The Analysis of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Guillain-Barre Syndrome as a Diagnostic and Prognostic Marker

Thesis

Submitted for Partial Fulfillment
of Master Degree in **Neuropsychiatry**

By

Khloud Adel Mohammed Hassan Tohlob
M.B., B.Ch.

Under Supervision of

Prof. Magd Fouad Zakaria
Professor of Neuropsychiatry
Faculty of Medicine - Ain Shams University

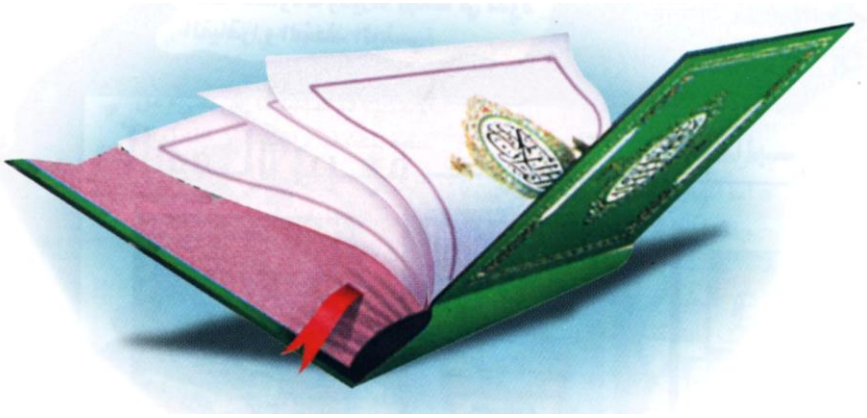
Prof. Nagia Aly Fahmy
Professor of Neuropsychiatry
Faculty of Medicine - Ain Shams University

Dr. Hossam Shokri Mohammed
Lecturer of Neuropsychiatry
Faculty of Medicine - Ain Shams University

Faculty of Medicine – Ain Shams University
2019

بسم الله الرحمن الرحيم

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ



صدق الله العظيم

[سورة: التوبة - الآية: ١٠٥]

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Magd Fouad Zakaria****, Professor of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for his meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Prof. Nagia Aly Fahmy****, Professor of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for her sincere efforts and fruitful encouragement.*

I am deeply thankful to ***Dr. Hossam Shokri Mohammed****, Lecturer of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for his great help, outstanding support, 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.

Khloud Adel Mohammed Hassan Tohlob

List of Contents

Title	Page No.
List of Tables	5
List of Figures	7
List of Abbreviations	9
Introduction	- 1 -
Aim of the Work	13
Review of Literature	
▪ Guillain–Barré Syndrome (GBS)	14
▪ Neutrophil-Lymphocyte Ratio and Platelet- Lymphocyte Ratio	33
Patients and Methods	41
Results	47
Discussion	77
Conclusion	83
Recommendations	84
Summary	85
References	88
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Diagnostic criteria for Guillain-Barré syndrome	21
Table (2):	Brighton criteria for Guillain-Barré syndrome diagnosis.	23
Table (3):	Clinical subtypes of GBS	28
Table (4):	Age and sex in control group and patients group	47
Table (5):	Antecedent infection (GIT & Upper respiratory tract infection) among 61 GBS patients	48
Table (6):	Baseline clinical data among 61 GBS patients	49
Table (7):	Disability score, NLR and PLR among 61 GBS patients 1st on admission, 2nd on discharge and after 3 months	50
Table (8):	Baseline laboratory data in patients group	51
Table (9):	Baseline CSF analysis and NCS data among 61 GBS patients	52
Table (10):	Follow up NCS after 3 months among 61 GBS patients	54
Table (11):	Comparison between control group and 61 GBS patients as regards NLR and PLR on admission	55
Table (12):	Comparison between AIDP group and other subtypes group as regards age and sex.	57

List of Tables cont...

Table No.	Title	Page No.
Table (13):	Comparison between AIDP group and other subtypes group as regards antecedent infection.	58
Table (14):	Comparison between AIDP group and other subtypes group as regards disability score on admission, on discharge and after 3 months	59
Table (15):	Comparison between AIDP group and other subtypes group as regards NLR and PLR on admission, on discharge and after 3 months	61
Table (16):	Comparison between AIDP group and other subtypes group as regards ESR and CRP on admission	65
Table (17):	Comparison between AIDP group and other subtypes group as regards Cyto-alb. Dissociation	66
Table (18):	Comparison between AIDP group and other subtypes group as regards NCS after 3 months	67
Table (19):	Correlation of NLR and PLR with the other parameters on admission	68
Table (20):	Correlation of NLR and PLR with disability score after 3 months	71
Table (21):	Relation of NCS after 3 months with NLR and PLR (on admission and after 3 months)	73

List of Figures

Fig. No.	Title	Page No.
Fig. (1):	Major Guillain-Barré syndrome subtypes in which antibody-mediated effector pathways, including complement activation, cause glial or axonal membrane injury with consequent conduction failure	34
Fig. (2):	Antecedent infection among 61 GBS patients.	48
Fig. (3):	Baseline clinical data among 61 GBS patients.	49
Fig. (4):	Cyto.alb. dissociation in 61GBS patients	53
Fig. (5):	Nerve conduction study in 61 GBS patients on admission.	53
Fig. (6):	Comparison between GBS patients group and control group as regard NLR on admission.	56
Fig. (7):	Comparison between GBS patients group and control group as regard PLR on admission.	56
Fig. (8):	Antecedent infection in AIDP group and other subtypes group.	58
Fig. (9):	Comparison between AIDP group and other subtypes group as regard disability score on discharge.	60
Fig. (10):	Comparison between AIDP group and other subtypes group as regard disability score after 3 months.	60
Fig. (11):	Comparison between AIDP group and other subtypes group as regard NLR on admission.	62
Fig. (12):	Comparison between AIDP group and other subtypes group as regard PLR on admission.	62

List of Figures cont...

Fig. No.	Title	Page No.
Fig. (13):	Comparison between AIDP group and other subtypes group as regard NLR on discharge.	63
Fig. (14):	Comparison between AIDP group and other subtypes group as regard PLR on discharge.	63
Fig. (15):	Comparison between AIDP group and other subtypes group as regard NLR after 3 months.	64
Fig. (16):	Comparison between AIDP group and other subtypes group as regard PLR after 3 months.	64
Fig. (17):	Comparison between AIDP group and other subtypes group as regard NCS after 3 months.	67
Fig. (18):	NLR and disability score on discharge.	69
Fig. (19):	NLR and disability score after 3 months.	69
Fig. (20):	PLR and disability score on discharge.	70
Fig. (21):	PLR and disability score after 3 months.	70
Fig. (22):	NLR and disability score after 3 months.	72
Fig. (23):	PLR and disability score after 3 months.	72
Fig. (24):	NLR on admission and NCS after 3 months.	74
Fig. (25):	PLR on admission and NCS after 3 months.	74
Fig. (26):	NLR and NCS after 3 months.	75
Fig. (27):	PLR and NCS after 3 months.	75
Fig. (28):	Receiver operating characteristic curve (ROC) for NLR and PLR as a predictor for AIDP cases at admission.	76

List of Abbreviations

Abb.	Full term
AIDP	*Acute inflammatory demyelinating polyneuropathy*
AMAN	*Acute motor axonal neuropathy*
AMSAN	*Acute motor and sensory axonal neuropathy*
Anti-GQ1b	*Anti-ganglioside complex*
AUC	*Area under curve*
CMV	*Cytomegalovirus*
CSF	*Cerebrospinal fluid*
EDSS	*Expanded Disability Status Scale*
EGRIS	*Erasmus GBS Respiratory Insufficiency Score*
GBS	*Guillain–Barré Syndrome*
HS	*Highly significant*
IQR	*Inter-quartile range*
IVIG	*Intravenous immunoglobulins*
LPS	*Lipopolysaccharide*
MFS	*Miller Fisher Syndrome*
MMPs	*Matrix Metallo Proteinase*
MNCV	*Motor nerve conduction velocity*
MRC	*Medical research council*
MS	*Multiple sclerosis*
NCS	*Nerve conduction study*
NLR	*Neutrophil lymphocyte ratio*
NO	*Nitric oxide*

List of Abbreviations cont...

Abb.	Full term
NPV	*Negative predictive value*
NS	*Non significant*
PLR	*Platelet lymphocyte ratio*
PPV	*Positive predictive value*
RA	*Rheumatoid Arthritis*
ROC curve	*Receiver operating characteristic curve*
S	*Significant*
SLE	*Systemic lupus erythematosus*
SPSS	*Statistical Package for Social Science*
TAK	*Takayasu's arteritis*
TRFs	*Treatment-related fluctuations*
UC	*Ulcerative colitis*
VGSC	*Voltage gated sodium channel*

INTRODUCTION

Guillain-Barre syndrome (GBS) is an acute immune mediated inflammatory demyelinating polyradiculoneuropathy. It is characterized by rapid regressive ascending weakness and diminished or absent deep tendon reflexes **(Doorn et al., 2008)**.

GBS occurs in all age groups, men are affected more than women. The incidence of GBS is 1-2 cases per 100,000 populations per year **(Sejvar et al., 2011).**

GBS can be classified into four subtypes; the most common type is acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), Miller Fisher Syndrome (MFS). In AIDP, the immune response damages the myelin sheaths that protect peripheral nerve axons and produce the efficient transmission of nerve impulses. In AMAN, the damage affects the axons of motor neurons only, whereas the axons of sensory neurons are also damaged in AMSAN. In MFS, anti-ganglioside complex (anti-GQ1b) antibody target occulomotor and bulbar nerves **(Hughes and Cornblath, 2005).**

Some neurological disorders such as GBS can produce high level of inflammation, this leads to an increase or decrease in acute phase reactants such as proteins, neutrophil to

lymphocyte ratio (NLR) and platelet to lymphocyte ratio(PLR) **(Mungan et al., 2014).**

Recently, the NLR and the PLR are considered new biomarkers indicating the presence of inflammation **(Akıl et al., 2014).** They are useful biomarkers that can be used as diagnostic or prognostic markers in some inflammatory diseases**.** Ozler and Gunak reported that in Bell's palsy, as an example of inflammatory neuropathy, there was a significant correlation between increased NLR and poor prognosis **(Ozler and Gunak, 2014).** Alan et al. reported that the NLR and PLR might be associated with the presence and severity of Behçet's syndrome **(Alan et al., 2015). Uslu et al.** showed that NLR and PLR could be also used in assessing rheumatoid arthritis activity (RA) **(Uslu et al., 2015). Qin et al.** reported that NLR and PLR could reflect the disease activity in systemic lupus erythematosus (SLE) patients **(Qin et al., 2016)**. **Demirci et al.** reported that NLR might be simple inexpensive and quick biomarker to predict multiple sclerosis (MS) patient's prognosis **(*Demirci et al.*, 2015).** Celikbilek et al. supported the role of NLR as a marker of prognosis in acute ischemic stroke **(Celikbilek *et al.*, 2014).**

AIM OF THE WORK

We aimed from this work to evaluate the NLR and PLR as a diagnostic and prognostic markers in GBS patients.

Chapter 1

GUILLAIN–BARRÉ SYNDROME (GBS)

Guillain–Barré syndrome (GBS) is an acute immune-mediated inflammatory disorder of peripheral nerves and spinal roots. Immune response is the major cause of GBS. In this syndrome, auto-antibodies triggered by previous infections cross-react with gangliosides and result in peripheral nervous system injury **(Van den et al., 2014).**

Guillain–Barré syndrome (GBS) is the most frequent cause of acute flaccid paralysis, characterized by rapid ascending symmetrical weakness of the extremities, and diminished or absent deep tendon reflexes, which reaches a maximum severity within 4 weeks **(Yuki et al., 2012).**

GBS is a post infectious autoimmune disorder that often follow an upper or lower respiratory illness or gastroenteritis by 10 to 14 days. Approximately 70% of patients can identify a preceding illness, although it is often benign and may be minimized or forgotten by the patient **(Willison et al., 2016).**

When patients present with rapidly progressive ascending paralysis, the diagnosis of Guillain-Barré syndrome needs to be made as soon as possible. GBS pathogenic conditions are rapidly progressing usually takes day to 2 weeks to reach the maximal effect. It can be diagnosed mostly with the help of CSF examination and electrophysiological study.

Elevated concentration of CSF protein is usually observed in these patients. These proteins are involved in the arrangements of axonal domain and certain cytokines secreted in response to the bacterial infections **(Ziganshin et al., 2016).**

All patients with Guillain-Barré syndrome need close monitoring and supportive care **(Hughes et al., 2005).** Early initiation of treatment (intravenous immunoglobulins (IVIG) or plasma exchange) has benefits and life saving, especially in patients with rapidly progressive weakness **(Hughes et al., 2014).**

Epidemiology:

Most studies that estimate incidence rates of Guillain-Barré syndrome were done in Europe and North America, and showed a similar range of 0.8–1.9 (median 1.1) cases per 100.000 people per year **(Sejvar et al., 2011).** The annual incidence rate of Guillain-Barré syndrome increases with age (0.6 per 100000 per year in children and 2.7 per 100000 per year in elderly people aged 80 years and over) and the disease is slightly more frequent in males than in females. Seasonal fluctuations, presumably related to variations in infectious antecedents, have been reported, but these observations are rarely statistically significant **(Webb et al., 2015).**

Recently, a new study has been done about regional variation of GBS, the full clinical spectrum of guillian-barre syndrome was observed in patients from all countries participating in the international Guillian-barre syndrome