



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



MONA MAGHRABY



Expression of NKG2A Inhibitory Receptor on Cytotoxic Lymphocytes as an Indicator of Severity in Corona Virus Disease 2019 (COVID- 19) Patients

Thesis

*Submitted for Partial Fulfillment of master's degree in
Basic Medical Sciences (Medical Microbiology and Immunology)*

Presented by

Marwa Mustafa Mounir Yasin

M.B.B.Ch,

Faculty of Medicine, Ain Shams University

Under supervision of

Prof. Dr. Eman Hussein Shehata

Professor of Medical Microbiology and Immunology

Faculty of Medicine, Ain Shams University

Dr. Marwa Shabban Elsayed Ibrahim

Assistant Professor of Medical Microbiology and Immunology

Faculty of Medicine, Ain Shams University

Dr. Nesma Gamal Ahmed Elsheikh

Lecturer of Geriatric and Gerontology medicine

Faculty of Medicine, Ain Shams University

Faculty of Medicine

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا أنك لا تعلم لنا
إلا ما علمتنا أنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgment

*First thanks to **ALLAH** to whom I relate every single successful step toward achieving any work in my life.*

*I wish to express my deepest gratitude and appreciation to **Prof. Dr. Eman Hussein Shehata**, Professor of Medical Microbiology and Immunology, Faculty of Medicine, Ain Shams University, for her expert, sincere and valuable guidance throughout the work.*

*I also want to express my great thanks to **Dr. Marwa Shabban Elsayed Ibrahim**, Assistant Professor of Medical Microbiology and Immunology, Faculty of Medicine, Ain Shams University, for her meticulous supervision, sincere efforts and fruitful encouragement.*

*Also, I want to express my great thanks to **Dr. Nesma Gamal Ahmed Elsayed**, Lecturer of geriatric medicine, Faculty of Medicine, Ain Shams University for her help and encouragement.*

Also, I want to express my greatest thanks and best regards to my colleagues in the department of Microbiology and Immunology, for their cooperation and advice.

Lastly, I wish to express my appreciation to my family, without their support and help this work would have not been fulfilled.

Marwa Mustafa Mounir

List of Contents

Title	Page No.
List of Tables	i
List of Figures	ii
List of Abbreviations.....	iv
Introduction	1
Aim of the Work.....	4
Review of Literature	
☞ Corona- Virus Disease 2019 (COVID-19)	5
☞ Immunologic Features in Coronavirus Disease 2019	34
☞ Natural Killer Group 2 Member A Receptor	51
Patients and Methods.....	62
Results	71
Discussion	82
Summary	88
Conclusions and Recommendations	91
References	93
Arabic Summary	١

List of Tables

Table No.	Title	Page No.
Table (1):	The demographic and personal data of the Three studied groups.....	71
Table (2):	Laboratory parameters measured in case and control groups.....	73
Table (3):	NK cell count and markers measured between control and case groups.	74
Table (4):	CD8 +T Cell count and markers measured between control and case groups.	75
Table (5):	Lab Parameters measured within cases groups.....	77
Table (6):	NK cell count and markers measured between moderate and severe cases.	78
Table (7):	CD8 +T Cell count and markers measured between moderate and severe cases.	79
Table (8):	Correlations between NKG2A Expression on CD8-Cell% and NKG2A Expression on NK-Cell% among all participants.....	81

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Structure of coronavirus	8
Figure (2):	Genome and nonstructural proteins of Severe Acute Respiratory Syndrome Coronavirus-2	9
Figure (3):	Mechanism of entry and life cycle of Severe Acute Respiratory Syndrome Coronavirus	16
Figure (4):	Potential roles of NK cells and NK cell-based interventions in COVID-19.....	39
Figure (5):	Potential model of T cell responses during COVID-19 progression	47
Figure (6):	Antibody-Mediated Immunity in SARS-CoV-2	50
Figure (7):	NKG2A Chromosomal location.....	52
Figure (8):	Receptor interaction of HLA-E with NKG2A&B/CD94 and NKG2C/CD94.....	54
Figure (9):	NK cell surface receptors, both activating and inhibitory receptors, carry out NK cell functions through a balance of signals	55
Figure (10):	Structure and ligands of activating and inhibitory receptors of NK cells.....	56
Figure (11):	NK Cell Inhibitory Receptors Signaling pathway	58
Figure (12):	Comparison of NKG2A expression on NK cells between cases and control groups.	74
Figure (13):	Comparison of NKG2A expression on CD8+ T cells between cases and control groups.	76
Figure (14):	Comparison of NKG2A expression on NK cells between moderate and severe groups of cases.	78

List of Figures (Cont...)

Fig. No.	Title	Page No.
Figure (15):	Comparison of NKG2A expression on CD8+ T cells between moderate and severe groups of cases.....	80
Figure (16):	Scatter diagram showing the correlation between NKG2A Expression on CD8-Cell% and NKG2A Expression on NK-Cell%.....	81

List of Abbreviations

Abb.	Full term
<i>2019-nCoV</i>	<i>2019-novel coronavirus</i>
<i>ALI</i>	<i>Acute lung injury</i>
<i>ARDS</i>	<i>Acute respiratory distress syndrome</i>
<i>ALT</i>	<i>Alanine aminotransferase</i>
<i>ACE2</i>	<i>Angiotensin converting enzyme 2</i>
<i>AT1R</i>	<i>Angiotensin receptor 1</i>
<i>ACEIs</i>	<i>Angiotensin converting enzyme inhibitors</i>
<i>SHP-1</i>	<i>Anti-Src Homology Phosphatase-1</i>
<i>SHP-2</i>	<i>Anti-Src Homology Phosphatase-2</i>
<i>AST</i>	<i>Aspartate aminotransferase</i>
<i>BAL</i>	<i>Bronchoalveolar lavage</i>
<i>BALF</i>	<i>Bronchoalveolar Lavage Fluid</i>
<i>CHB</i>	<i>Chronic hepatitis B</i>
<i>CT</i>	<i>Computed tomography</i>
<i>COVID-19</i>	<i>Coronavirus disease 2019</i>
<i>CSS</i>	<i>Cytokine storm syndrome</i>
<i>CCR2</i>	<i>C-C Chemokine receptor type 2</i>
<i>CCL27</i>	<i>C-C Motif Chemokine Ligand 27</i>
<i>CXCL8</i>	<i>C-X-C Motif Chemokine Ligand 8</i>
<i>DCs</i>	<i>Dendritic cells</i>
<i>DMARD</i>	<i>Disease-modifying anti-rheumatic drug</i>
<i>R</i>	<i>Effective reproductive number</i>
<i>ERGIC</i>	<i>Endoplasmic reticulum-Golgi intermediate compartment</i>
<i>eIF2α</i>	<i>Eukaryotic initiation factor 2 subunit α</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>ECMO</i>	<i>Extracorporeal membrane oxygenation</i>
<i>favipiravir-RTP</i>	<i>Favipiravir ribofuranosyl-5B-triphosphate</i>
<i>FGF</i>	<i>Fibroblast growth factor</i>
<i>FiO2</i>	<i>Fraction of inspired oxygen</i>
<i>G-CSF</i>	<i>Granulocyte colony-stimulating factor</i>
<i>GM-CSF</i>	<i>Granulocyte-macrophage colony-stimulating factor</i>
<i>HCWs</i>	<i>Health care workers</i>
<i>HGB</i>	<i>Hemoglobin level</i>
<i>HCV</i>	<i>Hepatitis C virus</i>
<i>CHB-H</i>	<i>High HBV DNA titer</i>
<i>HCoV</i>	<i>Human coronaviruses</i>
<i>HCQS</i>	<i>Hydroxychloroquine</i>
<i>ITIM</i>	<i>Immunoreceptor tyrosine-based inhibitory motif</i>
<i>IP-10</i>	<i>Interferon γ-induced protein 10</i>
<i>ISGs</i>	<i>Interferon stimulated genes</i>
<i>IFN-γ</i>	<i>Interferon γ</i>
<i>IL-1B</i>	<i>Interleukin 1beta</i>
<i>IL-15</i>	<i>Interleukin-15</i>
<i>KLRD1</i>	<i>Killer Cell Lectin Like Receptor D1</i>
<i>KIRs</i>	<i>Killer immunoglobulin Ig-like receptors</i>
<i>KIRs</i>	<i>Killer immunoglobulin receptors</i>
<i>LIR-1</i>	<i>Leukocyte Ig-like receptor-1</i>
<i>CHB-L</i>	<i>Low HBV DNA titer</i>
<i>M-CSF</i>	<i>Macrophage Colony Stimulating Factor</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>MIP-1A</i>	<i>Macrophage Inflammatory Protein-1 Alpha</i>
<i>MHC-I</i>	<i>Major histocompatibility complex I</i>
<i>MBL</i>	<i>Mannose-binding lectin</i>
<i>M</i>	<i>Matrix protein</i>
<i>MASP-2</i>	<i>MBL-associated serine protease 2</i>
<i>MAP</i>	<i>Mean arterial pressure</i>
<i>MFI</i>	<i>Mean intensity of fluorescence</i>
<i>MAC</i>	<i>Membrane attack complex</i>
<i>MERS</i>	<i>Middle East Respiratory Syndrome</i>
<i>mAbs</i>	<i>Monoclonal antibodies</i>
<i>MCP-1</i>	<i>Monocyte Chemoattractant Protein-1</i>
<i>MCP-3</i>	<i>Monocyte Chemotactic Protein 3</i>
<i>NK</i>	<i>Natural killer</i>
<i>nAbs</i>	<i>Neutralizing IgG anti- bodies</i>
<i>N/L Ratio</i>	<i>Neutrophil to Lymphocyte Ratio</i>
<i>NKC</i>	<i>NK gene complex</i>
<i>NLRs</i>	<i>NOD-like receptors</i>
<i>NCIP</i>	<i>Novel coronavirus-infected pneumonia</i>
<i>NAAT</i>	<i>Nucleic acid amplification Test</i>
<i>N</i>	<i>Nucleoprotein</i>
<i>NOD</i>	<i>Nucleotide-binding and oligomerization domain</i>
<i>OAS</i>	<i>Oligoadenylate synthase</i>
<i>PAMPs</i>	<i>Pathogen-associated molecular patterns</i>
<i>PRRs</i>	<i>Pattern recognition receptors</i>
<i>PBMCs</i>	<i>Peripheral blood mononuclear cells</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>PPE</i>	<i>Personal Protective Equipment</i>
<i>PLT</i>	<i>Platelet count</i>
<i>PDGF</i>	<i>Platelet-derived growth factor</i>
<i>PEEP</i>	<i>Positive end-expiratory pressure,</i>
<i>PD-1</i>	<i>Programmed cell death protein-1</i>
<i>PKR</i>	<i>Protein kinase R</i>
<i>rRT-PCR,</i>	<i>Real-time reverse transcription polymerase chain reaction</i>
<i>RBD</i>	<i>Receptor binding domain</i>
<i>RIG-I</i>	<i>Retinoic acid-inducible gene I</i>
<i>RdRp</i>	<i>RNA dependent RNA polymerase</i>
<i>SARS</i>	<i>Severe acute respiratory syndrome</i>
<i>SARS-CoV-2</i>	<i>Severe acute respiratory syndrome coronavirus-2</i>
<i>S</i>	<i>Spike structural protein</i>
<i>SH2</i>	<i>Src Homology 2</i>
<i>TIGIT</i>	<i>T cell immunoreceptor with immunoglobulin and ITIM domains</i>
<i>RO</i>	<i>The basic reproduction</i>
<i>TLRs</i>	<i>Toll-like receptors</i>
<i>TLC</i>	<i>Total leucocytic count</i>
<i>TMPRSS2</i>	<i>Transmembrane serine protease 2</i>
<i>TNFα</i>	<i>Tumor necrosis factor alpha</i>
<i>IFN-I</i>	<i>Type I interferons</i>
<i>TMPRSS2</i>	<i>Type II transmembrane serine protease</i>
<i>VEGF</i>	<i>Vascular endothelial growth factor</i>
<i>E</i>	<i>Viral envelope</i>
<i>WHO</i>	<i>World Health Organization</i>

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel beta coronavirus firstly identified during a burst of respiratory illness cases in Wuhan City, Hubei Province, China (*Li et al., 2020*). In a few weeks the disease became a global pandemic with 5, 593, 631 cases and 353, 334 confirmed deaths as reported by the World Health Organization on 28 May 2020. A wealth of recent data highlights the dysregulated immune response and its inflammatory component as the main cause of morbidity and mortality (*Blanco-Melo et al., 2020*).

This novel virus is associated with higher mortality than other respiratory viruses, it also demonstrates a broader variation in its clinical presentation (*Xu et al., 2020*). The majority of COVID-19 cases (about 80%) are asymptomatic or exhibit mild to moderate symptoms, but approximately 15% progress to severe pneumonia and about 5% develop critical disease with respiratory failure and organ dysfunction (*Huang et al., 2020*). Pneumonia is the most frequent serious manifestation of infection, while acute respiratory distress syndrome (ARDS) is the major complication in patients with severe illness. Other complications include: coagulopathy, microvascular thrombosis such as myocardial infarction and stroke, arrhythmias, acute cardiac injury, liver injury, acute kidney injury, and shock (*Arentz et al., 2020*).