Value of NLR, PLR in Disease Activity and Lupus Nephritis Severity in Patients with Systemic Lupus Erythematosus

Thesis

Submitted in Partial Fulfillment of Master Degree of Physical Medicine, Rheumatology and Rehabilitation

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2017

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to ALLAH, the Most Kind and Most Merciful.

I'd like to express my respectful thanks and profound gratitude to ***Prof. Dr. Nahed Mouneir Sherif,*** *Head of the Department and Professor of Physical Medicine, Rheumatology and Rehabilitation - Faculty of Medicine- Ain Shams University for her keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Prof. Dr. Iman Mahmoud Ghanima,*** *Professor of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to ***Dr. Mohja Ahmed Abdel-Fattah,*** *Assistant Professor of Physical Medicine, Rheumatology and Rehabilitation, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Wafaa Mahmoud Soliman

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List of Abbreviations

Abb.	Full term
ACR	*American college of rheumatology*
ANOVA	*Analysis of variance*
Anti-β2GPI	*Anti–β2-glycoprotein I antibody*
APL	*Antiphospholipid antibodies*
APRIL	*a proliferation-inducing ligand*
AUC	*Area under curve*
BAFF	*B cell-activating factor of the TNF family*
CBC	*Complete Blood count*
CI	*Confidence interval*
CRP	*C reactive protein*
DCs	*Dendritic cells*
DNA	*Deoxyribonucleotide*
dsDNA	*Double-stranded DNA*
ESR	*Erythrocyte sedimentation rate*
FDC	*Follicular dendritic cell*
FIDA	*Flow-Induced Dispersion Analysis*
FTH	*Follicular T Helper Cells*
GC	*Germinal centers*
GFR	*Glomerular filtration rate*
HMGB1	*High mobility group box 1 protein*
Hs-CRP	*High sensitivity-CRP*
HSPG	*Heparan sulphate proteoglycans*
IC	*Immune complex*
IFNα	*Interferon alpha*
IIF-Hep2	*Indirect immunofluorescence on Hep-2 cells*
IQR	*Interquartile range*
LAC	*Lupus anticoagulant*

List of Abbreviations (Cont...)

Abb.	Full term
LN	*Lupus nephritis*
MSK	*Muscloskeletal*
NETs	*Neutrophil extracellular traps*
NL	*Neonatal lupus*
NLR	*Neutrophil to lymphocyte ratio*
PCI	*Percutaneous coronary intervention*
PLR	*Platelet to lymphocyte ratio*
pSS	*Primary sjögren's syndrome*
PTEC	*Proximal renal tubular epithelial cells*
ROC	*Receiver operating characteristic curve*
SD	*Standard deviation*
SLE	*Systemic lupus erythematosus*
SLEDAI	*SLE disease activity index*
SLICC	*Systemic Lupus International Collaborating Clinics*
Sm	*Smith*
SPSS	*Statistical Package for social sciences*
SSc	*Systemic sclerosis*
TACI	*Transmembrane activator and cyclophilin ligand interactor*
TBM	*Tingible body macrophages*
TH	*T helper*
TReg	*Regulatory T cells*
UV	*Ultraviolet*
WBC	*White blood cell*

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with unknown etiology which has different clinical manifestations, course of illness and prognosis ***(Oehadian et al., 2013).***

The clinical assessment of SLE patients is therefore difficult for the physician in their daily practice. On the other hand, treatment could be different according to the disease severity and activity. SLE can be categorized as mild, moderate, severe and life threatening disease ***(Hepburn et al., 2011).***

A lot of patients with SLE develop kidney affection related to this systemic underlying disease process ***(Dooly et al., 2004)***.

Renal failure is also the leading cause of death in these patients. So early diagnosis of LN is helpful for patients. The overall mortality has decreased remarkably in SLE patients over the last decades because of its early detection ***(Grande, 2011)***.

Lupus nephritis (LN) is the most common and severe clinical manifestation of SLE ***(Borchers et al., 2012).*** LN is defined as clinical and laboratory manifestations that was described by the American College Of Rheumatology criteria "2012" (once the SLE diagnosis was established, and clinically

persistent proteinuria >0.5 g/d or greater than 3+ by dipstick, and/or cellular casts including hemoglobin, granular, red cell, tubular or mixed). The renal biopsy is considered the gold standard investigation in confirming the diagnosis of LN ***(Hanh et al., 2012).***

Many clinical and laboratory methods can be used to assess the disease activity. The laboratory indictors of disease activity are low complement, increased deoxyribonucleotide (DNA) binding, thrombocytopenia and leukopenia. The problem is how to evaluate disease activity with simple laboratory indictors that is available in almost every health care facility ***(Chua et al., 2011).***

Immune complex (IC) formation and precipitation are the main cause of SLE renal damage mechanism ***(Cook et al., 2006)***. IC can activate complement and inflammatory cell infiltration, thus cause kidney damage ***(Koscielska et al., 2014)***.

White blood cell and its differential count can be done as part of routine investigations ***(Chua et al., 2011).***

White blood cell (WBC) count is a serum indictor for systemic inflammation ***(Zahorec, 2001)***. Neutrophils and lymphocytes play an important role in inflammatory processes ***(Motomura et al., 2013)***. Under inflammatory conditions, neutrophil and lymphocyte counts may undergo temporary changes ***(Balta et al., 2014).*** Well understanding of these

lymphocyte subsets and autoantibodies will help in developing new ways for monitoring of disease activity and treatment for LN ***(Liu & Anders, 2014).***

Neutrophil to lymphocyte ratio (NLR) is an available indicator that can give important information about the patient inflammatory activity. Recent studies showed that an abnormal NLR level is associated with autoimmune disease. ***Hu et al. (2014),*** detected that NLR level was increased in primary sjögren's syndrome (pSS) and positively correlated with pSS disease activity.

Sen et al. (2014), reported that NLR might reflect systemic inflammation in patients with psoriasis. In another study, NLR was found to be increased in patients with ulcerative colitis when compared with inactive patients or controls ***(Celikbilek et al., 2013)***.

Platelet to lymphocyte ratio (PLR) is suggested to be a potential indicator to determine inflammation. Similar to NLR, PLR is also used as a marker for differential diagnosis or prognostic prediction of different diseases such as cancer and inflammatory diseases ***(Feng et al., 2014)***.

The study of ***Qin et al. (2015)*** has detected that NLR and PLR were increased in SLE patients, and that NLR and PLR were positively correlated with the inflammatory markers and the disease activity. These findings suggest that NLR and PLR

might prove to be useful indexes in determining inflammation and evaluating the disease activity of SLE.

The study of ***Li et al. (2015)*** detected that NLR is independently correlated with LN as compared with the traditional indicators, such as Creatinine and 24 h proteinuria, NLR is cheaper, quick and easily to be measured; it may be a promising indicator that reflects renal affection in patients with SLE.

Because of early recognition and management of SLE, end-stage renal failure affects less than 5% of cases , So The present study is conducted to measure (NLR), (PLR) as novel indicators of inflammation in SLE patients. NLR and PLR are easily calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and by calculating the absolute platelet count divided by the absolute lymphocyte count from a complete blood count. It is simple and cheap laboratory investigations, So this will facilitate early diagnosis and management of LN to improve the outcome and to decrease the mortality rate due to LN.

AIM OF THE WORK

This study is designed to Assess:

The correlation of Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) to disease Activity and lupus nephritis severity in patients with systemic lupus erythematosus. NLR and PLR are simple, available and cheap laboratory investigations.

Chapter 1

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systemic lupus erythematosus (SLE), is a systemic autoimmune disease (or autoimmune connective tissue disease) in that the immune system of the body wrongly attacks healthy tissue. Systemic lupus erythematosus (SLE) affects many internal organs in the body (heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system) ***(Oehadian et al., 2013)***.

The disease course is unpredictable, with periods of flare up alternating with remissions. It may be because of environmental, hormonal, or genetic triggers. It may result in a misdirected immune response in those who have genetic predisposition. A normal immune system makes antibodies which protect against pathogens such as viruses and bacteria. Lupus is characterized by the presence of antibodies directed against the patient's healthy tissues such as proteins. The most common protein to be affected is anti-nuclear antibodies, which may be found in a lot of cases. These antibodies lead to inflammation ***(Murphy et al., 2013)***.

The rate of SLE varies between both sexes. Female to male ratio is 9:1 with peak onset in the second and third decades. The onset and persistence of SLE can show

differences between genders. The global prevalence of SLE is approximately 20-70/100, 000 people. There is no sufficient evidence to conclude that SLE is less common in some countries compared to the others, since there is significant environmental variability in these countries. For example, different countries receive different levels of sunlight, and exposure to Ultraviolet (UV) rays affect dermatological symptoms of SLE. Prevalence was lowest in areas where the member of rheumatologists are few, suggesting underdiagnosis and likely unequal access to treatment ***(Feldman et al., 2013).***

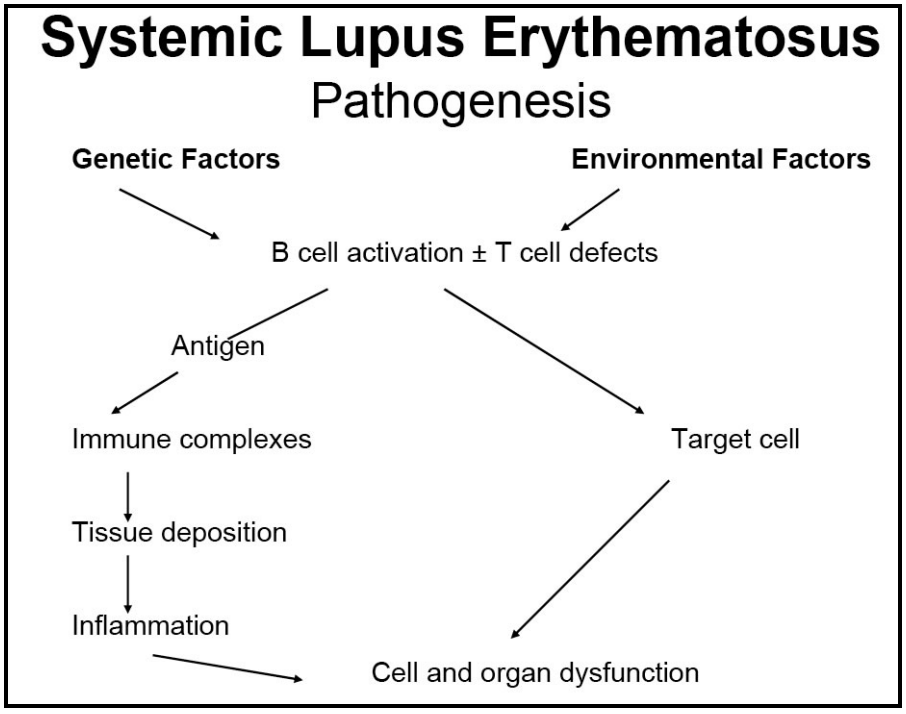

Figure (1): Shows SLE pathogensis ***(Scheinfeld et al., 2003).***