The Correlation Between Asthma Severity and Neutrophil to Lymphocyte Ratio

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Abstract—

Background—The prognosis is essential in management and follows up of asthmatic patients. Neutrophil to lymphocyte ratio is considered as the common prognostic marker for many diseases especially the asthma.

Aim of study—To assess the relationship between asthma severity and neutrophil to lymphocyte ratio in comparison to healthy controls.

Patients and methods—This study is a cross sectional study conducted in Respiratory Consultancy Clinic in Baghdad Teaching Hospital in Medical City during the period from 1st of October, 2018 to 31st of March, 2019 on sample of 50 asthmatic patients and 50 healthy controls. The diagnosis of asthma was confirmed by the supervisor through clinical symptoms, signs, spirometry with reversibility test (according to GINA guideline.).

Results—A highly significant difference was observed between asthmatic cases and controls regarding age ($p < 0.001$). A significant association was observed between obesity and asthmatic cases ($p = 0.001$). There was a highly significant association between high neutrophil/lymphocyte ratio and asthmatic cases ($p < 0.001$). The neutrophil/lymphocyte ratio was significantly increased with advanced age, females, severe and uncontrolled asthma.

Conclusions—The neutrophil to lymphocyte ratio is useful biomarker in assessment of asthma severity.

Index Terms—Asthma, Neutrophil to Lymphocyte Ratio.

I. INTRODUCTION

Asthma is the most common chronic inflammatory disease of the airways in the population. Chronic inflammation caused by mediators released from mast cells, eosinophils, neutrophils, macrophages, lymphocytes, and some other cells has been detected in the airways of asthmatic patients [1].

Recent studies have demonstrated that neutrophilic inflammation is related to an increase in the severity of the disease [2]. In addition, the existence of eosinophilic inflammation in asthma has been shown to be related to atopy and symptoms of persistent asthma [3].

A definition of the similar biological indicators that play a role in inflammation in asthma is important since this will open the gate for further developments in diagnosis and treatment. During childhood asthma, in particular, special

non-invasive asthma indicators for monitoring and follow-up are of great importance because existing diagnostic techniques cannot be used properly due to their invasiveness or the need for cooperation. Commonly used Spiro metric measurements require effective cooperation, whereas bronchoalveolar lavage (BAL) is invasive [4]. Therefore, there is a need for non-invasive methods that can be used to monitor asthma. Chronic inflammation is also present in asthma.

Cytokines in the pathogenesis of asthma cause an increase in neutrophils, as noted above [1], [2]. Based on this information, we consider that the NLR is increased in asthmatics. However, our knowledge regarding NLR in Asthmatic patients is incomplete [5], [6]. Although a previous study in adults revealed no relationship between asthma and NLR, [5] NLR was found to be associated with neutrophilic asthma in the second study [6]. Neutrophil to-lymphocyte ratio (NLR) has been studied in medical and surgical populations.

It is a prognostic marker of morbidity and mortality for numerous conditions, including cardiovascular disease [7], oncology [8], critical care medicine [9], liver disease [10], general surgery, and vascular surgery [11]. It was recently associated with all-cause mortality in hemodialysis (HD) patients [12].

A. Neutrophils and respiratory diseases

With the changing of global environment, especially the increased air Pollution worldwide, respiratory diseases are becoming a main killer to Human health. According to recent researches, asthma is ranked as the 14th most important chronic disease, affecting 334 million individuals of all ages worldwide [13]. Lung is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths [14].

As for COPD, affecting 64 million people all over the world, it would be the third most common cause of death by 2030. Community acquired pneumonia is a common cause of sepsis, leading to 10 million deaths annually [15]. While epidemiology data of idiopathic pulmonary fibrosis (IPF) worldwide cannot be obtained, IPF incidence is still increasing and carries a high risk of respiratory failure and death [16].

Respiratory diseases not only increase the economic burden of global health care but also cause a terrible effect on the quality of daily life.

Although the precise treatment of respiratory diseases has made a great progress, the pathogenesis of them still needs further elucidation [17].

Innate together with adaptive immunity, as natural systematic defensive barrier, is composed of immune organs, cells, and cytokines [18]. The innate immunity is a

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natural defense that shapes in the process of long-time biological evolution. As the first barrier to defend infection, innate immunity participates in the resistance to pathogenic invasion and the clearance of aging, injured and even mutant cells nonspecifically. Innate immunity was firstly reported in the development of immunology and was becoming the focus of immunological research in recent twenty years, especially after the discovery of various kinds of pattern recognition receptors (PRRs) and innate lymphoid cells (ILCs) [19]. When the exogenous threats cannot be removed by innate immunity successfully, adaptive immunity will take part in the important defensive battle. Adaptive immunity system including humoral and cellular immunity often plays a leading role in the final clearance of invasive pathogens. The executors are T lymphoid cells and B lymphoid cells, who can both recognize antigens specifically. Different immune cells can exert protective and defensive effect synergistically with the help of multiple cytokines and protein molecules. The mechanism of adaptive immunity has been being gradually clarified since the birth of immunology. Various monoclonal antibody medicines related with adaptive immunity such as rituximab and infliximab have brought a wonderful curative effect in many refractory diseases including respiratory diseases [20].

Traditionally, neutrophils, originating in bone marrow stem cells, had only been considered as a kind of innate immune cell [21]. As an essential component of innate immunity, neutrophils play an important role in killing pathogens and removing cellular debris [22]. The migration and activation of neutrophils could cause inflammation and sensitization directly or indirectly. Inflammation caused by self-immune system is really important for the solution of infection and clearance of pathogens. But the persistent inflammation in respiratory system frequently leads to some adverse diseases such as asthma, COPD, and pulmonary fibrosis. In addition, neutrophils can synergize with lymphocytes and other granulocytes, such as Th2/Th17 and eosinophils, to participate in not only innate but also adaptive immune process and promote airway inflammation [23]. The interaction between neutrophils and other immune cells, endogenous composition, and foreign matter is very complex and being clarified thoroughly [22].

There have been more and more studies on the role of neutrophils in respiratory diseases. Recently, exosomes, neutrophil extracellular traps (NETs), deriving from neutrophil and the higher autophagy of neutrophils have been reported in multiple respiratory diseases [24]. Despite that the pathogenesis of respiratory diseases are being studied extensively, there is still a long way to go to clarify the complexity and heterogeneity, especially the participation of various immune components in the development of respiratory diseases [20].

B. Asthmatic neutrophils

As Global Initial for Asthma (GINA, updated in 2017) elucidated [25], asthma is a heterogeneous disease, always characterized by expiratory airflow limitation and chronic inflammation. Asthma is usually categorized as different phenotypes and endotypes according to its different clinical characteristics and distinct pathological mechanism.

Traditionally, asthma was classified as four different

phenotypes [26], eosinophilic, neutrophilic, mixed granulocytic asthma, and paucicellular asthma according to the cellular counts of sputum, bronchoalveolar lavage fluid (BALF), or peripheral blood [27]. For example, Jodie et al. distinguished asthmatics with neutrophil proportion in sputum over 61% as neutrophilic asthma [28]. However, more and more researches have demonstrated the instability of asthma phenotypes [29]. Neutrophil as an essential granulocyte has been reported by many investigators to play a critical role in many immunity-associated diseases including asthma, especially steroid-refractory severe asthma [30]. High blood neutrophils counts are associated with an increased risk of moderate, but not severe asthma exacerbation. At the same time, the neutrophil-predominant asthmatics also tend to show a lower bronchial liability [31].

C. Neutrophils participation in asthma

Lower respiratory tracts used to be considered as sterile. But more and more evidence had already showed us the conflicted results. *Moraxella catarrhalis* or a member of the *Haemophilus* or *Streptococcus* genera was discovered colonizing in the lower airways of asthmatics [32]. These species' colonization was associated with more differential sputum neutrophil counts and worse clinical disease status. The altered colonization would participate in the development of asthma phenotype. Infection of *H. influenza* could synergize with allergic airway diseases to induce Th17 immune responses that drive the development of neutrophilic asthma. The process above is mediated by IL-17 responses.

In addition, subclinical infection likely contributes to neutrophilic inflammation in airways [33].

Microbial components, which contain LPS and β -glucan, could synergistically cause neutrophilic asthma mediated by TLR-4 and dectin-1, whose deficiency could significantly attenuate the recruitment of neutrophils induced by house dust mite (HDM) into airways [34]. Blood neutrophils from allergic asthma also show the chemotactic and phagocytic activities towards LPS and asthmatic serum [35].

Asthmatics challenged with inhaled *Dermatophagoides pteronyssinus* (DP) would promote the production of neutrophil chemotaxis. Siew et al. demonstrated that neutrophil chemotaxis induced by smoke and other environmental stimulations could also be helpful for developing inflammation in airways [36].

As described above, smoking and other infectious factors can cause the accumulation of neutrophils in BALF. This is associated with the activation of phosphatidylinositol 3-kinase (PI3K) signal. Phosphatidylinositol 3-kinases (PI3Ks), as the key elements in the signaling cascades, play an important role in the chemotaxis of neutrophils. In particular, PI3K δ and PI3K γ isoforms contribute to inflammatory cell recruitment and subsequent activation [37].

The traditional role of different PI3K isoforms in the chemotaxis of neutrophils had already been reviewed previously [38]. PI3K γ deficiency could significantly reduce the influx of neutrophils into BALF.

PI3K δ inhibition may also prevent recruitment of neutrophils. The PI3K-related inflammation and steroid insensitivity should partly be attributed to microRNA-

21/PI3K/histone deacetylase 2 (HDAC2) axis as Kim et al. reported. In addition, the activation of PI3K is accompanied with the release of all kinds of chemokines and cytokines, such as IL-6 and IL-8, which are related with the increased chemotactic activity of neutrophils towards the inflamed sites. Not only the chemotactic activity of neutrophils but also the concrete details of neutrophil activation mechanism have been making progress in recent years [39].

D. Potential Targeted Therapy

It is believed that the failure of targeting neutrophils could be attributed to an incomplete understanding of underlying mechanism of neutrophilic asthma. New insights into emerging neutrophil biology and underlying mechanisms of neutrophil phenotype might come to be the evidences of precision-based medicine. ICS is still the first-line medicine for ameliorating syndromes. Coinhalation of roflumilast and fluticasone, which reduces the counts of both neutrophils and eosinophils in BALF, could significantly improve the inflammatory condition in OVA-induced mice compared with the combination of formoterol and fluticasone [52].

Manually synthetic chemical drugs have an important curative effect on various diseases all along. Simvastatin, as an effective serum cholesterol-lowering agent could reduce the percentage of neutrophil in BALF and improve airway inflammation and remodeling in obese asthma mice. Tamoxifen had a direct action on equine peripheral blood neutrophils and dampened the respiratory burst production. Rosiglitazone (RSG), a peroxisome proliferator-activated receptor- γ agonist, has been reported to attenuate airway inflammation by inhibiting the proliferation of effector T cells in a murine model of neutrophilic asthma in vivo. It can also downregulate the ratio of Treg and Th17 cells, inhibit the secretion of Th2 cytokines, and further inhibit the airway inflammatory response in asthma mice effectively [53]. AZD5069 as an antagonist of CXCR2, a receptor promoting neutrophils back to the inflamed airways, could reversibly reduce circulating neutrophils' count. SCH527132, a selective CXCR2 receptor antagonist, can reduce sputum neutrophils and tend to improve the Asthma Control Questionnaire scores of asthma [52].

Medicine from various plants has composed a large part in health care field. Ligustrazine, water extract of *Helminthostachys zeylanica* (L.) Hook, astragaloside as an anti-inflammatory flavonoid present in persimmon leaves and green tea seeds, hydroethanolic extract (70%) of *M. longiflora* (HEMI), bufalin and cordycepin could target to the neutrophils, intervene the different inflammatory signaling pathways, and improve the prognosis of asthma. Biopharmaceutical has become a new treatment for asthma in recent years. Recombinant human activated protein C (rhAPC) could attenuate HDM + LPS-induced neutrophil migration in allergic asthma. Another recombination protein, recombinant human IL-4, could inhibit airway inflammation in bronchial asthma by reducing the cytokines and inflammatory cells including neutrophils. Medicine from plants and targeted biopharmaceuticals has a huge potential to play a major role in future medical field [54].

E. Aim of study

To assess the relationship between asthma severity and

neutrophil to Lymphocyte ratio in comparison to healthy controls.

II. PATIENTS AND METHOD

A. Study design and settings

This study is a cross sectional study conducted in Respiratory Consultancy Clinic in Baghdad Teaching Hospital in Medical City during the period from 1st of October, 2018 to 31st of March, 2019.

B. Study population

All asthmatic patients presented to Respiratory Consultancy Clinic in Baghdad Teaching Hospital was the study population.

C. Inclusion criteria

1. Adults (age ≥ 20 years).
2. Confirmed diagnosis of asthma. (According to GINA guideline.)

D. Exclusion criteria

1. Children and adolescents.
2. Smokers.
3. Signs of infection like fever, cough and sputum.
4. Renal diseases.
5. Liver diseases.
6. Cardiovascular diseases.
7. Other chronic diseases.

E. Sampling

A sample of 50 asthmatic patients presented to Respiratory Consultancy Clinic in Baghdad Teaching Hospital was selected after eligibility to Inclusion and exclusion criteria. A convenient sample of 50 healthy controls was selected from relatives accompanying patients in the Clinic.

F. Data Collection

The data was collected by researcher from study participants directly and filled in a prepared questionnaire. The questionnaire was designed by the supervisor and researcher. The questionnaire included the followings.

1. Demographic characteristics of study participants: Age and gender.
2. Educational level of study participants.
3. Body mass index of study participants.
4. Blood film of study participants: WBC, Hb, neutrophils and lymphocyte.
5. Spirometry findings of study participants: FVC, FVC%, FEV1, FEV1%, FEV/FVC.
6. Neutrophil to lymphocyte ratio (NLR).

G. Assessment of study participants

The diagnosis of asthma was confirmed by the supervisor through clinical symptoms, signs, spirometry with reversibility test which were done in Respiratory Clinic of Baghdad Teaching Hospital. After taking full history and examination of study participants, a sample of 5 ml venous blood was drawn from patients and sent for Laboratory of Baghdad Teaching Hospital to acquire the blood film and specifically NLR of all study participants. The normal limit

values of NLR were: 0.78-3.53 [55].

H. Ethical considerations

1. The ethical approval was taken from hospital authorities.
2. The researcher helped in diagnosis and management of asthma.
3. An oral informed consent was taken from all study participants.

I. Statistical analysis

All study participants' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 20 was used. Descriptive statistics presented as (mean $\pm$ standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi square test was used for categorical variables (Fishers exact test was used when expected variable was less than 20% of total variable). Independent sample t-test was used to compare between two means and one-way ANOVA analysis was used to compare between more than two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs. Statistical analysis of the study was done by Specialist in Community Medicine.

III. RESULTS

In present study 100 study participants were included; 50 asthmatic cases and 50 healthy controls. A highly significant difference was observed between asthmatic cases and controls regarding age ($p < 0.001$); 16% of asthmatic cases were 50 years age and more. No significant differences were observed between asthmatic cases and controls regarding gender ($p = 0.6$) and educational level ($p = 0.2$). A significant association was observed between obesity and asthmatic cases ($p = 0.001$); 42% of asthmatic cases were obese. All these findings were shown in Table I and Fig. 1.

TABLE I: DISTRIBUTION OF GENERAL CHARACTERISTICS ACCORDING TO ASTHMATIC CASES AND CONTROLS

Variable	Asthmatic		Control		P
	No.	%	No.	%	
Age					
<30 years	14	28.0	18	36.0	
30-39 years	12	24.0	28	56.0	<0.001* S
40-49 years	16	32.0	4	8.0	
≥ 50 years	8	16.0	0	-	
Gender					
Male	24	48.0	26	52.0	0.6** NS
Female	26	52.0	24	48.0	
BMI					
Normal	17	34.0	20	40.0	0.001** S
Overweight	12	24.0	25	50.0	
Obese	21	42.0	5	10.0	
Educational level					
Illiterate	7	14.0	7	14.0	0.2** NS
Primary	20	40.0	12	24.0	
Secondary	13	26.0	14	28.0	
College	10	20.0	17	34.0	

*Fishers exact test, **Chi-square test, NS=Not significant, S=Significant.

Fig. 1. Distribution of BMI according to asthmatic cases and controls

Mean WBC count of asthmatic patients was 8.3 which was significantly higher than 7.3 mean of WBC for controls ($p = 0.03$). No significant differences were observed between asthmatic cases and controls regarding neutrophils mean ($p = 0.2$), lymphocytes mean ($p = 0.2$) and Hb mean ($p = 0.8$). Mean FVC of asthmatic cases was 3.3 which was significantly lower than mean FVC of 3.7 for healthy controls ($p = 0.04$). Mean FVC% of asthmatic cases was 67.8 that was significantly lower than FVC% for controls ($p < 0.001$). The FEV1 mean of asthmatic cases (2.2) was significantly lower than FEV1 of (3) for controls ($p < 0.001$). Mean FEV1% for asthmatic cases was 62.7% that was significantly lower 85.6% for controls ($p < 0.001$). Mean FEV1/FVC for asthmatic cases was 66.5% that was significantly lower than FEV1/FVC of 81.4% for controls ($p < 0.001$). All these findings were shown in Table II and Fig. 2.

TABLE II: DISTRIBUTION OF INVESTIGATIONS MEASURES ACCORDING TO ASTHMATIC CASES AND CONTROLS

Variable	Asthmatic Mean $\pm$ SD	Control Mean $\pm$ SD	P
WBC ($\times 10^3$)	8.3 $\pm$ 3	7.3 $\pm$ 1.3	0.03* S
Neutrophil	62.7 $\pm$ 19.3	66.5 $\pm$ 9.5	0.2* NS
FVC	3.3 $\pm$ 0.9	3.7 $\pm$ 1.1	0.04* S
FVC%	67.8 $\pm$ 14.3	84.3 $\pm$ 5.5	<0.001* S
Lymphocyte	30.4 $\pm$ 16.9	27.5 $\pm$ 4.1	0.2* NS
FEV1	2.2 $\pm$ 0.9	3 $\pm$ 0.9	<0.001* S
FEV1%	62.7 $\pm$ 18.1	85.6 $\pm$ 6.5	<0.001* S
Hb	13.9 $\pm$ 2.7	13.9 $\pm$ 1.1	0.8* NS
FEV1/FVC%	66.5 $\pm$ 16.9	81.4 $\pm$ 6.9	<0.001* S

* Independent sample t-test, S=Significant.

Fig. 2. Distribution of FEV1/FVC mean according to asthmatic cases and controls

There was a highly significant association between high neutrophil/lymphocyte ratio and asthmatic cases ($p < 0.001$); 8% of asthmatic cases had low NLR while 24% of asthmatic cases had high NLR ratio in comparison to 2% of controls with high NLR. All these findings were shown in Table III

and Fig. 3.

TABLE III: DISTRIBUTION OF NLR ACCORDING TO ASTHMATIC CASES AND CONTROLS

Variable	Asthmatic		Control		P
	No.	%	No.	%	
NLR					
Low	4	8.0	0	-	<0.001 *S
Normal	34	68.0	49	98.0	
High	12	24.0	1	2.0	

* Fishers exact test, S=Significant.

Fig. 3. Distribution of NLR according to asthmatic cases and controls

The mean NLR of asthmatic cases was significantly increased to 3.2 with increased age to 50 years and more ($p=0.02$). All these findings were shown in Table IV.

TABLE IV: DISTRIBUTION OF NLR OF ASTHMATIC CASES ACCORDING TO AGE GROUPS

Variable	<30 years	30-39 years	40-49 years	≥50 years	P
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
NLR	2.5±1.2	2.3±0.7	2.4±0.8	3.2±1.6	0.02 *S

* One way ANOVA analysis, S=Significant.

The mean NLR of asthmatic cases was significantly higher among females in comparison to males (2.8 vs. 2.3) ($p=0.04$). All these findings were shown in Table V.

TABLE V: DISTRIBUTION OF NLR OF ASTHMATIC CASES ACCORDING TO GENDER

Variable	Male	Female	P
	Mean±SD	Mean±SD	
NLR	2.3±1.1	2.8±1.1	0.04 *S

* Independent sample t-test, S=Significant.

No significant differences were observed in NLR between BMI categories of asthmatic cases ($p=0.3$). All these findings were shown in Table VI.

TABLE VI: DISTRIBUTION OF NLR OF ASTHMATIC CASES ACCORDING TO BMI

Variable	Normal	Overweight	Obese	P
	Mean±SD	Mean±SD	Mean±SD	
NLR	2.7±1.4	2.3±0.6	3.6±1.3	0.3 *NS

* One way ANOVA analysis, NS=Not significant.

The mean NLR of asthmatic cases was significantly increased to 3.7 with increase of severity of asthma ($p<0.001$). All these findings were shown in Table VII and Fig. 4.

TABLE VII: DISTRIBUTION OF NLR OF ASTHMATIC CASES ACCORDING TO SEVERITY

Variable	Mild	Moderate	Severe	P
	Mean±SD	Mean±SD	Mean±SD	
NLR	0.8±0.7	2.2±1.1	3.7±1.4	<0.001 *S

* One way ANOVA analysis, S=Significant.

Fig. 4. Distribution of NLR according to severity of asthmatic cases

No significant differences were observed in NLR between duration groups of asthma for cases ($p=0.1$). All these findings were shown in Table VIII.

TABLE VIII: DISTRIBUTION OF NLR OF ASTHMATIC CASES ACCORDING TO DURATION OF ASTHMA

Variable	<10 years	≥10 years	P
	Mean±SD	Mean±SD	
NLR	2.5±1.5	3.2±1.5	0.1 *NS

* Independent sample t-test, NS=Not significant.

The mean NLR of asthmatic cases was significantly increased to 3.7 with no control of ACT categories of asthma ($p<0.001$). All these findings were shown in Table IX.

TABLE IX: DISTRIBUTION OF NLR OF ASTHMATIC CASES ACCORDING TO ACT CATEGORIES OF ASTHMA

Variable	Well controlled	On target	No control	P
	Mean±SD	Mean±SD	Mean±SD	
NLR	0.8±0.7	2.2±1.1	3.7±1.4	<0.001 *S

* One way ANOVA analysis, S=Significant.

IV. DISCUSSION

Continuous monitoring of asthma management is the cornerstone in management. Assessment and follow up of management for asthmatic patients requires some methods like asthma control test (ACT) or assessing inflammation indicators like C-reactive protein and neutrophil to lymphocyte ratio (NLR) [56].

Present study showed that high neutrophil/lymphocyte ratio was significantly associated with asthmatic patients in comparison to controls ($p<0.001$). This finding is consistent with results of Gungen and Aydemir study in Turkey [57] which found a significantly higher mean of NLR in asthmatic cases in comparison to controls. Many authors reported higher NLRs that commonly accompanied the inflammation, severity of disease, bad nutrition, long hospital stay duration, chronic diseases and high death rates related to these chronic diseases [58]-[60]. In other study, Nacaroglu et al [61] found that NLR is an effective predictor of acute asthmatic exacerbation in children. In China, Shi et al [62] study revealed that high NLR and platelets to lymphocyte ratio (PLR) are helpful in diagnosis and assessment of asthma. Elevated NLR is explained as the inflammatory markers are important in development of asthma specifically cytokines.

Increased levels of cytokines are associated with increased level of neutrophils [63]. These pro-inflammatory cytokines interleukin-6 and tumor necrosis factors are

elevated in asthma which in turn increases immune cells like neutrophils and natural killer cells which also initiate the liver production of acute phase proteins like C-reactive protein in asthma [63], [64].

Current study showed that mean NLR of asthmatic cases was significantly increased among patients with severe asthma ($p < 0.001$).

This finding coincides with results of Liu et al [54] study in China which stated that NLR level is obviously increased among patients with severe asthma. Recent Japanese study by Mochimaru et al [65] proved that NLR level is elevated among asthmatic adults with acute exacerbations.

Multiple studies detected the relationship between severe asthma and neutrophilic inflammation. The relationship between neutrophils and severe asthma could be seen in eosinophilic and non-eosinophilic asthma [66]. The type 2 helper cells induced the neutrophilic inflammation [2].

In addition to asthma, higher levels of NLR is related to severity of many diseases like chronic obstructive pulmonary diseases, [64] inflammatory bowel diseases [67], liver diseases [68], renal diseases [69] and others.

Regarding ACT, our study showed that mean NLR of asthmatic cases was significantly increased with no control of ACT categories of asthma, while decreased with good control of asthma ($p < 0.001$). This finding is similar to results of Hendy et al [70] study in Egypt which found that neutrophil to lymphocyte ratio predicts accurately uncontrolled asthma according to ACT categories among patients with bronchial asthma. Bruijnzeel et al [71] study in Netherlands stated that neutrophils phenotypes are predictor of severity in severe neutrophilic asthma and NLR plays major role in prediction of asthma disease course and reflects the control of asthma with its positive direct relation to asthma control test (ACT).

In present study, there was a highly significant association between increased age and asthmatic patients ($p < 0.001$). Similarly, Tarraf et al [72] documented that asthma in Middle East countries ranges from 4.4% to 6.7% prevalence and the demographic distribution revealed tendency toward be prevalent among adults and increased with increased of age.

Current Italian study reported that asthma in elderly population is difficult to diagnose and associated with many co-morbidities [73]. Our study showed that mean NLR of asthmatic cases was significantly increased with increased age to 50 years and more ($p = 0.02$). Consistently, Imtiaz et al [74] study in Pakistan reported that mean NLR of patients with chronic diseases was increased with increased age of patients. In USA, Zein et al [75] study revealed that older age patients had more severe asthma than younger age patients and this might be due to effect of age and duration of asthma. As a result, the NLR ratio was increased with severe asthma that is related to increased age [57]. Our study showed a significantly higher NLR among females in comparison to males ($p = 0.04$). This finding is in agreement with results of Lin et al [76] study in Netherlands which found that NLR and PLR are heritable and affected by age, gender and environmental factors. In this study, a significant association was observed between obesity and asthmatic cases ($p = 0.001$). This finding is consistent with results of Mohanan et al [77] study in USA which suggested more

concentration on treatment of obesity during treatment of asthma due to strong relationship between them. Previous Iraqi study detected a significant correlation between obesity, age, gender and utilization of steroids with leptin level [78]. Our study showed higher white blood cells count for asthmatic patients in comparison to controls ($p = 0.03$). Zhang et al [6] found that blood count parameters such as white blood cell count are useful in monitoring of uncontrolled asthma. Present study showed a significantly lower means of FVC and FVC1 of asthmatic patients in comparison to healthy controls. The FVC and FVC1 are spirometry parameters which are significantly reduced among asthmatic patients in comparison to healthy population and are regarded as diagnostic measures of asthma [79]. Similarly, our study showed a significantly lower means of FEV1, FEV1% and FEV1/FVC% among asthmatic patients in comparison to healthy controls. Many literatures proved the accuracy of spirometry measures of FEV1, FEV1% and FEV1/FVC% in diagnosis of asthma with lower means of these measures in comparison to normal population [80], [81]. The main limitations in present study were single center study, selection bias and small sample size.

V. CONCLUSIONS

1. The neutrophil to lymphocyte ratio is possibly important in severity assessment of asthma.
2. The neutrophil to lymphocyte ratio is possibly applicable in monitoring the management of asthma.
3. The neutrophil to lymphocyte ratio is dependable on age, gender, severity of asthma and asthma control test.
4. The asthma is more prevalent among older age and obese population (in this group of study)
5. The blood count and spirometry parameters are common in assessment of asthma severity.

VI. RECOMMENDATIONS

- 1- Encouraging physicians to adopt neutrophil to lymphocyte ratio as diagnostic measure and severity categorization of asthma.
- 2- Monitoring and following up asthmatic patients under management using neutrophil to lymphocyte ratio is hopeful.
- 3- Risk factors for neutrophil to lymphocyte ratio should be taken in consideration.
- 4- Further national large sized studies on neutrophil to lymphocyte ratio application in diagnosis and management of asthma must be supported.

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