شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

HANAA ALY

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

HANAA ALY

Platelet Glycoprotein VI Genetic Polymorphism T13254C in Neonatal Sepsis

A thesis

Submitted for Partial Fulfillment of M.D. Degree
in Clinical Pathology

Presented by

Marina Mounir William Labib
M.B.B.Ch., M. Sc. Clinical Pathology
Faculty of Medicine, Ain Shams University

Under supervision of

Professor/ Abeer Attia Saadeldin
Professor of Clinical Pathology
Faculty of Medicine - Ain Shams University

Professor/ Rania Ali El-Farrash
Professor of Pediatrics and Neonatology
Faculty of Medicine - Ain Shams University

Doctor/ Mona Fathey Abdelfattah Hassan
Assistant Professor of Clinical Pathology
Faculty of Medicine - Ain Shams University

Doctor/ Yasmin Nabil ElSakhawy
Assistant Professor of Clinical Pathology
Faculty of Medicine - Ain Shams University

Doctor/ Menna Allah Zakaria Mohammad Ali Abou Elwafa
Lecturer of Clinical Pathology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2021-2022

Acknowledgment

First of all, thanks to *God,* for his constant grace.

It has been a great honor to proceed into this work under the supervision of ***Prof. Dr. Abeer Attia Saadeldin,*** *Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University,* I would like to express my endless appreciation for her keen guidance, kind supervision, scientific criticism and continuous encouragement, which made possible the completion of this work.

I am delighted to express my gratitude to ***Prof. Dr. Rania Ali El-Farrash,*** *Professor of Pediatrics and Neonatology, Faculty of Medicine, Ain Shams University***,** for her kind care, valuable instructions and great assistance throughout this work.

I am deeply thankful to ***Ass. Prof. Dr. Mona Fathey Abdelfattah Hassan*** *Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University* for her great help, valuable advice and cooperation.

Indeed, words do fail to express my special thanks and appreciation to ***Ass. Prof. Dr. Yasmin Nabil ElSakhawy,*** *Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University*, for her constant help, active participation and guidance.

I wish to introduce my deep respect and thanks to ***Dr. Menna Allah Zakaria Mohammad Ali Abou Elwafa,*** *Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University*, for her kindness, patience, creative suggestions and encouragement in this work.

I would like to express my thanks and gratitude to all my ***Family*** for their support and for pushing me forward in every step in my life.

Special thanks to all the patients who have contributed to this work.

Marina Mounir William Labib

List of Contents

List of Tables

List of Tables (Cont...)

List of Figures

List of Abbreviations

Abb.	Full term

ACS ..... Acute coronary syndrome
ADP ..... Adenosine diphosphate
aPTT..... Activated partial thromboplastin time
CD..... Cluster of differentiation
CONS ..... Coagulase-negative Staphylococcus
COX-1 ..... Cyclooxygenase-1
CRP ..... C-reactive protein
CXCL ..... Chemokine (C-X-C motif) ligand
DAMPs..... Damage associated molecular patterns
DIC ..... Disseminated intravascular coagulation
dNTPs..... Deoxyribonucleotide triphosphates
DVT..... Deep vein thrombosis
EDTA ..... Ethyl diamine tetra-acetic
EOS ..... Early-onset sepsis
ESR..... Erythrocyte sedimentation rate
FMASU ..... Faculty of Medicine, Ain Shams University
FcRγ ..... Fc receptor γ chain
FiO2 ..... Fraction of inspired Oxygen
GAG ..... Glycosaminoglycans
G-CSF ..... Granulocyte-colony stimulating factors
GP..... Glycoprotein
GBS ..... Group B streptococcus
GIT ..... Gastrointestinal tract
GNB3..... Guanine nucleotide-binding protein beta-3 subunit variant
GPO..... Glycine– proline–hydroxyproline
IAP ..... Intrapartum antibiotic prophylaxis.
ICAM-1..... Soluble Intercellular Adhesion Molecule 1
ICU…….Intensive care unit

List of Abbreviations *(Cont...)*

Abb.	Full term
IFN- γ	Interferon gamma
IL-1	Interleukin 1
INR	International normalization ratio
ITAM	Immunoreceptor tyrosine-based activation motif
ITG	Integrin
ISTH	International Society on Thrombosis and Hemostasis
IQR	Inter-quartile range
LAT	Linker of activated T cells
LOS	Late-onset sepsis
MAC	Membrane attack complex
MGB	Minor groove binder
MMP9	Metalloproteinase 9
MPs	Microparticles
NETs	Neutrophil extracellular traps
NF-κB	Nuclear factor kappa- light- chain enhancer of activated B cells
NICU	Neonatal intensive care units
NOS2	Nitric Oxide Synthase 2
PAMPs	Pathogen associated molecular patterns
PARs	Protease Activating Receptors
PCR	Polymerase chain reaction
PCT	Procalcitonin
PF4	Platelet factor 4
PG	Proteoglycans
PLC γ2	Phospholipase Cγ2
PMN	Polymorphonuclear neutrophils
PMNL-MPs	Polymorphonuclear leucocyte-derived microparticle
PolyP	Polyphosphates
PR	Purinogenic receptor
PSGL-1	P-selectin glycoprotein ligand 1
PT	Prothrombin time

List of Abbreviations *(Cont...)*

Abb.	Full term
PTGS1	Prostaglandin-endoperoxide synthase 1
RANTES	Regulated upon activation normal T cell expressed and secreted
RGD	Arginine-glycine-aspartic acid
ROM	Rupture of membranes
ROS	Reactive oxygen species
SD	Standard deviation
SH3	Src homology 3
SIC score	Sepsis induced coagulopathy score
SIRS	Systemic inflammatory response syndrome
SNAP II score	Score for neonatal acute physiology II
SNPs	Single nucleotide polymorphisms
SOFA	Sequential organ failure assess
Spa	Staphylococcus aureus protein A
SPSS	Statistical package for Social Science
SrpA	Serine-rich protein A
TBXA2R	Thromboxane A2 receptor
TLRs	Toll-like receptors
TF	Tissue factor
TNF-alpha	Tumor necrosis factor alfa
TPO	Thrombopoietin
TxA2	Thromboxane A2
VLBW	Very low birthweight
vWF	Von Willebrand factor
WBC	White blood cell count

INTRODUCTION

Neonatal sepsis is a systemic infection occurring in infants at ≤28 days of life ***(Edwards and Baker, 2004)***. It is classified into two clinical patterns of illness, that of early and late onset. Early-onset sepsis (EOS) is more fulminant, it is commonly diagnosed within the first 48 hours and almost always during the first week of life ***(Chacko and Sohi, 2005).***

Several risk factors for EOS have been recognized, including preterm birth, low birth weight, rupture of membranes for longer than 18 hours, chorioamnionitis and meconium passed ***(Good and Hooven, 2019).*** However, associations between each individual risk factor and EOS are weak, and some risk factors are inconsistently diagnosed ***(Adatara et al., 2018).*** It is a common and devastating cause of neonatal mortality and morbidity ***(Camacho-Gonzalez et al., 2013)*** with life-long impact plagued by a lack of accurate diagnostic and prognostic testing. Management options and outcomes have not been changed for the last 30 years ***(Wynn, 2016).***

Platelet activation plays an important role in the development of sepsis. During sepsis, platelet activation leads to endothelial cell injury and promotes neutrophil extracellular traps (NETs) and microthrombus formation, exacerbating septic coagulation and inflammatory reactions. The resultant induction of disseminated intravascular coagulation (DIC) leads to organ damage ***(Wang et al., 2018).***

The GPVI protein is the platelet activator receptor for collagen ***(Watkins et al., 2006).*** It was found to support the host defense and modulate inflammation, platelet influx, activation, and platelet–leukocyte complex formation at the primary site of infection during gram-negative derived sepsis ***(Claushuis et al., 2018).*** It also has been confirmed as possible participants in the process of platelet-induced NETs formation ***(Wang et al., 2018).***

In terms of prognostic information; ***Asafi et al. (2019)*** identified a significant difference in the morbidity outcome for pediatric sepsis patients with different GPVI haplotypes. Also, ***Montague et al. (2018)*** proved it to be an important marker for platelet activation that predicts sepsis progression and mortality in injured patients.

Changes to genes of sepsis mediators (polymorphism and mutations) have an important role in the susceptibility to the severity and outcome. With the advance of molecular genetic methods, genetic testing and screening of patient groups at high risk of sepsis may become reality in the future ***(Elek et al., 2017)***. Mapping the genetic basis of human diseases and their risk factors is important in the current trend of individualization of patient care ***(Sionova et al., 2017).*** This, however, necessitates further research to clarify in detail the role of most powerful predictors in neonatal sepsis.