IJASRM

International Journal of Advanced Scientific Research and Management, Vol. 2 Issue 7, July 2017.

www.ijasrm.com

ISSN 2455-6378

Neutrophil CD64 and Neutrophil/Lymphocyte ratio as predictors of hospital outcome in acute exacerbation COPD

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Abstract

AE-COPD is accompanied with deterioration in lung function. As a marker of host immune response to bacterial infection, neutrophil CD64 (nCD64) increases about 1 hour after invasion. Also, neutrophil/ lymphocyte ratio (NLR) is an emerging parameter that reflects systemic inflammation. It is cost effective, rapid and easy, and can predict activity and adverse outcomes of AECOPD. Setting: Assiut University Hospitals. Objective: to investigate the role of nCD64 and NLR in AECOPD as predictors for in-hospital outcome. Methods: In a case control study, clinical and laboratory data were collected from 74 patients with AECOPD, and 74 stable COPD in whom nCD64 and NLR and other markers were measured. The ROC curves were used to determine the optimal cut-off levels for nCD64, NLR that discriminate severity and short term prognosis. Results: the sensitivity and specificity of NLR in predicting outcome are 93 % and 90% respectively at cut off value 1.5. The nCD64 has sensitivity and specificity in predicting outcome 96.7%, 83.3% respectively at cut-off limit of 2.5. Conclusion: NLR is accurate for detecting true positive cases, in addition it is cheap, simple, easy detectable in blood picture. It correlates positively with nCD64 so we recommend its usage routinely in AECOPD.

Keywords: *COPD; acute exacerbation; neutrophil CD64; Neutrophil/lymphocyte ratio; prognosis*

1. Introduction

Acute exacerbation of COPD (AECOPD) is among the most frequent reasons for hospitalisation. Approximately 4% of the general population in the western world is admitted with an acute respiratory disease at least once a year and nearly one fifth of hospital visits is due to AECOPD[1]. Early identification and management of AE-COPD is an important issue in clinical practice. AE-COPD is accompanied with various worsening respiratory symptoms and deterioration in lung function. Also the frequency and severity of attacks are associated with increased mortality[2].

During exacerbations, the inflammation in COPD is amplified in comparison with stable periods. The increased level of inflammatory markers is associated with lung function decline[3]. As infection is the main cause leading to clinical AECOPD, white blood cell counts and ESR are the common markers to show the existence of infection in patients with COPD. Recently, other biomarkers

are used. Authors have found that the high-affinity Fc receptor-CD64 is expressed by monocytes and only weakly on resting neutrophils. The high-expression of neutrophil CD64 (nCD64) is an early step in the host- immune response to bacterial infection[4]. Studies have shown that the nCD64 might be used as a biomarker for early-onset sepsis or bacterial infection. However, authors agreed that the value of the nCD64 in COPD prognosis is unknown[5-6].

As most of novel biomarkers that identify the severity of acute exacerbation in COPD are time consuming and expensive, there is a need to use more simple tests. The Neutrophil–lymphocyte ratio (NLR) is a rapid, easy and cost-effective method derived from routine complete blood count (CBC)[7]. The NLR could be an important marker that assess inflammatory status in patients with COPD and could identify early, acute exacerbations[8]. However, NLR has not been widely used in the diagnosis of AECOPD.

The purpose of the present study is: 1- To measure the values of the nCD64 and NLR in patients with AE-COPD and stable COPD, 2- to correlate between nCD64, NLR and the usual routine biomarkers as WBC count and ESR, 3- to investigate the role of nCD64 and NLR as predictors for short term hospital outcome in AECOPD.

2.Patients and methods:

One hundred forty eight patients diagnosed as AECOPD and stable COPD (74 patients in each group) were recruited from Chest Department, Assiut University Hospital in the period between January 2016 and October 2016 (random selection by 1:1 cross over). A diagnosis of COPD was made by a clinical history, examination and spirometer (forced expiratory volume in 1st second/forced vital capacity (FEV_1/FVC)ratio of <0.7). The severity of COPD was graded according to the Global Initiative for Chronic Obstructive Lung Disease guidelines[9] (Stage I, mild COPD: $FEV_1 \geq 80.0\%$ predicted; Stage II, moderate COPD: FEV_1 80-50.0%; Stage III, severe COPD: FEV_1 50- 30.0%; Stage IV, very severe COPD: $FEV_1 < 30.0\%$). The exacerbation of COPD was defined as the patient being diagnosed with COPD with two or more of the following three symptoms of exacerbations: new or worsening cough, worsened dyspnea, and worsened sputum volume and/or change in its color. The following clinical data were recorded: age, gender, pulmonary function parameters, on admission X ray chest, arterial blood gas, and laboratory data. The blood samples were collected within 24 hours of hospitalization. Blood samples were centrifuged at 1000g/min for 15 minutes, and then the serum was separated and stored under -80°C.

The neutrophil CD64 was assessed by flow cytometry (FACScalibur, Becton Dickinson, San José, CA, USA). Sampling: 5ml of venous blood were collected from each patient and control under aseptic precautions and were divided as follow: 2 ml blood was placed in EDTA (Ethylene Diamine Tetra-acetic Acid) containing vacutainer tube for complete blood count in an automated hematology analyzer cell dyne-1800 (Abbott diagnostics, USA). The NLR calculated by dividing absolute neutrophil count by the absolute lymphocyte count. Then 3ml of the blood was placed in EDTA containing vacutainer tube for flow-cytometric determination of CD64 using FACS caliber flowcytometer (BD, Bectom Dickinson). All antibodies were obtained from Bectom Dickinson.CD64 expression by flow cytometry: CD64 expression was measured using FITC CD 64 monoclonal antibodies as follow :100 µL from blood samples and 10 µl of FITC CD64 conjugated monoclonal antibody or matched iso-type controls was added each in prepared tube then vortex and incubated in dark for 15 min at room temperature. After incubation, RBCS lysing solution 1 ml;1x (BD Biosciences) was added and incubated for an additional 10 min at room temperature. Cells were centrifuged at 3500 rpm for 5 minute. The pellet was washed twice with phosphate buffered saline then they were suspended in BD Biosciences fluid sheath for analysis on a FACS Calibre flow cytometer, , Becton Dickinson, San José, CA, USA. Acquisition and analysis were performed using cell Quest software. The acquisition and analysis of immuno-marked cells was Standardized for 10,000 events per sample Lymphocytes and neutrophil were gated in the R1 ,R2 region on the basis of characteristic linear forward and side scatter features and CD 64 expression was evaluated on a logarithmic scale for two regions using Cell Quest Pro software (BD Biosciences) Figure(1)

Exclusion criteria included a history of current respiratory disorders other than COPD, malignancy, systemic auto-immune disorders, recent surgery and severe endocrine, hepatic or renal diseases. Patients with pneumonia, cardiovascular and metabolic diseases were also excluded from the study.

Ethical approval was provided by the medical ethics committee of Assiut University, Faculty of Medicine. Informed consent was obtained either from the patients or the patients' families.

Statistical analysis:

Descriptive data are presented as mean and standard deviation and range. Continuous data were tested for normality. Comparisons between groups were made using the t test (for continuous variables

such as pH, $PaCO_2$, PaO_2, NLR and nCD64 or Mann-Whitney U test (for categorical variables). Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off level for the serum nCD64 and NLR. A two-sided P value <0 .05 was considered statistically significant. All of the statistical analyses were performed using the statistical software package (SPSS 16.0).

3.Results

Table 1 shows that patients with AECOPD have significantly diminished pH level, PaO_2 ($p<0.05$ and 0.001), higher partial pressure of CO_2 and HCO_3 ($P<0.01$ each), and have more co-morbidities ($P<0.05$). The traditional markers of inflammations as WBCs and ESR (first hour) are significantly higher in AECOPD compared to stable COPD (17.7±.8 vs. 7.4±3.8, $p<0.01$ and 31.6±3.3 vs. 15.2±1.6, $p<0.01$) **Table 2.** The mean value of nCD64 is significantly higher in AECOPD compared to stable COPD (2.44±0.3 vs. 0.56±0.2, $p<0.01$). The NLR is 3.7±0.3 in AECOPD compared to 1.2±0.7 in stable COPD ($p<0.05$). **Figure 2** shows that there is a significant positive correlation between the levels of NLR and nCD64 (r= 331, $P<0.005$) in patients with COPD.

The results in **Table 3** demonstrate that there is significant positive correlation between the level of the traditional markers as WBC count, ESR and the level of neutrophil CD64 (P <0.01). Also, there is significant positive correlation between WBC count, ESR and the neutrophil/lymphocyte ratio ($P<0.05$ and <0.01 respectively). The nCD64 level correlates significantly with patient's pH ($P<0.05$), $PaCO_2$ ($P<0.01$) and severity of AECOPD ($P<0.01$) and. Similarly, the NLR correlates significantly with patient's pH, PaO_2 ($P<0.05$), $PaCO_2$ and AECOPD severity ($P<0.01$).

Moreover, table 4 illustrates that there is significant positive correlation between the level of nCD64 and the patient outcome. Higher nCD64 is associated with more days of hospital stay, need for ICU and in-hospital new morbidities ($P<0.01$, 0.05 and 0.05 respectively). Similar results of significant correlation between high levels of NLR and patients outcome parameters is recorded ($P<0.01$, 0.05 and 0.05).

The ROC curve in **figures 3A** demonstrates that at diagnostic cut-off limit of 1.5, the NLR sensitivity is 93 % and specificity is 90% (area under the ROC curve was 0.684, 95 % CI 0.54–0.81 and $P<0.01$) . While at diagnostic cut-off limit 2.5 for nCD64, the sensitivity is 96.7% and specificity is 83.3% (area under the ROC curve for nCD64 was 0.667, 95 % CI 0.35–0.98 and P=0.03) **(Figure 3B)**.

4.Discussion:

Acute exacerbation of chronic obstructive pulmonary diseases (COPD) means worsening patient's symptoms beyond normal day to day variability with subsequent need for increased medications[9]. The most common cause of exacerbation is infection. About 50% of COPD patients has bacteria in their lower airway during exacerbation as evidenced by bronchoscopic studies[10]. An easily measurable and non-invasive parameter which might reflect systemic inflammation is required. For many years, white blood cell (WBC), neutrophil counts, ESR and CRP were the most frequently used infection markers in daily clinical practice. These traditional markers are helpful also in monitoring systemic inflammation in patients with stable COPD, in addition to assessing the severity of inflammation in AE-COPD. However, ESR and CRP measurements are not routinely viable in clinical practice, especially in emergency service departments because the additional time and staff required. Other infection markers such as pro-calcitonin, cytokines, endothelin-1 and co-peptin show promising results in the assessment of infection risk and in predicting outcome. The implementation of these relatively "new" markers is hampered by validation, cost, and accessibility factors.

To clarify the value of traditional and new markers of inflammation in patients admitted with AECOPD and in stable COPD, the results of this study shows that the white blood cells (WBCs), erythrocyte sedimentation rate (ESR), neutrophil CD64 and neutrophil/lymphocyte ratio (NLR), are significantly increased in COPD in acute exacerbation compared to stable COPD. The increases in white blood cell count and ESR during bacterial infection have long been approved in many studies. It is agreed that the ESR and WBCs are significantly increased in COPD patients during exacerbation compared to stable COPD and control, and this is attributed to presence of infection and it decreases with treatment[11-12-13].

In the present study the level of NLR is 3.7±0.3 compared to 1.2±0.7 in stable COPD ($p<0.05$). Many authors found that NLR significantly increases in COPD both stable and during acute exacerbation compared to control, and it is positively correlated with CRP, and ESR. They added that NLR can detect increased inflammation as WBCs, and ESR. The AECOPD is characterized by local and systemic inflammation with increasing inflammatory and pro-inflammatory mediators, and also inflammatory cells (neutrophil, CD8 lymphocyte, and macrophage), with subsequent parenchymal destruction[11-14-15]. Cockayne et al., suggested that neutrophil release oxygen free radicals, and

proteolytic enzymes e.g. neutrophil elastases and matrix metaloprotease during acute exacerbation of COPD which results in increasing severity of COPD[16]. Taylan et al., approved that ESR, WBCs, CRP, and NLR all increased during acute exacerbation of COPD. They added that NLR is cost effective simple parameter in detecting inflammation and predicting activity and outcome of many chronic diseases[14].

The nCD64 in the study group is 2.44±0.3 in AECOPD versus 0.56±0.2 in stable COPD (P<0.01). The significant increasing level of nCD64 during AECOPD might be attributed to the host immune response to bacterial infection, as the nCD6 expression increases about 1 hour after invasion and is stable for more than 24 hours[17]. Several studies examined neutrophil CD64 in COPD, and healthy control. They observed that it significantly increased in acute exacerbation in comparison to stable disease and healthy subjects[18-19-20-21]. Xu et al., observed that nCD64 significantly increased during COPD exacerbation and they explained this increase as an early response of immune system to infection. However, they added that several non-infectious conditions also associated with increased expression of CD64 (e.g. pancreatitis, adenoid hypertrophy) so it is not only a marker of infection, but it reflect immune response to infectious and non-infectious conditions[18].

The current study observed that nCD64 is sensitive and specific in predicting outcome of acute exacerbation of COPD (96.7%, 83.3% respectively) when the diagnostic cut-off limit is 2.5 (AUC= 0.667 and 95 % CI =0.35–0.98). This suggests an important role of nCD64 in evaluating prognosis of acute exacerbation of COPD. Xu and colleagues agreed that it is a valuable marker for both short term and long term prognosis of COPD[18]. Moreover, expression of neutrophil CD64 is most marked one hour after infection, and it remains stable for more than 24 hours. Its prognostic accuracy in predicting sepsis in critically ill patients had been approved to be better than CRP, and procalcitonin[19-20] . Cortegiani et al., observed that CD64 index had a high sensitivity and specificity (94.6% and 86.8% respectively) in predicting intensive care (ICU) admission after 72 hours of emergency department admission. They concluded that nCD64 is not only predictor of positive culture in cases of suspected infection and sepsis but it can also be used for detection of infection in daily use in emergency department setting[21].

The present study showed that the sensitivity and specificity of NLR in predicting prognosis and outcome of acute exacerbation (as days of hospital stay, need for ICU and in-hospital new morbidities and mortality) were 93 % and 90% respectively (AUC 0.684) at cut off value (1.5). The level of NLR had significant positive correlation with outcome. Taylan et al., [14] examined the sensitivity and specificity of NLR in predicting acute exacerbation of COPD and observed that it had sensitivity and specificity 80.4%, 77.7% with area under the curve 0.894 at cut off value 3.29. Several studies examined NLR in COPD patients and concluded that it was marker of systemic inflammation that increased with COPD progression, and it was associated with causes of mortality. They added that the NLR was simple and practical marker for detection of metabolic syndrome of COPD, and so in worsening prognosis [22-23-24-25-26].

Although the sensitivity of nCD64 in the present study in predicting outcome of COPD exacerbation is higher than that of NLR (96.7%. 93% respectively) but the specificity of NLR is higher (83.3% for nCD64 versus 90% for NLR). The NLR level was more accurate for detecting true positive cases. In addition it is cheap, simple, easy detectable in blood picture, and it is significantly positively correlated with nCD64.

Limitations of this study are: limited number of cases, larger numbers of control was better to be included and we didn't study CRP and compare them with NLR, and nCD64.

5. Conclusion

In conclusion, both nCD64 and NLR are valuable markers for early detection of AECOPD. They correlated significantly with the disease severity and prognostic parameters that determine the short term in hospital outcome (as days of hospital stay, need for ICU, new morbidities and mortality). NLR is more accurate for detecting true positive cases and it is cheap, simple, easy detectable in blood picture. It correlates positively with nCD64 so we recommend its usage routinely in AECOPD.

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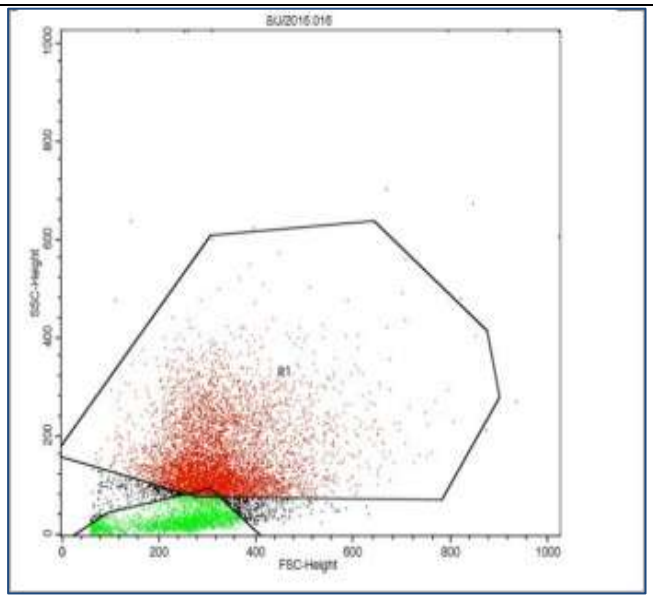
Figure 1. Example of flow-cytometry graph presentation of neutrophil CD 64 in patient with acute exacerbation of COPD



IJASRM
International Journal of Advanced Scientific Research and Management, Vol. 2 Issue 7, July 2017.
www.ijasrm.com
ISSN 2455-6378

Table 1. Demographic characteristics and disease status of the study population

	AE COPD (n=74)	**Stable COPD(n=74)**	**P value**
Age, mean± SD	57.3±18.2	58.9±15.7	NS
Gender, n (%)	54/20 (73/27)	10/4 (71/29)	NS
Smoking, n (%) - Smokers - Ex-smoker - Non-smokers	 37 (49.3) 18 (24) 19 (25)	 21 (28.3) 37 (49.3) 16(22.2)	 NS
pH, mean± SD	7.31±0.1	7.36±0.03	<0.05
$PaCO_2$, mean± SD	59.6±2.1	45.2±4.2	<0.01
PaO_2, mean± SD	59.7±2.2	91.9±2.6	<0.001
HCO_3, mean± SD	31.6±2.1	24.8±2.7	<0.01
Exacerbations last year, n (%) - 1 - ≥2	 49 (65.3) 25 (33.3)	 7 (9) 0 (0)	 <0.01
GOLD stage, n (%) Stage 1 Stage 2 Stage 3 Stage 4	 0 (0) 7 (9.4) 42 (56.7) 25(33.3)	 7 (9) 17(22.9) 25(33.7) 25(33.7)	 <0.01
Severity of AECOPD, n (%) Moderate Severe	 5 (6.7) 69 (93.3)	 - -	 -
Days of hospital admission , mean± SD	12.6±1.3	0	-
Use of ICS, n (%)	65 (87.8)	37 (50)	<0.05
Co morbidities, n (%)	47 (62.7)	24 (32.4)	<0.05

AECOPD= acute exacerbation chronic obstructive pulmonary disease, PaO2= partial pressure of arterial oxygen, $PaCO_2$= partial pressure of arterial carbon dioxide, ICS= inhaled corticosteroid,

Table 2. Levels of different bacterial inflammation markers in the study groups

Variable	AE COPD (n=74)	Stable COPD(n=74)	P value
WBCs, mean± SD	17.71±2.8 (3.1-16.4)	7.4±3.8	<0.01
ESR, mean± SD	31.6±3.3 (2-105)	15.2±1.6	<0.01
n CD64, mean± SD	2.44±0.3 (0.2-12)	0.56±0.2	<0.01
NLR, mean± SD	3.7±0.3 (1-32)	1.2±0.7	<0.05

AECOPD= acute exacerbation chronic obstructive pulmonary disease, WBC= white blood cells, NLR= neutrophil lymphocytic ratio, ERS= erythrocyte sedimentation rate, n CD64= neutrophil cluster of differentiation 64 (nCD64 was measured in 74 AECOPD and only 14 patients with stable COPD)

IJASRM
International Journal of Advanced Scientific Research and Management, Vol. 2 Issue 7, July 2017.
www.ijasrm.com
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Figure 2. Correlation between Values of neutrophil/lymphocyte ratio (NLR) and neutrophil CD 64 (nCD64) in blood samples taken from patients with AE-COPD on admission to the hospital (Spearman's rho)

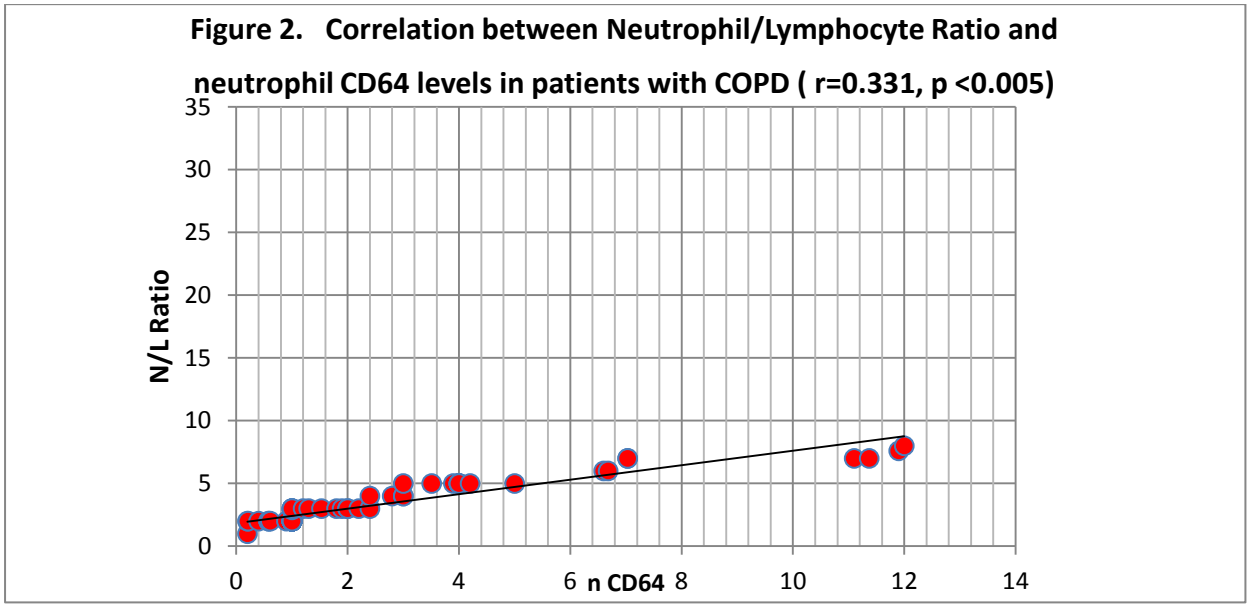


Table 3. Correlation analysis between the studied inflammatory biomarkers in patients with AE-COPD on admission and COPD severity (Spearman's rho)

Variables	WBCs	ESR	nCD64	NLR
nCD64	r= 0.382 p<0.05	R=0.431 P<0.01	-	R=0.331 P<0.005
NLR	R=0.330 P<0.05	R=0.558 P<0.01	R=0.331 P<0.005	-
pH	R= -0.216 P=NS	R= -0.200 P=NS	R= -0.365 P<0.05	R= -0.341 P<0.05
PaO_2	NS	NS	NS	R= -0.327 P<0.05
$PaCO_2$	r=0.370 p<0.05	R=0.211 P=NS	R=0.428 P<0.01	R=0.451 P<0.01
Severity of AECOPD	R=0.328 P<0.01	R=0.372 P<0.05	R=0.424 P<0.01	R=0.498 P<0.01

AECOPD= acute exacerbation chronic obstructive pulmonary disease, WBC= white blood cells, NLR= neutrophil lymphocytic ratio, ERS= erythrocyte sedimentation rate, n CD64= neutrophil cluster of differentiation 64, PaO_2= partial pressure of arterial oxygen, $PaCO_2$= partial pressure of arterial carbon dioxide, GOLD= global initiative of obstructive lung disease

Table 4. Correlation analysis of nCD64 and NLR in patients with AE-COPD on admission and short term in-hospital outcome (Spearman's rho)

Variables	nCD64	NLR
Days of hospital stay	R=0.522 P<0.01	R=0.421 P<0.01
Need for ICU	R=0.331 P<0.05	R=0.495 P<0.01
In- hospital new morbidities	R=0.365 P<0.05	R=0.341 P<0.05
In-hospital mortality	NS	NS

NLR= neutrophil lymphocytic ratio, nCD64= neutrophil cluster of differentiation 64.

IJASRM
International Journal of Advanced Scientific Research and Management, Vol. 2 Issue 7, July 2017.
www.ijasrm.com
ISSN 2455-6378

Figure 3 A,B .ROC curve of neutrophil/ lymphocyte ratio (NLR) and neutrophil CD64 as markers of prognosis in AE-COPD patients

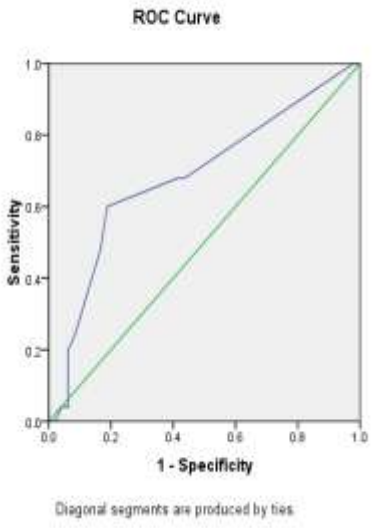
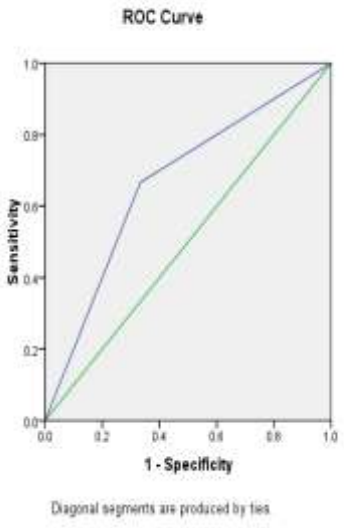
Figure 3A	Figure 3 B
	

Figure legends:

Figure 1. The acquisition and analysis of immuno-marked cells was Standardized for 10,000 events per sample Lymphocytes and neutrophil were gated in the R1 ,R2 region on the basis of characteristic linear forward and side scatter features and nCD 64 expression was evaluated on a logarithmic scale for two regions using Cell Quest Pro software (BD Biosciences)

Figure 2. Correlation between Values of neutrophil/lymphocyte ratio (NLR) and neutrophil CD 64 (nCD64) in blood samples taken from patients with AE-COPD on admission to the hospital (Spearman's rho)

Figure 3A. Receiver operating characteristic (ROC) curve for NLR measured in samples taken at admission. The area under the ROC curve was 0.684 (95 % CI 0.54–0.81), P<0.01. The curve shows sensitivity 93 % and specificity 90% when the diagnostic cut-off limit is 1.5.

Figure 3B. Receiver operating characteristic (ROC) curves for nCD64 measured in samples taken at admission. The area under the ROC curve was 0.667 (95 % CI 0.35–0.98), P=0.03. The curve shows sensitivity 96.7%, specificity 83.3% when the diagnostic cut-off limit is 2.5.