
		1.8[c,d]
		0.4
Proteus mirabilis + Rhinovirus PCR positive		0.9[c]
Influenza A virus subtype H1N1		1.7[c]
Enterobacter cloacae		0.9[c]
Candida albicans	1.1	1.3[c]
Acinetobacter baumannii		0.5[d]
Gram-negative bacteria	2.2[b]	

[a] Treated with antibiotics before admission

[b] Treated with steroids per os before admission

[c] Treated with both steroids and antibiotics

[d] CD64 results from samples 6h after admission

AECOPD acute exacerbations of chronic obstructive lung disease, *p-AECOPD* AECOPD with pulmonary infiltrate on chest X-ray at admission, *np-AECOPD* AECOPD without pulmonary infiltrate on chest X-ray at admission

The strength of the present study is the clinical validity of the study population prospectively included when admitted to hospital because of an AECOPD and the clinically relevant diagnostic procedure of p-AECOPD by chest X-rays without any knowledge of the value of CD64 or any other laboratory tests.

Conclusion

When used for diagnosing pneumonia in patients with an acute exacerbations of COPD, CD64 had about the same diagnostic accuracy as CRP, and CD64 did not seem to add to the diagnostic accuracy of CRP and WBC counts.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no financial or non-financial conflicts of interests.

Research Involving Human Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the Regional Committee for Medical and Health Research Ethics (REC) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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