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ALTERATIONS IN NEUTROPHIL-LYMPHOCYTE RATIO AND C-REACTIVE PROTEIN IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS ADMITTED TO HOSPITAL WITH AN ACUTE EXACERBATION

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***Background**: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major cause for hospital admission and COPD(chronic obstructive pulmonary disease) related morbidity. This encouraged clinicians to search for useful and easy inflammatory biomarkers for recognizing AECOPD. **Objective**: To evaluate the role of the neutrophil/lymphocyte ratio (NLR) and C-reactive protein (CRP) in COPD patients for recognition of an acute exacerbation requiring hospital admission.**Patients and Methods**: A prospective study included 100 hospitalized AECOPD patients, 88 stable COPD, and 80 sex and age matched healthy subjects. NLR and CRP were measured twice for each patient, first at hospital admission and the second was 3 months later as follow up. NLR was calculated from the complete blood count (CBC).**Results:** The total white blood cell count (WBCs), Neutrophils, and NLR ratio were significantly higher in AECOPD group (P< 0.05 for each). CRP and forced expiratory volume in first second (FEV1% predicted) showed a significant correlation with NLR (P< 0.05). At cut off value> 3.26 for NLR the sensitivity and specificity were 84.7% and 78.0% respectively, while at cut off value> 4.11 for CRP the sensitivity and specificity were 77.9 % and 68.2% respectively for the prediction of AECOPD. **Conclusion:** Elevated NLR can be used as a marker similar to WBCs and CRP, in the detection of increased inflammation in hospitalized acutely exacerbated COPD patients.*

***Keywords:** acute exacerbations of COPD, neutrophil/lymphocyte ratio, hospitalization, CRP.*

INTRODUCTION

COPD is characterized by the presence of airflow limitation and chronic airway inflammation[1]. During acute exacerbation of COPD more airway obstruction and systemic inflammation are observed, which in turn are responsible for worsening of clinical symptoms, reduction of lung functions, increased hospitalization and rate of admission to intensive care unit, and need for more intense treatments[2&3].

Several authors reported increased level of some inflammatory biomarkers in COPD patients like tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6); however, their use has limitations in daily clinical practice[4]. Neutrophil/lymphocyte ratio (NLR) and CRP are biomarkers of inflammation[5] and are estimated from routine investigations done at hospital admission. NLR in peripheral blood, have been reported to be increased in AECOPD compared to stable state[6&7]. However, data published regarding the diagnostic performance and cut off level for NLR and CRP in COPD patients during acute exacerbation requiring hospitalization is limited.

The aim of the current study was to evaluate the ability of the NLR and CRP to detect an acute exacerbation requiring hospital admission in COPD patients.

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Patients and Methods

A prospective study was conducted and enrolled patients admitted to Chest Department, Assiut University Hospital with AECOPD between December 2019 and May 2020.

The study included 100 COPD patients with acute exacerbation [8&9], 88 patients during stable COPD periods[10] and 80 age and sex matched healthy control subjects.

Within 2 h of hospital admission, NLR and CRP (ADVIA 2120i Hematology Systems, Siemens Healthcare Diagnostics, Ireland) were measured in blood samples withdrawn from AECOPD patients. NLR was reported as a part of the complete blood count (CBC) results. Normal reference range of NLR was 1.33- 2 % according to software of the hematology analyzer used. During the stable period of COPD (three months later after an acute exacerbation), NLR and CRP were measured again for the same patients. Twelve patients were missed during the follow up. The same investigations were done for the control group. Spirometry **(**Cosmed SrL, Quark PFTs ergo, P/N Co9035 – 12-99 made in Italy) was done for the study groups.

Exclusion criteria: (1) bronchial asthma; (2) bronchiectasis; (3) tuberculosis; (4) active inflammatory disease other than COPD; and (5) malignancy.

The Local Ethics Committee approved the study protocol and all patients or those responsible for them gave written informed consent.

Statistical analysis

SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York) was used for analysis of data. Mean ± SD and frequency (percentage) were used for data expression.

Chi²-test and student t-test were used to compare the study groups. Pearson correlation was calculated to detect the presence of correlation between NLR and FEV1 % predicted and CRP. Diagnostic performance of NLR and CRP in predicting AECOPD was determined by receiver operating characteristic (ROC) curve. Confidence interval was kept at 95% and P value< 0.05 was considered significant**.**

Table 1: Demographic and laboratory data of study participants

Variable	Healthy controls (n= 80)	Stable COPD (n= 88)	AECOPD (n= 100)	P Value
Age(years)(Mean± SD)	52.43 ± 2.1	54.12 ± 3.10	54.12 ± 3.10	0.205
Gender (n, %)				
Male Female	54(67.5%) 26(32.5%)	70(79.5%) 18 (20.5%)	74(74.0%) 26(26.0%)	0.570
Body mass index (kg/m2)	20.7 ± 2.3	21.6 ± 4.0	22.1 ± 2.8	0.063
Blood count				
Total WBCs(x 10^3/ul)	8.25 ± 2.06	10.61 ± 2.49	13.83 ± 3.95	0.035*
Neutrophils (x10^3/ul)	6.4 ± 1.40	9.27 ± 2.05	13.16 ± 2.67	0.013*
Lymphocytes (x10^3/ul)	4.03 ± 2.33	2.80 ± 1.29	1.77 ± 2.06	0.020*
Neutrophils / Lymphocytes ratio (NLR)	2.52 ± 0.90	3.14 ± 1.84	8.31 ± 5.09	<0.001*
FEV1 % predicted	78.11 ± 7.39	52.47 ± 10.21	38.32 ± 12.50	0.016*
FVC% predicted	87.14 ± 8.62	55.73 ± 10. 59	47.03 ± 12.13	0.038*
CRP (mg/dl)	0.5 ± 1.1	1.8 ± 0.79	6.5 ± 2.4	0.015*

Data expressed as number (n) and percentage (%), Mean± SD. WBCs= white blood cells; FEV1= forced expiratory volume in first second; CRP= C-Reactive protein;* significant

RESULTS AND DISCUSSION

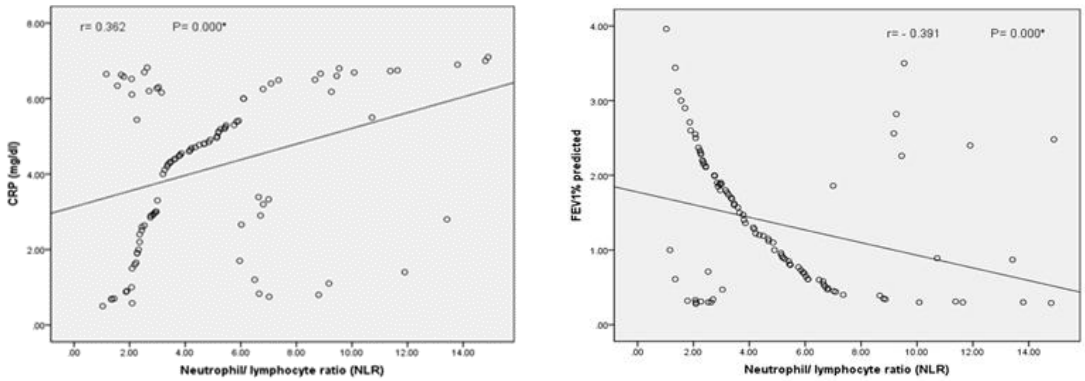
Results

Table (1) shows that, the majority of COPD patients were males (74% in the AECOPD group and 79.5% in stable COPD group).Total WBCs, CRP and NLR were significantly higher in AECOPD in comparison to stable COPD and control groups (P< 0.05 for each). The Lymphocytes count was significantly lower in AECOPD group. FEV1 % predicted and FVC % predicted were significantly lower in the AECOPD group. FEV1% predicted and CRP showed significant correlations with NLR (P< 0.05 for each) (Table 2 and Figure 1).

Table 2: Correlations between Neutrophils / Lymphocytes ratio (NLR), CRP, and Forced expiratory volume in first second in AECOPD patients

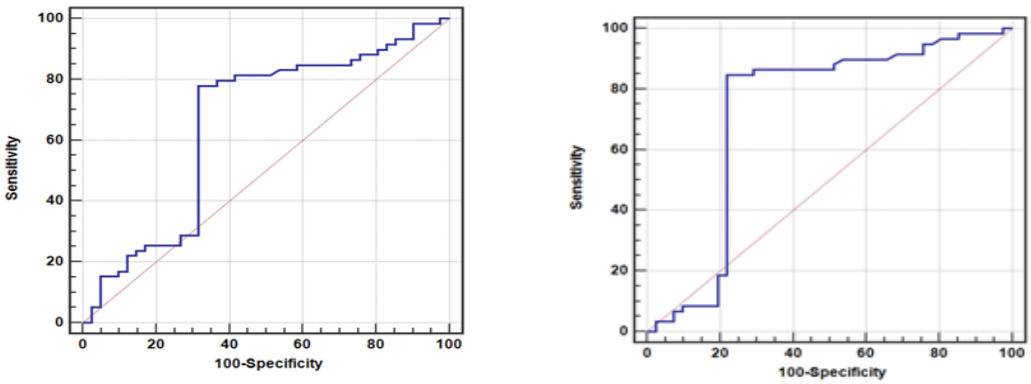
Variable	Neutrophil/ lymphocyte ratio (NLR)	
	r-value	P-value
CRP (mg/dl)	0.362	0.000*
FEV1% predicted	-0.391	0.000*

FEV1= forced expiratory volume in first second; CRP= C-Reactive protein; Neutrophil/ lymphocyte ratio (NLR), * significant



(a) **(b)**

Fig.1: Correlation between neutrophil/ lymphocyte ratio (NLR) and CRP (a), and FEV1%predicted (b)



(A) **(B)**

Fig. 2: Receiver operating characteristics for accuracy of CRP (A) and NLR (B) in detection of acute exacerbation of COPD

Table 3: Diagnostic accuracy of NLR and CRP in detection of acute exacerbation of COPD

Variable	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC
NLR	**> 3.26**	84.75	78.05	84.7	78.0	0.721
CRP	**> 4.11**	77.97	68.29	78.0	68.3	0.664

CRP= C-Reactive protein; NLR=Neutrophil/ lymphocyte ratio; PPV= positive predictive value; NPV= negative predictive value; AUC= area under the curve

Using ROC curve, the cut-off value for NLR in predicting AECOPD was > 3.26 with 84.7% sensitivity, 78.0% specificity, and 0.721 AUC while CRP at > 4.11 cut off value had 77.9% sensitivity, 68.2% specificity, and 0.664 AUC.(Figure 2 and Table 3).

Discussion

COPD is characterized by increased airway and systemic inflammation and during acute exacerbation; the severity of inflammation increases significantly.[11]

Oh and Sin reported that COPD patients have increased serum inflammatory biomarkers and up to ~70% of COPD patients have at least one raised serum inflammatory biomarker[12].

The persistently elevated inflammatory biomarkers are related to disease progression, clinical, pulmonary functions and the presence of comorbidities. CRP, IL6, and TNFα are the most studied serum inflammatory markers. However, using them in routine clinical practice is limited[13].

NLR is a simple, fast, cost-effective and easy method obtained from daily routine CBC test. NLR has been suggested as a beneficial indicator of outcome and severity of AECOPD.[14,15]

The present study showed that total WBCs, Neutrophils, and NLR were significantly higher while Lymphocytes count was significantly lower in AECOPD in comparison to stable COPD and control group (P< 0.05 for each).These results agreed with Farah et al, Yousef and Alkhiary, and Bilir et al.[16- 18].

In agreement with Günay et al[19], the current results found a significant difference between stable COPD and AECOPD regarding FEV1 % predicted and FVC % predicted.

In line with Taylan et al[20], the level of CRP was significantly higher in AECOPD group.

The current data reported that FEV1% predicted and CRP had a significant correlation with NLR. This agreed with Furutate et al, In et al, Yousef and Alkhiary[20, 21, 22] . To the contrary, Lee et al found a non-significant negative correlation between NLR and FEV1% predicted (r = – 0.285, p= 0.071).[21]

Kurtipek et al reported that the cut off point for NLR in predicting AECOPD was > 3.86 with 87% sensitivity, 82% specificity, and 0.98 AUC[22] while Yousef and Alkhiary found that the cut off point for NLR was > 3.12with 86.7% sensitivity, 76.7% specificity, and 0.88 AUC[22]. These results also agreed with this study.

The results obtained by Erdal et al.[23] were in concordant with the current results as they found that at > 3.34 cut off point for NLR, the sensitivity, specificity, and AUC were 78.7%, 73.2%, 0.86 respectively.

Taylan et al found that NLR at cut off of 3.29, showed 80.8 %sensitivity and 77.7% specificity while CRP at cut off of 1.17 showed 71.4 % sensitivity and 82.3 % specificity in predicting AECOPD[20]

Taken together, The present information suggest that NLR could be be used as a marker to evaluate the state of inflammation in COPD patients and foretell the inflammatory remission precipitating acute exacerbations.

Limitations of the study

The number of enrolled subjects was relatively small, patients with mild COPD exacerbation were not investigated to verify if the NLR performance will be the same during mild and severe exacerbation or not.

Conclusion

NLR is a beneficial, cost effective, and easily accessible marker for early detection of potential acute exacerbations in patients with stable COPD.

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نشرة العلوم الصيدلية
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التغييرات في النسبة بين خلايا العدلات المحببة و الخلايا اللمفاوية و بروتين سي المتفاعل في مرضي السدة الرئوية المزمنة الذين تم دخولهم للمستشفي بتفاقم حاد

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قسم الامراض الصدرية و التدرن ، كلية الطب ، جامعة اسيوط

التفاقم الحاد في مرض السدة الرئوية المزمنة هو سبب رئيسي لدخول المستشفي و ما يصاحبه من اعتلالات و هذا الامر شجع الباحثين للبحث عن دلالات التهابات لتمييز التفاقم الحاد في مرض السدة الرئوية المزمنة

تهدف هذه الدراسة الي تقييم دور النسبة بين خلايا العدلات المحببة و الخلايا اللمفاوية و بروتين سي المتفاعل لتمييز التفاقم الحاد في مرض السدة الرئوية المزمنة الذي يحتاج الي دخول المستشفي تضمنت الدراسة ١٠٠ مريض تفاقم حاد في مرض السدة الرئوية المزمنة و ٨٨ مريض سدة رئوية مزمنة مستقرة و ٨٠ انسان سليم

تم قياس النسبة بين خلايا العدلات المحببة و الخلايا اللمفاوية و بروتين سي المتفاعل في عينات الدم مرتين لكل المشاركين في الدراسة المرة الاولي في خلال ساعتين من دخول المستشفي و المرة الثانية بعد ثلاثة اشهر

تم حساب النسبة بين خلايا العدلات المحببة و الخلايا اللمفاوية من تحليل صورة الدم.

اظهرت النتائج فرق ذو دلالة احصائية بين عدد خلايا الدم البيضاء وعدد خلايا العدلات المحببة و النسبة بين خلايا العدلات المحببة و الخلايا اللمفاوية في مجموعات الدراسة

وجدت الدراسة علاقة ذات دلالة احصائية بين بروتين سي المتفاعل و حجم الهواء الذفيري المتدفق في الثانية الاولي و النسبة بين خلايا العدلات المحببة و الخلايا اللمفاوية

عند الحد القاطع لقيمة النسبة بين خلايا العدلات المحببة و الخلايا اللمفاوية > ٣.٢٦ كانت حساسية الاختبار تساوي ٨٤.٧% و النوعية تساوي ٧٨% و عند الحد القاطع لقيمة بروتين سي المتفاعل > ٤.١١ كانت حساسية الاختبار تساوي ٨١.٣% و النوعية تساوي ٧٥%.

استنتجت الدراسة انه يمكن استخدام النسبة بين خلايا العدلات المحببة و الخلايا اللمفاوية كمؤشر مماثل لعدد خلايا الدم البيضاء و بروتين سي المتفاعل التهابات لتمييز التفاقم الحاد في مرض السدة الرئوية المزمنة.