

HCV Core Antigen as an alternative test to Quantitative HCV RNA for assessment of SVR in Chronic HCV infected patients treated with Direct Acting Antiviral agents

Thesis

Submitted for partial fulfillment of master degree in Internal Medicine

By

Basant Moatz Abdelrhiem

M.B.B.Ch, Ain Shams University

Supervised by

Prof. Dr. Sherif Monier Mohamed

Professor of Internal Medicine and Gastroenterology Faculty of Medicine - Ain Shams University

Asst. Prof. Dr. Nevine Ibrahim Musa

Assistant Professor of Internal Medicine and Gastroenterology Faculty of Medicine - Ain shams University

Dr. Ramy Samir Ghait

Lecturer of Internal Medicine and Gastroenterology Faculty of Medicine - Ain shams University

Faculty of Medicine
Ain Shams University
2018

"raise to Allah, who has guided us to this; and we would never have been guided if Allah had not guided us". First and foremost, I'd like to express gratitude to Almighty Allah, the most gracious, the most merciful for helping throughout this work.

I would like to express my sincere appreciation to **Prof. Dr. Sherif Monier Mohamed** for his patience, motivation, enthusiasm, and immense knowledge. I could not have imagined having a better advisor and mentor for my study.

I am also most grateful for the generosity, kindness and endless support of **Asst. Prof. Dr. Nevine Ibrahim Musa.** The door to her office was always open whenever I ran into a trouble spot or had a question about my research or writing.

I am thankful as well for **Dr. Ramy Samir Ghait** who consistently allowed this paper to be my own work, but steered me in the right direction whenever he thought I needed it.

Finally, I must express my very profound gratitude to my parents for providing me with unfailing support and continuous encouragement throughout my years of study and the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

Basant Moatz Abdelrhiem

List of Contents

	Title	Page
•	List of Abbreviations	I
•	List of Tables	VI
•	List of Figures	XIII
•	Introduction	1
•	Aim of the Study	4
•	Review of Literature	5
•	Patients and Methods	67
•	Results	80
•	Discussion	138
•	Conclusion	151
•	Recommendations	152
•	Summary	153
•	References	155
	Arabic Summary	

 $\overline{X}d$ Mean's difference between pre and

post

 $\overline{X}1$ Mean of the first group

 \overline{X} 2 Mean of the second group. **AFP** Serum Alpha-Fetoprotein

Ag/Ab Antigen/Antibody

ALB Albumin

ALT Alanine Transaminase **ANOVA** Analysis of Variance

Apo Apolipoprotein

APRI Aminotransferase to Platelet Ratio

Index

ARFI Acoustic Radiation Force Impulse

AST Aspartate Transaminase

AUROC Area under the Receiver Operating

Characteristic Curve

CBC Complete Blood Count

CD Cluster of Differentiation

CI Confidence Interval

CIA Chemiluminescence Immunoassay

CLDN1 Claudin-1

CLDs Cytoplasmic Lipid Droplets

CLIA Chemiluminescent Immunoassay

CT Computed Tomography

CYP Cytochrome

DAAs Direct-Acting Antivirals

DAC Daclatasvir

DGAT1 Diacylglycerol Acyltransferase-1

DSV Dasabuvir **EBR** Elbasvir

ECG Electrocardiogram

EDHS Egypt Demographic and Health

Surveys

EGFR Epidermal Growth Factor Receptor **eGFR** Estimated Glomerular Filtration Rate

EHIS Egyptian Health Issue Survey

EIA Enzyme Immunoassay

ELISA Enzyme-Linked Immunosorbent

Assay

ER Endoplasmic Reticulum

FBS Fasting blood sugar level

FDA Food and Drug Administration

FIB4 Fibrosis-4
FU Follow up
GLE Glecaprevir
GT Genotype
GZR Grazoprevir

HAV Hepatitis A Virus

Hb Hemoglobin

HbA1c Hemoglobin A1c**HBV** Hepatitis B Virus

HCC Hepatocellular Carcinoma

HCV Hepatitis C Virus

HIV Human Immunodeficiency Virus

HRP Horseradish Peroxidase

IFN Interferon

INR International Normalized Ratio

IUs International Units

kPa Kilopascal

LDL Low-Density Lipoproteins

LDV Ledipasvir

LVPs Lipoviroparticles

MELD Model for End-Stage Liver Disease

MRI Magnetic Resonance Imaging

NAAT Nucleic Acid Amplification Test

NAT Nucleic Acid Test

NCCVH National Committee for Control of

Viral Hepatitis

Nis Nucleotide Inhibitors

NNIs Non-nucleotide Inhibitors
NPV Negative Predictive Value

NS Non Structural

OBV Ombitasvir;
OCLN Occludin

OD Optical Density

PAT Parenteral Anti-schistosomiasis

Treatment

PAUS Pelvi-abdominal Ultrasound
PCR Polymerase Chain Reaction

PegIFN Pegylated Interferon

P-gp P-glycoprotein
PIB Pibrentasvir

PIs Protease Inhibitors

PLT Platelets

PPV Positive Predictive Value

PTV Paritaprevir
PV Portal Vein

PWIDs People Who Inject Drugs

R Ritonavir

RAS Resistance Associated Substitutions

RBV Ribavirin

RdRP RNA-dependent RNA polymerase

RIBA Recombinant Immunoblot Assay

RIG-1 Retinoic acid–Inducible gene 1

RNA Ribonucleic acid

ROC Receiver Operating Characteristic

RT-qPCR Real-Time quantitative Polymerase

Chain Reaction

SD Standard Deviation

SE1 Standard error of the first group

SE2 Standard error of the second group

SEd Standard error of the difference

between pre and post

SOF Sofosbuvir

SPSS Statistical Package for the Social

Sciences

SR-BI Scavenger Receptor class B type I

SVR Sustained Virologic Response

TBR Total Bilirubin level

TLC Total Leucocytic Count

TMB Tetramethylbenzidine

USA United States of America

UTRs Untranslated Regions

VEL Velpatasvir

VLDL Very-Low-Density Lipoproteins

VOX Voxilaprevir

WHO World Health Organization

Table No.	Title Page
Table (1):	Non-invasive marker cut-offs for prediction of stages of fibrosis, including F3 (advanced fibrosis) and F4 (cirrhosis)
Table (2):	HCV DAAs approved in Europe in 2018
Table (3):	IFN-free, ribavirin-free combination treatment regimens available for treatment naïve patients
Table (4):	Treatment recommendations for patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients
Table (5):	Treatment recommendations for patients with chronic hepatitis C with compensated (Child-Pugh A) 49
Table (6):	Commonly used regimen of treatment for HCV by Egyptian national control program
Table (7):	Characteristics of studied subjects with regard to age81
Table (8):	Characteristics of studied subjects with regard to gender
Table (9):	Characteristics of studied subjects with regard to prevalence of Diabetes Mellitus

Table No.	Title Page
Table (10):	Characteristics of diabetic subjects with regard to HbA1c level
Table (11):	Characteristics of studied subjects with regard to baseline fibrosis score as assessed by fibroscan
Table (12):	Characteristics of studied subjects with regard to spleen and liver sizes and portal vein diameter, as assessed by PAUS before DAA treatment
Table (13):	Classification of studied subjects as easy to treat and difficult to treat 84
Table (14):	Characteristics of studied subjects with regard to the regimen of Direct Acting Antiviral treatment employed 85
Table (15):	Characteristics of studied subjects with regard to achievement of sustained virologic response (SVR) after 12 weeks of DAAs treatment as defined by Quantitative RNA measured via PCR
Table (16):	Characteristics of studied subjects with regard to achievement of sustained virologic response (SVR) after 12 weeks of DAAs treatment as defined by HCV core antigen level 87

Table No.	Title Page	
Table (17):	Characteristics of studied subjects with regard to HCV RNA as quantified by PCR, pre-treatment and 12 weeks after the end of treatment to define SVR 12	87
Table (18):	Characteristics of studied subjects with regard to the level of HCV core antigen pre-treatment and 12 weeks after the end of treatment to define SVR 12	90
Table (19):	Characteristics of studied subjects with regard to Total Leucocyte Count	93
Table (20):	Characteristics of studied subjects with regard to Hemoglobin level	95
Table (21):	Characteristics of studied subjects with regard to Platelet (PLT) count	97
Table (22):	Characteristics of studied subjects with regard to INR	99
Table (23):	Characteristics of studied subjects with regard to AST	101
Table (24):	Characteristics of studied subjects with regard to ALT	103
Table (25):	Characteristics of studied subjects with regard to Total Bilirubin level (TBR)	105

Table No.	Title Page
Table (26):	Characteristics of studied subjects with regard to serum Albumin (ALB) 107
Table (27):	Characteristics of studied subjects that had been treated with sofosbuvir and daclatasvir with regard to HCV RNA as quantified by PCR, pretreatment and 12 weeks after the end of treatment to define SVR 12
Table (28):	Characteristics of studied subjects that had been treated with sofosbuvir and daclatasvir, with regard to the level of HCV core antigen pretreatment and 12 weeks after the end of treatment to define SVR 12
Table (29):	Characteristics of studied subjects that had been treated with sofosbuvir and simeprevir with regard to HCV RNA as quantified by PCR, pretreatment and 12 weeks after the end of treatment to define SVR 12
Table (30):	Characteristics of studied subjects that had been treated with sofosbuvir and simeprevir, with regard to the level of HCV core antigen pretreatment and 12 weeks after the end of treatment to define SVR 12

Table No.	Title Page
Table (31):	Characteristics of studied subjects that had been treated with sofosbuvir and daclatasvir and ribavirin with regard to HCV RNA as quantified by PCR, pre-treatment and 12 weeks after the end of treatment to define SVR 12
Table (32):	Characteristics of studied subjects that had been treated with sofosbuvir, daclatasvir and ribavirin, with regard to the level of HCV core antigen pre-treatment and 12 weeks after the end of treatment to define SVR 12
Table (33):	Characteristics of studied subjects with regard to HCV RNA levels pretreatment and 12 weeks after the end of treatment in male subjects as compared to female subjects
Table (34):	Characteristics of studied subjects with regard to HCV core antigen levels pre-treatment and 12 weeks after the end of treatment in male subjects as compared to female subjects
Table (35):	Correlation between baseline HCV RNA and HCV core antigen levels 129

Table No.	Title	Page
Table (36):	Correlation between HCV HCV core antigen levels after the end of treatment.	12 weeks
Table (37):	Correlation between age RNA level (baseline and post-treatment) as well a HCV core antigen level (ba 12 weeks post-treatment).	12 weeks s age and seline and
Table (38):	Correlation between different and abdominal US paramed DAAs treatment, and base core antigen levels	ters, before seline HCV
Table (39):	Correlation between different parameters and HCV core ar 12 weeks after the end of trea	ntigen levels
Table (40):	Correlation between baselisstage and baseline HCV collevels	re antigen
Table (41):	Correlation between base core antigen levels and levels in studied subjects v to the DAAs regimen emplo	HCV RNA vith regard
Table (42):	Correlation between Hantigen levels and HCV Rantigen levels and HCV Rantigen levels post-treatment, subjects with regard to regimen employed	in studied the DAAs

Table No.	Title	Page	
Table (43):	Diagnostic performance of HCV core		
	antigen in detecting	chronic HCV	
	infection		37