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ADAMTS13 and von Willebrand Factor Levels in Patients with Chronic Hepatitis C: Relations to Hemostatic Imbalance and Bacterial Infection

Thesis

Submitted for Partial Fulfillment of Master Degree
in Clinical & Chemical Pathology

By

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Faculty of Medicine
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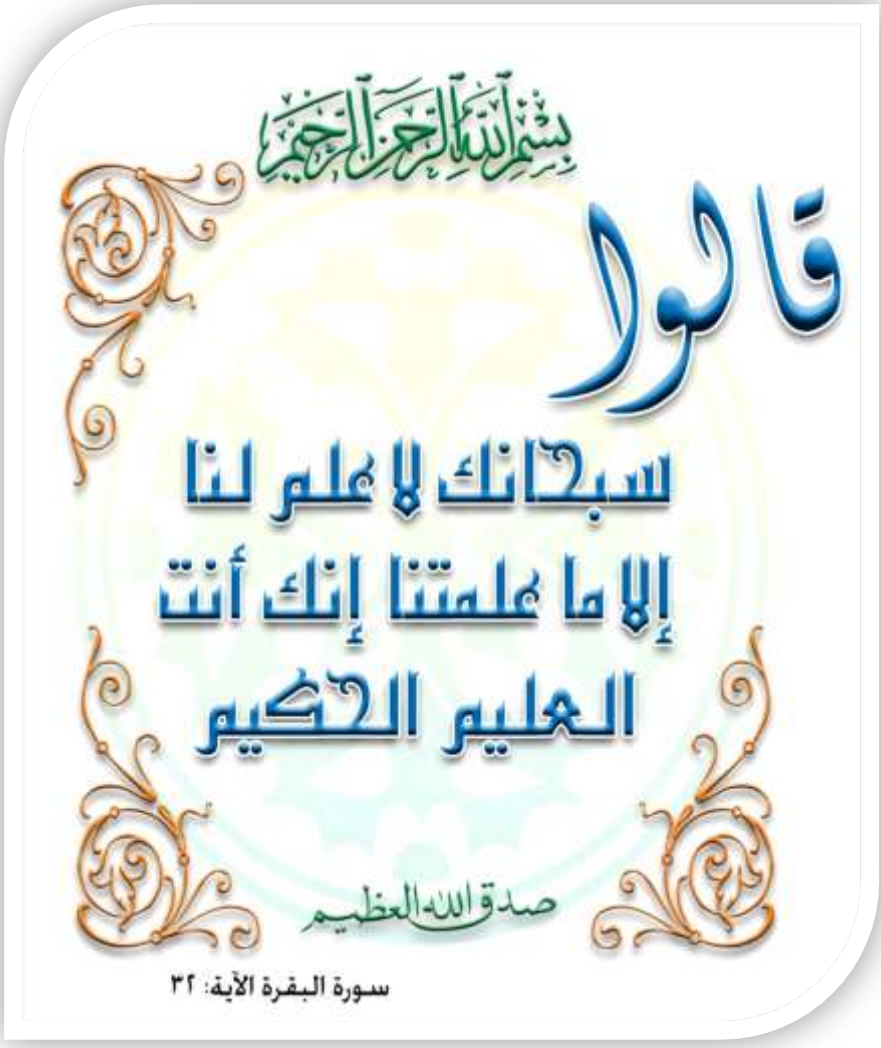
2021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Acknowledgment

First and foremost, thanks to **Allah**; to whom I relate any success in achieving any work in my life.

Words stand short when they come to express my gratefulness to my supervisors. I wish to express my deepest gratitude to **Prof. Dr. Mona Ahmed Wahba,** Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her effective guidance, unlimited help and support. No words of gratitude would be enough for her. I really have the honor to complete this work under her supervision.

I wish to express my deep appreciation and profound gratitude to **Prof. Dr. Nora El-Bassiouni Ibrahim El-Bassiouni,** Professor of Clinical and Chemical Pathology, Theodor Bilharz Research Institute, for her indispensable guidance, instructional supervision, continuous support, unlimited help and close supervision throughout the entire work.

A special tribute is paid to **Prof. Dr.Nariman Zahran,** Professor of Hematology, Hematology Department, Theodor Bilharz Research Institute, for her generous help, valuable advice and continuous support.

I am greatly honored to express my sincere gratitude and deep appreciation to **Assist. Prof. Dr. Yasmin Nabil ElSakhawy,** Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her help and support.

I am extremely grateful to **Dr. Raffat A. Ibrahim,** Assistant Professor of Tropical Medicine, Liver and Gastroentrology Departement, Theodor Bilharz Research Institute, for his cooperation and kind help.I

I would like to thank all the staff members and colleagues of the Haematology Department, Theodor Bilharz Research Institute who supported me a lot throughout this entire work.

Last but not least, my deepest appreciation is expressed to all members in my family, especially my *Mother, soul of Father* and *my sisters* for their continuous support, love and encouragement.

Hend Gamal El Din

2021

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List of Abbreviations

Abbr.		Full-term
ADAM	**:**	A Disintegrin and Metalloprotease
ADAMTS13	**:**	A dis-integrin and metalloproteinase with a Thrombospondin type-1 motif
AF	**:**	Ascitic fluid
ALT	**:**	Alanine amino transferase
ANC		Absolute neutrophil count
aPTTs	**:**	Activated partial thromboplastin times
AST	**:**	Aspartate amino transferase
AT	**:**	Antithrombin III
CRP	**:**	C reactive protein
CUB	**:**	Complement component C1r/C1s, Uegf, and bone morphogenic protein 1 domain.
cys-rich	**:**	Cysteine-rich domain
dis-like	**:**	Disintegrin-like domain
EDTA	**:**	Ethylenediaminetetraacetic acid
EGF	**:**	Epidermal growth factor
GP Ib	**:**	Glycoprotein Ib
GP Ib-IX-V	**:**	Glycoprotein Ib-IX-V
Hb	**:**	Hemoglobin
HCT	**:**	Hematocrit value
HMWM	**:**	High molecular weight multimers
HSCs	**:**	Hepatic stellate cells
LBP		Lipopolysaccharide binding protein
MCV	**:**	Mean cell volume

mRNA	**:**	Micro ribonucleic acid
PAI-1	**:**	Plasminogen activator inhibitor-1
PAI-2	**:**	Plasminogen activator inhibitor-2
PC	**:**	Proteins protein C
PH	**:**	Portal hypertension
PHT	**:**	Portal hypertension
PMN	**:**	Polymorphonuclear
pro-VWF	**:**	Von Willebrand factor propeptide
PS	**:**	Protein S
PT	**:**	Prothrombin times
PVT	**:**	Portal vein thrombosis
RBCs	**:**	Red cell count
ROC	**:**	Receiver operating characteristics
RT-PCR	**:**	Reverse transcriptase-polymerase chain reaction
SBP	**:**	Spontaneous Bacterial Peritonitis
SP	**:**	Signal peptide
TAFI	**:**	Thrombin Activatable Fibrinolysis Inhibitor
TM	**:**	transmembrane domain
tPA	**:**	Tissue plasminogen activator
TSP1	**:**	Thrombospondin type-1 motifs
TTP	**:**	Thrombotic thrombocytopenic purpura
UL-VWF	**:**	Ultra large Von Willebrand factor
VWF	**:**	Von Willebrand factor
VWF Ag	**:**	Von Willebrand factor antigen
WBCs	**:**	White blood cell count

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Introduction

Von Willebrand factor (VWF) is a multimeric glycoprotein that is primarily secreted by activated endothelial cells. It supports platelet adhesion and aggregation in a high shear stress environment **(Van Mourik *et al.*, 1999)**. VWF levels are not only markers of portal hypertension but are also independently linked to bacterial translocation, inflammation and procoagulant imbalance. Their levels also predict most clinical events and mortality independently of the severity of portal hypertension **(Mandorfer *et al.*, 2018).**

The hemostatic and thrombogenic potential of VWF depends on its multimer size, which is regulated by ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type-1 motif, that cleaves VWF multimers to smaller forms less capable of activating platelets **(Soejima *et al.*, 2001)**. Decreased ADAMTS13 activity is a feature of thrombotic thrombocytopenic purpura associated with the abundance of unprocessed, ultra-large VWF in plasma facilitating a prothrombotic state **(Tsai *et al.*, 2003).**

ADAMTS13 mRNA is primarily expressed in the liver **(Levy *et al.*, 2001; Zheng *et al.*, 2001)**. The hepatic stellate cells are considered a major source of the circulating enzyme **(Zhou *et al.*, 2005; Uemura *et al.*, 2008).** Activation of quiescent stellate cells to activated liver myofibroblasts