Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Prognostic Markers of Systemic Lupus Erythematosus Activity

Thesis

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List of abbreviations

AAP	Acute abdominal pain
ACR	American College of Rheumatology
ANA	antinuclear antibodies
Anti-dsDNA	anti-double-stranded DNA
BILAG	British Isles Lupus Assessment Group
C3	Complement 3
C4	Complement 4
CBC	Complete blood count
CNS	Central Nervous System
CRC	colorectal cancer
CRP	C-reactive protein
CVD	Cardio Vascular Disease
DNA	deoxyribonucleic acid
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GI	gastrointestinal
HCC	Hepato Cellular Carcinoma
HF	Heart Failure
HRQOL	health-related quality of life
IL	interleukin
LDL	low-density lipoprotein

LFTs	liver function tests
LUMINA	Lupus in Minorities: Nature versus Nurture
MPV	Mean Platelet Volume
NLR	Neutrophil-lymphocyte ratio
NPSLE	neuropsychiatric SLE
NSAIDS	Nonsteroidal anti-inflammatory drugs
OS	Overall Survival rate
PGA	Physician Global Assessment
PLR	Platelet to lymphocyte ratio
RA	Rheumatoid Arthritis
SCORAD	SCORing Atopic Dermatitis
SFI	SELENA-SLEDAI Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
TAK	Takayasu's arteritis
US	United States
WBC	White blood cell
WHO	World Health Organization

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Introduction:

Systemic Lupus Erythematosus is a chronic multi- organ autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body. Symptoms vary between people and may be mild to severe. Common symptoms include painful and swollen joints, fever, chest pain, hair loss, mouth ulcers, enlarged lymph nodes, fatigue ***(Wu et al., 2016)***

The global rates of SLE are approximately 20-70 per 100,000 people. In females, the rate is highest between 16-45 year of age. The lowest overall rate exists in Iceland and Japan. The highest rates exist in US and France. SLE, like many autoimmune diseases, affects females more frequently than males, at a rate of about 9 to 1***.(Danchenko et al., 2006)***

Most patients with SLE develop kidney disease related to this systemic underlying disease process. Lupus nephritis is the most common and severe clinical manifestation of SLE ***(Borchers et al., 2012)***

White blood cell (WBC) count is a serum marker for systemic Inflammation. Neutrophil-lymphocyte ratio is easily calculated by dividing neutrophil

count by the absolute lymphocyte count from a complete blood count. It is simple and cheap. Many studies have shown that NLR is positively associated with inflammatory, different malignancies, ischemic injury, cardiovascular disease and diabetic nephropathy . Also , Pericarditis and pericardial effusions in SLE are well recognized in SLE ***(Ahsen et al., 2013) (Li et al., 2014) (Maharaj et al., 2015)***

Platelet to lymphocyte ratio (PLR) is an easy calculated parameter. Studies have shown that increased PRL is associated with neoplastic diseases like lung cancer .Moreover PLR is a better predictor than NLR for survival in patients with ovarian cancer***.(Feng et al., 2013)***

The most commonly used parameters of lupus is called the SLE Disease Activity Index, and the acronym for it is SLEDAI. The SLEDAI index is a global score index developed for the assessment of SLE disease activity depending on many signs , laboratory investigations and other criteria of the disease ***(Bombardier et al., 1992)***

The Aim of the work:

The aim of this study is to evaluate the value of neutrophil lymphocyte ratio and platelet lymphocyte ratio as simple and cheap prognostic markers of the activity of systemic lupus disease.

Understanding SLE

Definition:

Systemic Lupus Erythematous (SLE) is a chronic multi organ autoimmune disease in which the body immune system mistakenly attacks healthy tissue in many parts of the body. Symptoms vary between patients and may be mild to severe. Common symptoms include painful and swollen joints, fever, chest pain, loss, mouth ulcers, enlarged lymph nodes and fatigue ***(Wu et al., 2016)***

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Genetic Consideration

Concordance rates for SLE among monozygotic and dizygot twins are 25% and 2% respectively, suggesting a significant genetic contribution (***Gaubitz ; 2006***)

Pathogenesis of SLE

SLE is a complex disease process demonstrating dysregulation of the immune system at multiple levels .Autoantibodies against double-stranded DNA were first isolated from kidney specimens in patients with lupus nephritis in 1967***(Simard and Costenbader,2007)***

One manifestation of SLE is abnormalities in apoptosis, a type of Programmed cell death in which aging or damaged cells are disposed of as a part of normal growth or functioning. In SLE, the body's immune system produces antibodies against itself, particularly against proteins in the cell nucleus. SLE is triggered by environmental factors that are unknown. The immune system must balance between being sensitive enough to protect against infection, and become sensitized to attack the body's own proteins (autoimmunity). During an immune reaction to a foreign stimulus , such as bacteria, virus, or allergen, immune cells that would normally be deactivated due to their affinity for self-tissues can be abnormally activated by signaling sequences of antigen-presenting cells. Thus triggers may include viruses, bacteria, allergens (IgE and other hypersensitivity), and can be aggravated by environmental stimulants such as ultraviolet light and

certain drug reactions. These stimuli begin a reaction that leads to destruction of other cells in the body and exposure of their DNA, histones, and other proteins, particularly parts of the cell nucleus. The body's sensitized B-lymphocyte cells will now produce antibodies against these nuclear-related proteins. These antibodies clump into antibody-protein complexes which stick to surfaces and damage blood vessels in critical areas of the body, such as the glomeruli of the kidney; these antibody attacks are the cause of SLE . Researchers are now identifying the individual genes, the proteins they produce, and their role in the immune system. Each protein is a link on the autoimmune chain , and researchers are trying to find drugs to break each of those links. (***Mary;2008)***

Two major theories exist on how these auto-antibodies cause tissue damage. The first model suggests that anti-double-stranded DNA antibodies bind to circulating nucleosomes to form immune complexes that then get deposited in end-organ capillary beds such as the renal glomerulus and activate immune/inflammatory responses**.*(Sestak et al ., 2005)***

The second hypothesizes that these auto-antibodies cross-react with normal renal proteins causing tissue destruction ***(Moser et al., 2009)***

Medications, hormonal influences, and other factors such as sunlight have all been implicated in disease exacerbation. Drug-Induced lupus, most commonly due to procainamide, hydralazine, and quinidine, usually presents with disease involving the skin and joints with renal and CNS manifestations being much more rare ***(Costenbader et al.,2004)***

Clinical Features

A variety of disease manifestations are exhibited by SLE patients ,with the heterogenity of presentations often delaying diagnosis. Common manifestations include rashes, photosensitivity, arthritis, pleuritis, pericarditis, nephritis, neuropsychiatric disorders, and hematological disorders. There is also an array of less common but potentially hazardous complications.

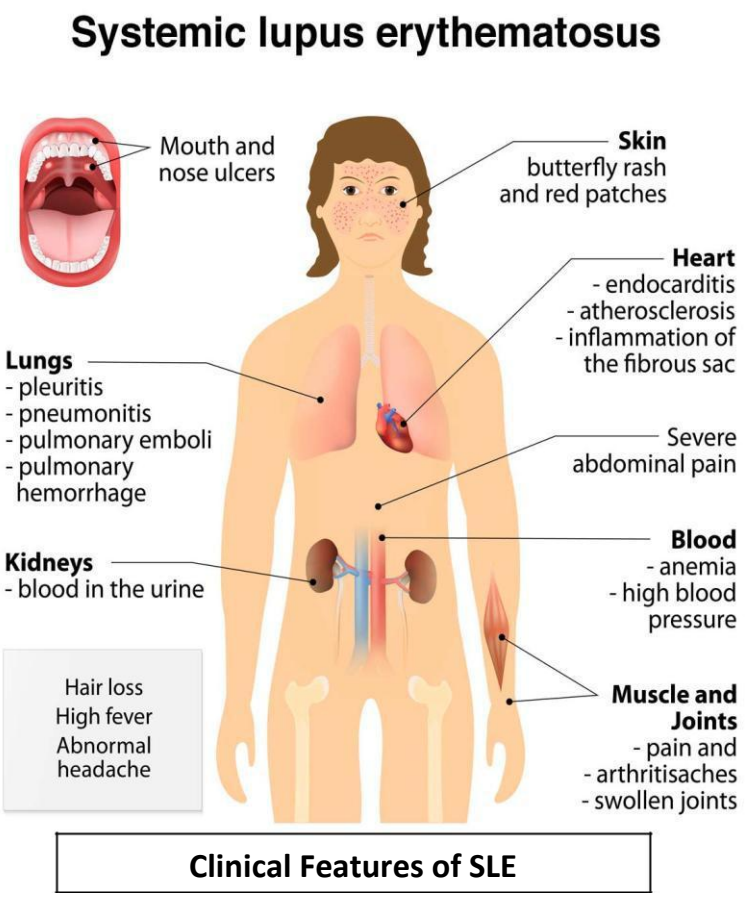

Fig (1): Clinical features of SLE (***Rullo and Tsao,2013)***