



بسم الله الرحمن الرحيم

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The Significance of Neutrophil-to-Lymphocyte Ratio as an Inflammatory Marker of COVID-19 in Hemodialysis Patients

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبَّحَانَكَ يَا عَلِيمَ لَنَا
إِلَٰهًا مَا عَلِمْنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Contents

Title	Page No.
List of Abbreviations	i
List of Tables.....	iv
List of Figures	vi
Introduction.....	1
Aim of the Work	4
Review of Literature	
Chapter 1: Coronavirus Disease 2019 (COVID-19).....	5
Chapter 2: COVID-19 -Triggered Cytokine Storm and its Inflammatory Markers	37
Chapter 3: COVID-19 and Kidney Disease.....	56
Patients and Methods	80
Results	83
Discussion	109
Summary.....	125
Conclusion.....	128
References.....	129
Arabic Summary	

List of Abbreviations

Abb.	Full term
3CLpro	<i>3-Chymotrypsin-Like Protease</i>
AAK1	<i>AP2- Linked Protein Kinase-1</i>
ACE2	<i>Angiotensin-Converting Enzyme-2</i>
AF	<i>Atrial Fibrillation</i>
AKI	<i>Acute Kidney Injury</i>
ALT	<i>Alanine Aminotransferase</i>
ARDS	<i>Acute Respiratory Distress Syndrome</i>
AT2	<i>Alveolar Cell Type 2</i>
BAL	<i>Bronchoalveolar lavage</i>
BUN	<i>Blood Urea Nitrogen</i>
C/EBP	<i>Homologous Protein (CHOP) Expression</i>
CATCO	<i>Canadian Treatments for COVID-19</i>
CBC	<i>Complete Blood Count</i>
cGAS	<i>Cyclic GMP–AMP Synthase</i>
CKD	<i>Chronic Kidney Disease</i>
CK-MB	<i>Creatinine Kinase-Muscle / Brain Activity</i>
CLD	<i>Chronic Liver Disease</i>
COPD	<i>Chronic Obstructive Pulmonary Disease</i>
CO-RADS	<i>Coronavirus Disease 2019 Reporting and Data System</i>
COVID-19	<i>Coronavirus Disease 2019</i>
CRP	<i>Serum C-reactive Protein</i>
CRS	<i>Cytokine Release Syndrome</i>
CSS	<i>Cytokine Storm Syndrome</i>
CT	<i>Computed Tomography</i>
DAMPs	<i>Damage-Associated Molecular Patterns</i>
DD	<i>D Dimer</i>
DM	<i>Diabetes Mellitus</i>
DNA	<i>Deoxyribonucleic Acid</i>
eGFR	<i>Estimated Glomerular Filtration Rate</i>
ESR	<i>Erythrocyte Sedimentation Rate</i>
ESRD	<i>End-Stage Renal Disease</i>
FDA	<i>Food and Drug Administration</i>

List of Abbreviations cont...

Abb.	Full term
GM-CSF	<i>Granulocyte Macrophage Colony-Stimulating Factor</i>
Hb	<i>Hemoglobin</i>
HD	<i>Hemodialysis</i>
HRCT	<i>High Resolution Computed Tomography</i>
HSP70	<i>70 Kilodalton Heat Shock Protein</i>
HTN	<i>Hypertension</i>
ICU	<i>Intensive Care Unit</i>
IFN	<i>Interferon</i>
IgG	<i>Immunoglobulin G</i>
IgM	<i>Immunoglobulin M</i>
IHD	<i>Ischemic Heart Disease</i>
IL	<i>Interlukins</i>
ILIAD	<i>Interferon Lambda for Immediate Antiviral Therapy at Diagnosis in COVID-19</i>
JAK-STAT	<i>Janus Kinase and Signal Transducer and Activator of Transcription</i>
KDIGO	<i>Kidney Disease Improving Global Outcomes</i>
KFRT	<i>Kidney Failure Receiving Replacement Therapy</i>
KTR	<i>Kidney Transplant Recipient</i>
LAMP	<i>Loop-Mediated Isothermal Amplification</i>
Lck	<i>Lymphocyte-Explicit Protein Tyrosine Kinase</i>
LDH	<i>Lactate Dehydrogenase</i>
LMR	<i>Lymphocyte-to-Monocyte Ratio</i>
LPS	<i>Lipopolysaccharide</i>
MHC	<i>Major Histocompatibility Complex</i>
MHC	<i>Meutrophil-to-Lymphocyte Ratio</i>
NAAT	<i>Nucleic Acid Amplification Testing</i>
NAK	<i>Numbassociated Kinase</i>
ND-CKD	<i>Non-Dialysis-Dependent CKD</i>
NETs	<i>Neutrophil Extracellular Traps</i>
NFκB	<i>Nuclear Factor Kappa B</i>

List of Abbreviations cont...

Abb.	Full term
NHC	<i>Beta-D-N4-Hydroxycytidine</i>
NK	<i>Natural Killer Cells</i>
NRF2	<i>Nuclear Factor Erythroid 2-Related Factor 2</i>
ORFs	<i>Open Reading Frames</i>
PAMPs	<i>Pathogen-Associated Molecular Patterns</i>
PCT	<i>Procalcitonin</i>
PLR	<i>Platelet-to-Lymphocyte Ratio</i>
PRR	<i>Pattern Recognition Receptors</i>
PUFA	<i>Polyunsaturated Fatty Acids</i>
RAS	<i>Renin-Angiotensin System</i>
RBC	<i>Red Blood Cells</i>
RBD	<i>Receptor-Binding Domain</i>
RCT	<i>Randomized Controlled Trial</i>
RdRp	<i>RNA-Dependent RNA Polymerase</i>
RFR	<i>Renal Functional Reserve</i>
RNA	<i>Ribonucleic Acid</i>
RRT	<i>Renal Replacement Therapy</i>
rRT-LAMP	<i>Real-Time RT-LAMP</i>
RTC	<i>Replication-transcription complex</i>
RT-LAMP	<i>Reverse Transcription LAMP</i>
RT-PCR	<i>Reverse-Transcription Polymerase Chain Reaction</i>
S1PR	<i>Sphingosine-1-Phosphate Receptor</i>
SARS-CoV-2	<i>Severe acute respiratory syndrome coronavirus 2</i>
SHERLOCK	<i>Specialised High-Sensitivity Enzymatic Reporter Unlocking Test</i>
STAT1	<i>Signal Transducer and Activator of Transcription 1</i>
TCR	<i>Toll like Receptor</i>
TMPRSS	<i>Transmembrane Protease Serine</i>
TNF	<i>Tumor Necrosis Factor</i>
URR	<i>Urea Reduction Rate</i>
WBC	<i>White Blood Cell</i>
WHO	<i>World Health Organization</i>

List of Tables

Table No.	Title	Page No.
Table 1:	Symptoms associated with coronavirus disease 2019 (COVID-19).....	10
Table 2:	Diagnostic tests for COVID-19.....	16
Table 3:	CO-RADS Categories and the corresponding level of suspicion for pulmonary involvement in COVID-19.....	18
Table 4:	Cytokine Storm Markers in COVID-19.....	43
Table 5:	Comparison between non-COVID-19 and COVID-19 group among demographic data.....	84
Table 6:	Comparison between non- COVID-19 and COVID-19 group among anthropometric measures and vital signs.....	86
Table 7:	The comparison between HD vintage and duration among both study groups.....	88
Table 8:	Co-morbidities distribution among both study groups.....	89
Table 9:	The laboratory data among both study groups.....	90
Table 10:	NLR, Neutrophils and lymphocytes among both study groups.....	96
Table 11:	CT Chest finding, Oxygen therapy, Medications and Outcomes among the COVID-19 group.....	99
Table 12:	Neutrophils, Lymphocytes and NLR specificity and sensitivity in COVID-19 infection.....	101
Table 13:	Correlation between neutrophils, lymphocytes and NLR and other laboratory findings.....	101
Table 14:	Correlation of CORAD score, oxygen therapy, anticoagulation, antiviral and outcome with the Neutrophils.....	103

List of Tables cont...

Table No.	Title	Page No.
Table 15:	Correlation of CORAD score, oxygen therapy, anticoagulation, antiviral and outcome with the lymphocytes.....	104
Table 16:	Correlation of CORAD score, oxygen therapy, anticoagulation, antiviral and outcome with NLR.....	105
Table 17:	The correlation between the anticoagulation, antiviral and the outcome.....	107

List of Figures

Fig. No.	Title	Page No.
Figure 1:	Schematic representation of SARS-CoV-2 structure.....	6
Figure 2:	Transmission and life cycle of SARS-CoV2 causing COVID- 19.....	8
Figure 3:	The main methods for diagnosing suspected COVID-19 cases are depicted in this diagram.....	13
Figure 4:	The estimated levels of IgM and IgG antibodies produced against SARS-CoV-2 along the weeks of being infected	15
Figure 5:	Use of anticoagulation in COVID-19 patients.....	36
Figure 6:	SARS-CoV-2 evades TLR recognition and thereby suppressing IFN-1 production.....	39
Figure 7:	Defective NK cell signals the production of a flurry of cytokines.....	41
Figure 8:	Different stages of COVID-19 -associated acute kidney injury	60
Figure 9:	Shared pathophysiology between lung and kidney injury in COVID-19	62
Figure 10:	Factors that may contribute to COVID-19 - associated acute kidney injury.....	72
Figure 11:	Interaction between SARS-CoV-2 and CKD.....	74
Figure 12:	Comparison between non- COVID-19 and COVID-19 group among mean age of the studied subjects.	85
Figure 13:	Comparison between non- COVID-19 and COVID-19 group among gender of the studied subjects.....	85
Figure 14:	Bar Chart showing the comparison between the two study groups regarding both the systolic and the diastolic blood pressures.....	87
Figure 15:	Comparison between COVID-19 and Non- COVID-19 group regarding HD duration	88

List of Figures cont...

Fig. No.	Title	Page No.
Figure 16:	Is a box blot figure demonstrating the distribution of values (median, lower and upper quartile) for CRP between both study groups.....	92
Figure 17:	Is a box blot figure demonstrating the distribution of values (median, lower and upper quartile) for ferritin between both study groups.....	92
Figure 18:	Is a box blot figure demonstrating the distribution of values (median, lower and upper quartile) for D dimer between both study groups.....	93
Figure 19:	Is a box blot figure demonstrating the distribution of values (median, lower and upper quartile) for BUN predialysis between both study groups.....	93
Figure 20:	Is a box blot figure demonstrating the distribution of values (median, lower and upper quartile) for BUN post dialysis between both study groups.....	94
Figure 21:	Comparison between the URR values of both COVID-19 and non-COVID-19 groups.....	94
Figure 22:	Comparison between Hb values of both COVID-19 and non-COVID-19 groups.....	95
Figure 23:	Comparison between serum albumin values of both COVID-19 and non-COVID-19 groups.....	95
Figure 24:	Is a box blot figure demonstrating the distribution of values (median, lower and upper quartile) for neutrophils.....	97
Figure 25:	Is a box blot figure demonstrating the distribution of values (median, lower and upper quartile) for lymphocytes.....	97

List of Figures cont...

Fig. No.	Title	Page No.
Figure 26:	Is a box blot figure demonstrating the distribution of values (median, lower and upper quartile) for NLR.....	98
Figure 27:	ROC curve of neutrophils, lymphocytes and NLR as a predictor of COVID-19.....	100
Figure 28:	Correlation between lymphocytes and serum albumin.....	102
Figure 29:	Correlation between NLR and CRP.....	102
Figure 30:	Correlation between NLR and the outcome.....	106
Figure 31:	Relation between the percentage of anticoagulation use with all its modalities and the patient's outcome.....	108
Figure 32:	The relation between the percentage of anti-viral use and the outcome.....	108

INTRODUCTION

End-stage renal disease (ESRD) patients have higher rates of mortality and morbidity compared to the general population (*Abe et al., 2014*).

Cardiovascular disease is the leading cause of death, accounting for 40%-50% of all-cause mortality in ESRD patients (*Junzhou et al., 2015*).

Infection is second to cardiovascular disease as the leading cause of death in patients with ESRD (*Mark and Jaber, 2000*).

Infection is the second leading cause of hospitalization and death of ESRD patients, and pneumonia consists 20% of infection. Nevertheless, patients on dialysis also have higher mortality rate and higher medical burden than non-dialysis individuals (*Rajiv et al., 2020*).

One of the emerging-rapidly spreading-leading causes of pneumonia worldwide is a novel Corona virus, severe acute respiratory syndrome (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) (*Jia et al., 2020*).

ESRD patients are at high risk for COVID-19-associated morbidity and mortality (*Kitty et al., 2020*).

Given the immunocompromised nature of ESRD and their high comorbidity burden, patients with ESRD are among the most vulnerable populations to COVID-19, especially given the

impractical nature of social distancing rules for patients who need in-centre hemodialysis (*Anthony et al., 2020*).

Patients on hemodialysis are recognized by their unique pathophysiology; that is, “reverse epidemiology” for cardiovascular risk factors (*Yannick et al., 2017*), worse outcome on normalization of hemoglobin, impaired innate and acquired immune system (*Sawako et al., 2008*) and an earlier calcification of the blood vessels (*Mizobuchi et al., 2009*).

Excessive oxidative stress status is also seen in hemodialysis patients due to the retention of a variety of toxins subsidized by uremia, nutrition deficient in antioxidants and antioxidant turnover, antioxidant loss during renal replacement therapy, and leukocyte activation that leads to the accumulation of oxidative products. Dialysis therapy duration, iron infusion, anemia, the presence of a central venous catheter, and bio-incompatible dialyzers are all variables that can lead to oxidative stress (*Vassilios et al., 2017*).

Thus, hindering them vulnerable to respond to the stress of a new disease like COVID-19, which has a double hazard of a cytopathic and a cytokine release effect (*Samia et al., 2021*).

Infectious disorders induce inflammation, and emerging data suggests that it plays an important role in the pathogenesis of different viral pneumonias, including COVID-19 (*Na et al., 2019*).