Evaluation of Blood Neutrophil Lymphocyte Ratio (NLR) & Platelet Lymphocyte Ratio (PLR) As Inflammatory Biomarkers in Childhood Asthma

Thesis

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بسم الله الرحمن الرحيم

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
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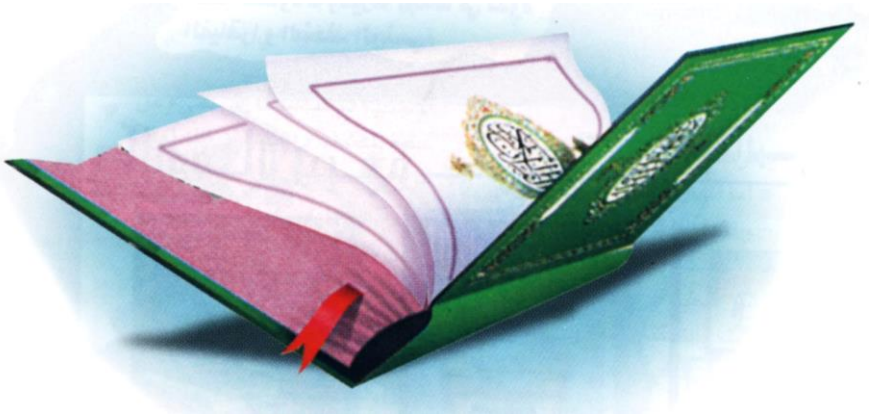

صدق الله العظيم

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Mostafa Mohammed Ibrahim

List of Contents

List of Tables

List of Tables cont...

List of Tables cont...

List of Figures

Fig. No.	Title	Page No.

List of Abbreviations

Abb.	Full term
A.Eosinoph. count	*Absolute Eosinophilic count*
ACQ	*Asthma control Questionnaire*
ALC	*Absolute lymphocytic count*
ANC	*Absolute neutrophilic count*
AUC	*Area under the curve*
BAL	*Broncho-alveolar lavage*
BMI	*Body mass index*
CBC	*Complete blood count*
CD	*Cluster of differentiation*
CDC	*Centers for Disease Control and Prevention*
COPD	*Chronic obstructive pulmonary disease*
DPI	*Dry powder inhaler*
EGEA	*Epidemiological study on the Genetics and Environment in Asthma*
ELR	*Eosinophil lymphocyte ratio*
EPR	*Expert Panel Report*
ERS	*European Respiratory Society*
FEV_1	*Forced expiratory volume in 1 second*
FN	*False negative*
FP	*False positive*
FVC	*Forced vital capacity*
GERD	*Gastroesophageal reflux disease*
GINA	*Global Initiative for Asthma WHO*
GM-CSF	*Graylocyte-macrophage colony-stimulaing factor*
HDM	*House dust mites*
ICS	*Inhaled corticosteroid(s)*
ICS	*Inhaled corticosteroid(s)*
ICU	*Intensive care unit*
IgE	*Immunoglobulin E*
IL	*Interleukin*
LABA / LABAs	*Long-acting beta2-agonist(s)*
LTRA	*Leukotriene receptor antagonist*

List of Abbreviations cont...

Abb.	Full term
MMEF	*Maximal mid-expiratory flow*
MMP 9	*Matrix metallopeptidase 9*
NAEPP	*National Asthma Education and Prevention Program*
NIH	*National Institutes of Health*
NLR	*Neutrophil/lymphocyte ratio*
NSAIDS	*Non-steroidal anti-inflammatory drugs*
OCS	*Oral corticosteroid(s)*
PEF	*Peak expiratory flow*
PICU	*Pediatric intensive care unit*
PLR	*Platelet/lymphocyte ratio*
PLT	*Platelet*
Pmdi	*Metered-dose inhaler*
PN%	*Percentage of Predictive Negative*
PP%	*Percentage of Predictive Positive*
ROC	*Receiver operating characteristic curve*
SABA	*Short-acting beta2-agonist(s) (inhaled)*
SCIT	*Subcutaneous immunotherapy*
SLIT	*Sublingual Immunotherapy*
Th1, Th2	*T cell helper 1, T cell helper*
TLC	*Total leucocytic count*
TN	*True Negative*
TP	*True Positive*
WBC	*White blood cell*
WHO	*World health organization*

INTRODUCTION

Asthma is a heterogeneous disease, characterized by chronic airway inflammation, history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation ***(GINA, 2018)***.

It is a major cause of chronic morbidity and mortality throughout the world and there is evidence that its prevalence has increased considerably over the past 20 years especially in children. The prevalence of asthma symptoms in children is more than 30% in different populations and is increasing in most countries ***(El-Seify, 2007)***.

The worldwide prevalence of allergies especially asthma has significantly increased in recent years ***(WHO, 2013).*** Several environmental risk factors have been attributed to the significant increase of these in both developed and developing countries. One major risk factor associated with the increase in asthma is increasing air pollution resulting from the rise in the number of motor vehicles ***(Brunekreef et al., 2009)*** and the presence of certain industrial processes ***(Wang and Chau, 2013)***.

In Egypt, asthma is the commonest cause of emergency and hospital admission where the prevalence among children aged 3-15 years estimated to be 8.2%, with 10% annual increase in mortality ***(Tageldin, 2007)***.

The diagnosis of asthma should be based on the history of characteristic symptom patterns and evidence of variable airflow limitation. This should be documented from bronchodilator reversibility testing or other tests ***(GINA, 2018)***.

The immunohistopathologic features of asthma include epithelial injury and infiltration of inflammatory cells, consisting of eosinophils, lymphocytes, mast cells, and phagocytes ***(Holgate, 2001)***.

Inflammatory subtypes of bronchial asthma are recognized based on sputum eosinophil and neutrophil proportions and include eosinophilic asthma, neutrophilic asthma, mixed granulocytic asthma and paucigranulocytic asthma ***(Simpson et al., 2006)***.

Eosinophilic asthma was defined as sputum eosinophils $\geq 3\%$. Neutrophilic asthma was defined as sputum neutrophils $\geq 61\%$. Participants with increased eosinophils and neutrophils were classified as mixed granulocytic asthma. Those with normal levels of both eosinophils and neutrophils were classified as having paucigranulocytic asthma ***(Schleich et al., 2014)***.

These different subtypes of inflammation may have different exacerbation risks ***(McDonald and Gibson, 2012)***. Recent studies have demonstrated that neutrophilic inflammation is related to an increase in the severity of the

disease ***(Marguet et al., 1999)***. Also, the existence of eosinophilic inflammation in asthma has been shown to be related to atopy and symptoms of persistent asthma ***(Moore et al., 2014)***.

Blood Neutophil to Lymphocyte Ratio **(NLR)** is a recent marker that can detect the overall inflammatory and stress status of the body ***(Sunbul et al., 2014)***.

The NLR is a parameter which combines neutrophils as a marker of innate inflammation and lymphocytes as a regulator of allergic inflammation ***(Park et al., 2013)***. It is considered to reflect a systemic inflammatory response, which can occur in asthma ***(Fu et al., 2013)***.

A high blood NLR was associated with poor clinical prognosis in many chronic diseases such as cardiac disease ***(Park et al., 2013)*** malignancy ***(He et al., 2013)*** and chronic kidney disease ***(Okyay et al., 2013)***. Moreover, patients with a high blood PLR also had adverse outcomes in cancers ***(Seretis et al., 2012)***, cardiovascular diseases ***(Gary, et al., 2013)*** and renal diseases ***(Turkmen et al., 2013)***.

The reason why NLR and PLR maybe increased in childhood asthma is unclear, but it may reflect systemic inflammation that is associated with airway inflammation ***(Wood et al., 2012)***.

Aim of the Work

To measure white blood cell counts in asthmatic children, their derived ratios (Neutophil to Lymphocyte, Platelet to Lymphocyte ratios), and to study the relationship between these ratios and asthma airway inflammatory subtypes, overall degree of asthma severity, level of asthma control during stable and exacerbation states.

REVIEW OF LITERATURE

Asthma is a common chronic airway disorder characterized by periods of reversible airflow obstruction known as asthma episodes or attacks ***(Akinbami et al., 2011).***

Epidemiological studies examining asthma prevalence trends among children in both developed and developing countries suggest that the prevalence of asthma and other allergic diseases is continuing to rise ***(Pearce et al., 2007).*** Current evidence suggests that gene environment interactions underlie most of the increase and worldwide variations ***(Ubarao et al., 2009).***

Asthma is a highly prevalent chronic respiratory disease affecting 300 million people world-wide and current trends suggest that an additional 100 million people may be living with asthma by 2025 ***(Iuatld, 2011).***

It is a major considerable cause of chronic morbidity and mortality throughout the world and there is evidence that its prevalence has increased over the past 20 years in children. The prevalence of asthma symptoms in children varies from 1 to more than 30 percent in different populations and is increasing in most countries, especially among young children ***(Stewart et al., 2001).***

Asthma is having a high mortality about 250,000 annually***, (Nathan et al., 2015)*** Low and middle-income