Evaluation of C-Reactive Protein, Interleukin-6, and Neutrophil-Lymphocyte Ratio as Inflammatory Markers in Patients with Chronic Bronchitis Taking Oral Prednisolone in Maysan City Population

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Abstract :

Background: Clinically, chronic bronchitis is defined as a persistent cough lasting at least three months over the course of two years in a patient where all other causes have been excluded. It is almost invariably described as a feature of Chronic Obstructive Pulmonary Disease (COPD) secondary to smoking.

Patients and methods: Ninety-five Iraqi patients newly diagnosed with chronic bronchitis were selected to participate in this study. Sixty patients (40 male and 20 female) were enrolled in the current study their ages were ranged from (40-65 years).

The patients were divided into two groups, in the first group (responders' group) the patients were responded to oral prednisolone therapy, and in the other group the patients were not responded to oral prednisolone therapy (non-responders' group). The assessment of responsiveness to prednisolone will be according to ATS (American Thoracic Society) which define the responders as those with a response of >12% baseline and >200 ml of FEV1. This study is a prospective observational clinical trial was carried out in thoracic consultant clinic at Al- Sader teaching Hospital in Maysan city from March 2022 until March 2023. The prednisolone tablets given in a dose of 30mg /day for 14 days.

Aim of the study: The current study was aimed to identify the association of the inflammatory markers C-reactive protein, interleukin-6 and neutrophils-lymphocytes ratio with the response of chronic bronchitis patients to oral prednisolone therapy.

Results and Conclusions: CRP, IL-6, and NLR consider as good predictive markers (*P* value<0.001) to determine the responsivity of patients with chronic bronchitis taking oral prednisolone tablets for 14 days.

Key words: chronic bronchitis, CRP, IL-6, NLR.

دراسة أنترلوكين -6 وبروتين سي التفاعلي ونسبة الخلايا المتعادلة الى اللمفاوية كعلامات التهابية في المرضى الذين يعانون من التهاب الشعب الهوائية المزمن الذين يتناولون بريدنيزولون عن طريق الفم في سكان مدينة ميسان.

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الخلاصة:

التهاب الشعب الهوائية المزمن سريريا يشبه السعال المزمن المصحوب بانتاج البلغم لمدة 3 أشهر على الأقل في كل سنتين متتاليتين في المريض الذين يتم استبعاد الأسباب الأخرى المسببة للالتهاب.

المرضى وطرق العمل: تم اختيار خمسة وتسعين مريضاً عراقياً والمشخصين حديثاً بإصابتهم بإلتهاب الشعب الهوائية المزمن للمشاركة في هذه الدراسة، 60 مريضاً (40 ذكر و20 أنثى) فقط تم اشراكهم في الدراسة الحالية أعمارهم كانت تتراوح بين (40-65 سنة). تم تقسيم هؤلاء المرضى إلى مجموعتين، واحدة منهم استجابت للعلاج بالبريدنيزولون عن طريق الفم (المرضى المستجيبين) والأخرى لم تستجيب للعلاج (الغير مستجيبين). تقييم الأستجابة لدواء البرزلون حسب تعريف الجمعية الأمريكية للأمراض الصدرية. هذه الدراسة هي تجربة سريرية قائمة على الملاحظة تم القيام بها في استشارية الأمراض التنفسية في مستشفى الصدر للفترة من شهر أذار 2022 ولغاية شهر أذار 2023. حبوب البرزلون أعطيت بجرعة 30 مع يوميا لمدة 14 يوم.

الغرض من الدراسة: هدفت الدراسة الحالية إلى تحديد ارتباط الواسمات الالتهابية CRP وIL-6 وNLR باستجابة مرضى التهاب الشعب الهوائية المزمن للعلاج بالبريدنيزولون الفموي.

النتائج والاستنتاجات: يعتبر بروتين سي التفاعلي والأترلوكين -6 ونسبة الخلايا المتعادلة الى اللمفاوية علامات تنبؤية جيدة (قيمة $p < 0.001$) لتحديد استجابة المرضى الذين يعانون من التهاب الشعب الهوائية المزمن الذين يتناولون أقراص بريدنيزولون عن طريق الفم لمدة 14 يومًا.

الكلمات المفتاحية: التهاب الشعب الهوائية المزمن، بروتين سي التفاعلي، أنترلوكين-6, نسبة الخلايا المتعادلة الى اللمفاوية.

Introduction

Charles Badham first described chronic bronchitis (CB) in 1814 as a cough that lasts for several weeks or months, breathing difficulties, frequently a feeling of weight or fluttering, and typically profuse, viscid, and persistent sputum [1]. Chronic bronchitis was eventually classified as having a persistent cough and sputum production for at least three months each year for two straight years [2, 3]. In the United States, chronic bronchitis affects roughly 10 million people, the majority of whom are between the ages of 44 and 65[4]. The occurrence of chronic bronchitis in general population has been documented to vary from 3% to 7% in healthy adults. However, it is estimated to be as high as 74% among those diagnosed to have COPD [5].. Sometimes chronic bronchitis is seen in 3.4 to 22.0% of adults. This wide range of prevalence estimates may be due to varying definitions of CB (such as chronic phlegm versus chronic cough and phlegm) as well as the possible inclusion of subjects with bronchiectasis)[6].

Exposure to cigarette smoke, whether from active or passive smoking, is the main contributing cause to chronic bronchitis. Additionally, a lot of respiratory irritants that are inhaled, like smog, industrial pollutants, and hazardous chemicals, might lead to chronic bronchitis [5]. Even though cigarette smoking is the primary cause of the disease, only 10–20% of smokers have CB, and 25–45% of COPD cases are linked to nonsmoking risk [7].

Persistent cough, production of phlegm, and shortness of breath are the symptoms of patients with CB [8]. The failure in clearance of mucociliary is the most prominent pathogenesis of CB [9] Overproduction and hypersecretion by goblet cells and reduced elimination of mucus is the mechanisms that responsible for increased mucus in CB [10, 11] . Hypersecretion of mucus is formed due to continuous exposure to cigarette smoke, acute and chronic viral infection, bacterial infection, or inflammatory cell activation of mucin gene transcription through the activation of epidermal growth factor receptor[12].

Recent research has suggested that the blood Neutrophil-Lymphocyte ratio (NLR), a generally accessible, and simple index calculated from whole blood counts, which might predict the intiation, progression, and prognosis of various chronic inflammatory diseases [13] including cancer [13, 14]. In a previous study a positive association of Body mass index, air flow obstruction, dyspnea, exercise capacity (BODE) index

with IL-6, TNF-α and CRP was recorded [14].. This study also showed that there is a negative association between IL-6 and forced expiratory volume in one second (FEV1), while there was a positive correlation of IL-6 with 6-minute walk test (6MWT) and modified Medical British Research Council dyspnea Questionnaire (mMRC). In another study, IL-6 was determined to be positively correlated with the CAT score and mMRC and negatively correlated with the forced vital capacity (FVC,L), FEV1 (L), FEV1 (%) and the 6MWT result [15]. Systemic inflammation is crucial for the development of CB, its progression, and mortality. Although CRP is linked to a number of diseases that are part of the natural course of COPD, its level can also be used to monitor the outcome of CB in the infected patients[16]. According to some research, CRP levels may be utilized with other biochemical indicators to choose the best preventative and treatment measures for this condition(17).

Aim of the study: The current study aimed to identify the association of the inflammatory markers C-reactive protein, interleukin-6 and neutrophils-lymphocytes ratio with the response of chronic bronchitis patients to oral prednisolone therapy.

Patients and Methods: This study is prospective interventional clinical trial involved 95 patients with CB who are newly diagnosed during their visit to Al-Sader teaching hospital in Maysan governorate. The patients are supervised and treated by a pulmonologist in thoracic consultant clinic at Al-Sader teaching hospital in Maysan governorate. Only 60 Iraqi patients (45 male and 15 female) there ages range from (40-65 years) completed the courses of the study successfully. Baseline demographic characteristic features of the enrolled participants (gender, age, body mass index, residency and smoking status) were recorded.

Serum level of C-reactive protein (CRP), interleukine-6 (IL-6), neutrophil – lymphocyte ratio (NLR) was measured at baseline and after 14 days of treatment with oral prednisolone tablets. The ethical approval of the current study was according to the approval decision (Approval No.11) by the research ethics committee / College of Pharmacy / Mustansiriyah University.

Inclusive criteria

1- Newly diagnosed patients with chronic bronchitis who are aged from (40-65) years of either sex, who are accepted to participate in the study with mild or moderate chronic obstructive pulmonary diseases according to GOLD guideline[18] .
2- Patients treated with prednisolone for 14 days.
3- Patients must be read and written in Arabic.
4- Patients with a post-bronchodilator FEV1/FVC ratio of <0.70[19].

Exclusive criteria

1- Patients with a contraindication to steroids.
2- Patients with other respiratory diseases such as asthma, emphysema, exacerbations of COPD, sever and very severe chronic obstructive pulmonary diseases or unable to perform acceptable spirometer analysis.
3- Patients with nephropathies or chronic renal failure.
4- Patients have various tumors of respiratory tract tissues.
5- Pregnant and lactating women.
6- Patients with corticosteroids hypersensitivity.

International Business Machines Statistical Package for the Social Sciences (IBM SPSS) Statistics Version 28.0.0.0(190) for Windows was used to evaluate the results of this study. Kolmogorov-Smirnov test was used to detect if the quantitative variables were normally distributed. The normal

distribution of variables were given as mean ± standard deviation and as median (with interquartile range) for the variables, which were not distributed normally. Our values were non-normally distributed**.** Receiver operating characteristic (ROC) curves were constructed to evaluate the NLR, CRP and IL6 variables in responder and non-responder groups of patients**.**

Independent samples t-test, paired t-test, Wilcoxon signed rank, Mann–Whitney U test and the Kruskal–Wallis H test were utilized for comparing continuous variables pre and post the treatment with prednisolone. Fisher's exact and Chi-square tests were utilized to analyze the categorical variables. $P < 0.05$ showed statistical significance.

RESULTS

Among 60 patients with chronic bronchitis who were included in this study, 15 (25%) were females and 45 (75%) were males, the mean age was (49.1 ± 7.5) years, the range was (40-64) years, the median was 47 years and interquartile range was 14, as illustrated in (table.1) that show demographic and clinical characteristics of patients with chronic bronchitis.

C-reactive protein, IL-6, and NLR level was measured for each patient in the first visit and after 14 days of taking oral prednisolone pills for identify the association of these variables with the response to treatment with prednisolone, according to the definition of the American Thoracic Society which define the responders as those with a response of >12% baseline and >200 ml of FEV1[20].

According to the last definition, in the current study, 35(58%) patients responded to prednisolone therapy and 25(42%) patients don't response. There are a significant decrease in the values of CRP, IL-6, and NLR in the patients before and after taking oral prednisolone tablets for two weeks in the responders group. For the patients responders' group, the CRP median range change from 7.9-5 (IQR 5.2-14.6 to 3.5-8.8), for IL-6 median change from 52.1-28.5 (IQR 43.2-65.6 to 21.5 -44.9) and NLR median change from 3.9-2.8 (IQR 2.9-4.9 to 2.2-3.7) respectively.

While there is a decrease in the values CRP, IL-6, and NLR in the patients of non-responders' group. This will occur in pre and post treatment with prednisolone but to a less extent than responder patients as a median of CRP change from 7.8-5.8 (IQR 5.6-13.1 to 4.7-8.9) , median of IL-6 change from 52.1-35.4 (IQR 37.7-80.5 to 20.2-52.5) , and NLR median change from 3.8-2.8 (IQR 2.8-4.4 to 2.2-3.8) respectively. There was a highly significant difference of CRP, IL-6, and NLR in patients with CB in the responders and non-responders group in pre and post treatment with oral prednisolone and the non-responders group (Table.2).

Table .1: Demographic characteristics of patients with chronic bronchitis

Age Mean±SD Range Median Interquartile Range	 49.1±7.5 (65-40) 47.0 14
BMI Mean ±SD Range Median Interquartile Range	 26.2 (±2.9) (35.1-22.0) 25.70 3.99

Sex	Male	N(%)	45 (75.0%)
	Female	N(%)	15 (25.0%)
Residence	Rural	N(%)	20 (33.3%)
	Urban	N(%)	40 (66.7%)
Smoke status	+VE	N(%)	36 (60.0%)
	-VE	N(%)	24 (40.0%)

Table. 2: Values of inflammatory markers pre and post prednisolone therapy in Responders and non-Responders patients with chronic bronchitis

	Responsivity						**P. Value [a]**
	Response n=35			**Non-response n=25**			
	Median	**IQR**		**Median**	**IQR**		
pre (CRP)	7.9	5.2	14.6	7.8	5.6	13.1	**0.845 [NS]**
post (CRP)	5.0	3.5	8.8	5.8	4.7	8.9	**0.358 [NS]**
P. Value [b]	**< 0.001****			**< 0.001****			
pre (IL-6)	52.1	43.2	65.6	52.1	37.7	80.5	**0.840 [NS]**
post (IL-6)	28.5	21.5	44.9	35.4	20.2	52.5	**0.264 [NS]**
P. Value [b]	**< 0.001****			**< 0.001****			
pre(NLR)	3.9	2.9	4.9	3.8	2.8	4.4	**0.621 [NS]**
post (NLR)	2.8	2.2	3.7	2.8	2.2	3.8	**0.675 [NS]**
P. Value [b]	**< 0.001****			**< 0.001****			

test used Data presented as median & interquartile range, [a] Mann–Whitney U-test used to test statistical differences between responsivity groups (Horizontally), [b Wilcoxon] signed-rank for comparison between (pre & post). [NS] No significant changes ($p \geq 0.05$), ** highly significant changes ($p < 0.01$).

For each of the inflammatory markers that measured in the current study, CRP, IL-6, and NLR, table.3 and figure 1 are showing the cutoff value and area under the curve of receiver operating characteristic curve (ROC).

The ROC curve analysis showed that IL6 has the highest area under the curve (AUROC) = 0.480, followed by NLR and CRP with corresponding AUOC of 0.465, 0.411 respectively, reflecting a high prognostic performance of these inflammatory parameters to assess chronic bronchitis.

Table 3. The cutoff value and Area under the ROC curve of inflammatory markers in patients with chronic bronchitis

Markers	**Cutoff**	**AUC**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**P. Value**	**Asymptotic 95% Confidence Interval**	
								Lower Bound	Upper Bound
CRP	4.91	0.411	54	40	65	51	0.242	0.262	0.560
IL6	19.78	0.480	52	48	59	42	0.793	0.333	0.627
NLR	2.82	0.465	54	48	59	43	0.642	0.309	0.620

AUC: Area under the ROC curve, ROC: receiver operating characteristic curve
PPV: Positive predictive value, NPV: Negative predictive value

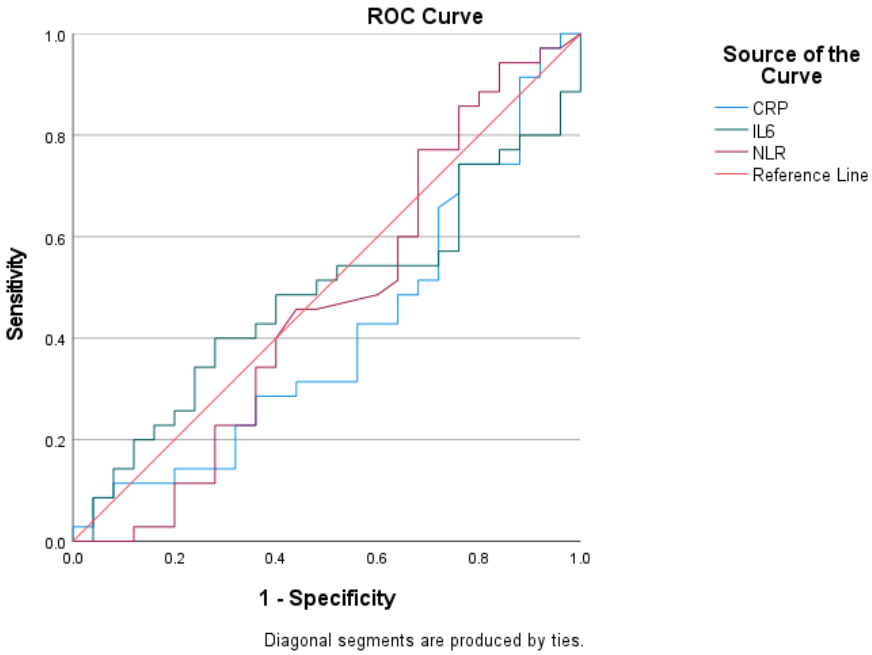

Figure 1: Receiver operating characteristic curve for measuring the area under curve for C-reactive protein, interleukin-6, and Neutrophil/Lymphocyte Ratio in responders and non-responders' groups.

In the context of Spearman's correlation between post (CRP) and post (NLR), the Spearman's rho value of 0.488 indicates a moderate positive monotonic relationship between the two variables. This means that as the post (CRP) values increase, the post (NLR) values tend to increase as well, or vice versa, but the relationship is not as strong as it could be.

The P-value of 0.003 indicates that the correlation is statistically significant. In other words, the probability of observing a correlation of this magnitude between the variables by chance alone is low. It suggests that the observed relationship between post (CRP) and post (NLR) is unlikely to be a result of random variation and is likely to be a true relationship.

Overall, the interpretation would be that there is a moderate positive monotonic relationship between post (CRP) and post (NLR), and this relationship is statistically significant as shown in (Table .4).

Table 4: Correlation between CRP, IL-6, and NLR in responders' group in post treatment with oral prednisolone

	Spearman's rho	**P. Value**	95% Confidence Intervals (2-tailed	
			Lower	Upper
post (CRP) - post (IL-6)	0.279	0.105	-.0070-	0.567
post (CRP) - post (NLR)	0.488	0.003*	0.175	0.711
post (IL-6) - post (NLR)	0.296	0.084	-0.052-	0.580

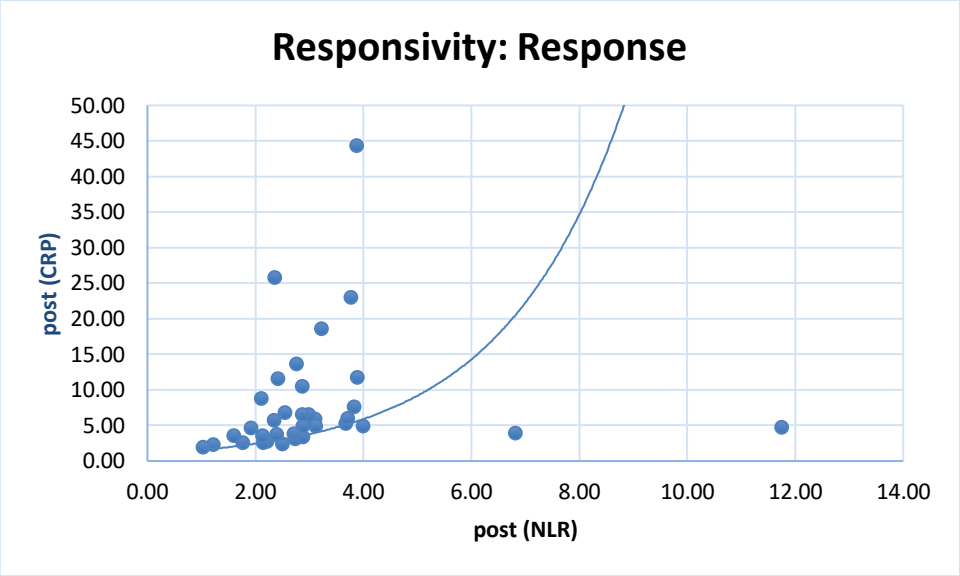

Figure 2: Correlation between CRP and NLR in responder's group post treatment with oral prednisolone

Discussion:

Chronic bronchitis is a type of COPD that causes hard breathing that worsens with time. The influences of genetic, biochemical, clinical, and environmental factors are significant in disease management and influencing the severity of chronic diseases. The chronic bronchitis which is a more important arm of COPD is linked to a faster loss of lung function, an elevated risk of exacerbations, and a higher mortality rate. An essential component of the etiology of chronic bronchitis is systemic inflammation [21] .

In the present study, for responder patients, the CRP was highly decreased after treatment with prednisolone therapy. As with the most other studies, the inflammatory biomarker (CRP) levels were significantly higher (P<0.01) in patients with chronic obstructive pulmonary [22, 23].

Interleukin-6 decreased in the patients that enrolled in this study and reduced to a lesser extent in non-responder chronic bronchitis patients. Despite the IL-6 had a negative association with FEV1 (%) (15), many studies proved a positive correlation between IL-6 as inflammatory marker and disease severity, prognosis and increased exacerbation of patients with COPD [24-26].

The ratio of neutrophils to lymphocytes is a commonly used, simple to measure, and inexpensive indicator that has undergone substantial research recently as a predictor of illness onset, progression, response to treatment, and prognosis [27]. It is well known that various chronic inflammatory disorders and malignancies have higher NLR levels [28].

The reduction in a median of NLR in pre and post prednisolone treatment for both responder and non-responder patients approximately was the same in this study.

In the present study the values of CRP, IL-6, NLR in patients with CB in pre and post prednisolone treatment are significant (P<0.001) in responder and non-responder patients with chronic bronchitis.

Neutrophil-lymphocyte ratio levels were not significantly affected by corticosteroid medication, making them useful prognostic indicators for individuals who are already receiving steroid therapy [29].

In our study, the sever decreased occur in the level of IL-6 pre and post treatment with prednisolone in responded

patients.Therefore, it is consider as a strong cytokine or inflammatory marker suppressed by corticosteroids (prednisolone) which is act as anti-inflammatory agents and this result agreed with the Chinese study conducted in 2021 by Wen Song *et al* [30].

In our study, the value of CRP consider as a useful tool for detecting the pathogenesis of chronic bronchitis. This result will agreed with the result of Chinese study conducted by 2019 by Tian-Lian *et al* , that concluded that inflammatory biomarker (CRP) levels were significantly higher in acute exacerbated COPD population in comparison to healthy controls more than sable COPD patients [31] .

The weak correlation between some inflammatory markers due to some patients may not take the correct dose (of oral prednisolone) in correct time every day regularly for 14 days.

The lower value of sensitivity and specificity of CRP, IL-6, and NLR may be due to small sample size included in the current study.

Conclusion:

In conclusion, increased values of (CRP, IL-6, and NLR) are significantly related to the pathological process of chronic bronchitis. There is a positive correlation between (CRP and NLR) in responder group of patients after treatment with oral prednisolone tablets. The values of these markers will elevate before prednisolone treatment and decrease after two weeks of treatment with prednisolone tablets in both responded and non-responded patients.

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