Role of liver fibrosis using APRI, FIB4, and GUCI in prediction of response to therapy in patients with HCV infection

Rawia Abdel Salam Elfiky; Essam Mohamed Bayomi; Azza Emam Mohamed; Ahmed Mohamed Helmy
Department of Internal Medicine and Gastroenterology,
Faculty of Medicine, Ain Shams University

Abstract

Background: Assessment of the stage of liver fibrosis is important for diagnosis, treatment, and follow-up both during treatment and after cessation of treatment. A liver biopsy is considered the gold standard for assessing liver histology but, with many limitations. Recently, many non-invasive markers (NIMs) for assessing liver fibrosis have been developed, and they are frequently used in clinical practice. They have been validated in different studies, and some were found to be highly accurate in the assessment of liver fibrosis compared with liver biopsies **(1).**

Aim of the Work: The aim of this work is to assess role of liver fibrosis using APRI, FIB4, and GUCI -as predictors of liver fibrosis- to assess responders and relapsers to Sofosbuvir-based regimen therapy in Egyptian patients with chronic HCV infection.

Patient and Methods: This study included eighty **80** egyptian patients divided into 2 groups according to response to treatment:

Group 1 (**50** patients) were patients maintaing sustained virological response and ***Group 2*** **(30** patients) were patients who failed the treatment either Non-responder or relapser.

Relapse and non-response are defined on the basis of the virological response to treatment.

Patients were subjected to pre-treatment laboratory workup. Pre-treatment blood samples were collected. After data collection, scores (AST-to-platelet ratio index, FIB4 score, and GUCI) were calculated according to each score equation.

Results: In APRI, there was a statistical significant difference between both groups (p=<0.001*) with a mean difference and standard deviation (1.215±1.011) versus (0.316± 0.181) respectively.In Lok index, there was a statistical significant difference between both groups (p=<0.001*) with a mean difference and standard deviation (0.487±0.272) versus (0.290± 0.162) respectively. In FIB-4, there was a statistical significant difference between both groups (p=<0.001*) with a mean difference and standard deviation (2.686±2.191) versus (1.025± 0.606) respectively. In GUCI, there was a statistical significant difference between both groups (p=<0.001*) with a mean difference and standard deviation (1.400±1.221) versus (0.329± 0.190) respectively.In CDS, there was statistical significant difference between both groups (p=<0.001*) with a mean difference and standard deviation (5.433±1.813) versus (3.780± 1.447) respectively.

Conclusion: This study concluded that there was evidence to recommend using APRI, FIB4, and GUCI -as predictors of liver fibrosis- to assess the virological response to Sofosbuvir-based regimen therapy in Egyptian patients with chronic HCV infection.

Key Words: Non-invasive liver fibrosis biomarkers – APRI - FIB4 - GUCI - liver fibrosis.

Role of liver fibrosis using indirect serological markers in prediction of non-responders and relapsers to sofosbuvir-based treatment in patients with HCV infection

Thesis

In partial fulfillment of Master degree of Internal medicine

Submitted by

Ahmed Mohamed Helmy
M.B.B.Ch

Supervised by

Prof. Rawia Abdel Salam Elfiky
Professor of Internal Medicine and Gastroenterology
Faculty of medicine, Ain Shams University

Prof. Essam Mohamed Bayomi
Professor of Internal Medicine and Gastroenterology
Faculty of medicine, Ain Shams University

Prof. Azza Emam Mohamed
Professor of Internal Medicine and Gastroenterology
Faculty of medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2017

List of Contents

Title	Page

- **List of Abbreviations**..... I
- **List of Tables**..... VI
- **List of Figures**..... VIII
- **Introduction**..... 1
- **Aim of the Work**..... 2
- **Review of Literature** 3
- **Patients and Methods** 95
- **Results** 104
- **Discussion** 119
- **Summary** 141
- **Conclusion** 143
- **Recommendations** 144
- **References**..... 145
- **Arabic Summary**..... --

List of Abbreviations

5HT .....Serotonin

A2M.....α2-macroglobulin

AAR .....AST/ALT ratio

AASLD .....American Association for the Study of Liver Diseases

ACEi .....Angiotensin Converting Enzyme Inhibitor

AEs.....Adverse events

AIH .....Autoimmune hepatitis

AIH .....autoimmune hepatitis

ALD .....Alcoholic liver disease

ALT.....Alanine aminotransferase

ApoE.....Apolipoprotein E

APRI .....AST/platelet ratio

ARB .....Angiotensin Receptor Blocker

AUROCs.....area under receiver operating curve

BM.....Bone Marrow

BMI.....Body Mass Index

CHB.....Chronic hepatitis B

CHC.....Chronic hepatitis C

CI.....confidence interval

CYP.....cytochrome

DAA .....direct-acting antiviral

DCV .....Daclatasvir

DDR2.....discoidin domain receptor

EASL.....European Association for the Study of the Liver

ECM.....Extracellular matrix

List of Abbreviations

ECM.....Extracellular Matrix

ELF.....European Liver Fibrosis Panel

EPO .....Erythropoietin

ERK.....Extracellular Signal-Regulated Kinases

ESRD.....End Stage Renal Disease

ET-1 .....Endothelin

EVR .....Early Virological Response

F3.....Hepatic Fibrosis 3 by Metavir Classification

F4.....Hepatic Fibrosis 3 by Metavir Classification

Factor V .....Factor V (Leiden)

FIB-4 .....Fibrosis-4 index

FT.....Fibro Test

FXR .....Farnesoid X Receptor

GGT .....gamma-Glutamyl-Transferase

GT1a.....Genotype I a

GT1b.....Genotype I b

HA .....Hyaluronic Acid

HAI.....Histological Activity Index

HALT-C.....Hepatitis C Anti-viral Long-term Treatment Against Cirrhosis

Hb.....Haemoglobin

HBV.....Hepatitis B Virus

HCC.....Hepatocellular Carcinoma

HCV.....Hepatitis C Virus

HFE .....Hereditary Hemochromatosis Gene

HFE .....Human Hemochromatosis

List of Abbreviations

HIC .....Hepatic Iron Concentration

HIV .....Human Immunodeficiency Virus

HLA .....Human Leukocyte Antigen

HMG-CoA.....3-Hydroxy-3-Methylglutaryl Coenzyme A

HOMA.....Homeostasis Model Assessment

HSCs.....Hepatic Stellate Cells

IDSA .....Infectious Diseases Society of America

IFN .....Interferon

IL.....Interleukin

ISGs.....Interferon-Stimulated Genes

LB.....Liver Biopsy

MCP-1.....Monocyte Chemotactic Protein Type-1

MCP-2.....Monocyte Chemotactic Protein Type-2

MEH .....Microsomal Epoxide Hydroxylase

MIP-2.....Macrophage Inflammatory Protein–2

MMPs.....Matrix Metalloproteinase Enzymes

NAFLD .....Non-Alcoholic Fatty Liver Disease

NASH.....Non-Alcoholic Steato-Hepatitis

NFSA .....NAFLD Fibrosis Score

NIM.....Non-Invasive Biomarker

NK .....Natural Killer

NNRTIs.....Non-Nucleoside Reverse Transcriptase Inhibitors

NNRTIs.....Nucleoside Reverse Transcriptase Inhibitors

NO .....Nitric Oxide

List of Abbreviations

NPV .....Negative Predictive Value

NS3.....Nonstructural Protein 3

NS5.....Nonstructural Protein 5

NS5A .....Nonstructural Protein 5A

NS5B .....Non-Structural Protein 5B

PAF.....Platelet-Activating Factor

PBC .....Primary Biliary Cirrhosis

PBC .....Primary Biliary Cirrhosis

PBMC.....Peripheral Blood Mononuclear Cells

PCICP .....Procollagen I Amino Terminal Peptide

PCIIINP.....Procollagen III Amino Terminal Peptide

PDGF .....Platelet-Derived Growth Factor

PEG .....Pegylated-Interferon

peg-IFN.....Pegylated-Interferon

P-gp .....P-Glycoprotein

PKR .....Protein Kinase

PPARγ .....Peroxisome Proliferator-Activated Receptor

PT-INR.....Prothrombin Time-International Normalized Ratio

PXR .....Pregnane X Receptor

RAV .....Resistance - Associated Variant

RBV .....Ribavirin

RNA .....Ribo-Nucleic Acid

ROS .....Pro-Inflammatory Cytokines

RVR.....Rapid Virological Response

List of Abbreviations

SAFE .....Sequential Algorithm for Fibrosis Evaluation

SmPC.....Summary of Product Characteristics

SNPs .....Single Nucleotide Polymorphisms

SOCS3 .....Suppressor of Cytokine Signaling 3

SOF .....Sofosbuvir

SVR .....Sustained Virologicl Response

TDF .....Tenofovir Disoproxil Fumarate

TFA.....Total Flavonoids of Astmgali Radix

TGF-α .....Transforming Growth Factor-α

TGF-β1 .....Transforming Growth Factor-β

TGF-β1 .....Transforming Growth Factor-β1

TGF-β1 .....Transforming Growth factor-β1

TIMP.....Tissue Inhibitors of Matrix Metallo-Proteinases

TNF .....Tumor Necrosis Factor

TNF-α .....Tumour Necrosis Factor-α

List of Tables

Table No.	Title	Page
Table (1):	Pharmacokinetic parameters of Sofosbuvir	9
Table (2):	Treatment recommendations for HCV mono-infected or HCV / HIV coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis including treatment -naïve patents and patients who failed on a treatment based on pegylated IFN- and ribavirin (treatment – experienced. DAA-naïve patients) in genotype 4	21
Table (3):	Genetic and non-genetic factors associated with fibrosis progression in Chronic Hepatitis C	38
Table (4):	Main anti-fibrotic drugs in development for the treatment of liver fibrosis	49
Table (5):	Bonacini cirrhosis discriminant score (CDC)	81
Table (6):	Bonacini cirrhosis discriminant score	100
Table (7):	Child score	101
Table (8):	Showing gender, age, smoking, HTN and DM of group (1) and group (2)	105

List of Tables

Table No.	Title	Page
Table (9):	Showing ultra-sonographic findings (coarse liver and splenomegaly) in group (1) and group (2) before the treatment start	107
Table (10):	Showing FBS, HbA1C, WBC, Hb, PLT, AST, ALT, Total bilirubin, Albumin, INR, Creatinine, AFP and PCR in group (1) and group (2) before the treatment start	108
Table (11):	Child score in group (1) and group (2) showing a statistical significant difference	112
Table (12):	Calculated scores	113
Table (13):	Correlation between the 3 major scores p-values and other demographic, clinical and laboratory data of patients using Chi Square test	115
Table (14):	Correlation between the 3 major scores Cut-off value, Sensitivity, Specificity, PPV, NPV and Accuracy using Chi Square test	116

List of Figures

Figure No.	Title	Page
Fig. (1):	Hepatitis C global prevalence 2010 (%)	4
Fig. (2):	Chemical structure of sofosbuvir	8
Fig. (3):	Changes in the hepatic architecture	40
Fig. (4):	Expression of collagen α1(I) in a model of cholestasis-induced liver fibrosis	42
Fig. (5):	Cellular mechanisms of liver fibrosis	45
Fig. (6):	Reversibility of liver fibrosis in a patient with chronic hepatitis B virus infection after successful treatment with lamivudine	48
Fig. (7):	Bar chart represention of ultra-sonographic findings (coarse liver and splenomegaly) in group (1) and group (2) before starting treatment showing a statistical significant difference between both groups	107
Fig. (8):	Representation of child score	112
Fig. (9):	Receiver–operator curve (ROC) curve of GUCI	116
Fig. (10):	Receiver–operator curve (ROC) curve of APRI	117
Fig. (11):	Receiver–operator curve (ROC) curve of FIB-4	117
Fig. (12):	Receiver–operator curve (ROC) curve of the 3 major scores	118

INTRODUCTION

HCV infection is one of the main causes of chronic liver disease worldwide. In Egypt, which has the highest prevalence of chronic HCV, the treatment poses an economic burden on the government ***(El-Zanaty and Way, 2009).***

Assessment of the stage of liver disease is important for diagnosis, treatment, and follow-up both during treatment and after cessation of treatment. A liver biopsy is considered the gold standard for assessing liver histology but, with many limitations ***(Sebastiani and Alberti, 2006).***

Recently, many non-invasive markers (NIMs) for assessing liver fibrosis have been developed, and they are frequently used in clinical practice. They have been validated in different studies, and some were found to be highly accurate in the assessment of liver fibrosis compared with liver biopsies ***(Castera, 2011).***

Ogawa and his colleagues (2015) study showed that non-invasive fibrosis assessments (FibroScan, APRI, FIB-4) are valuable in predicting SVR by prior partial or null responders in telaprevir-based triple therapy.

Aim of the Work

The aim of this work is to assess role of liver fibrosis using APRI, FIB4, and GUCI -as predictors of liver fibrosis- to assess responders and relapsers to Sofosbuvir-based regimen therapy in Egyptian patients with chronic HCV infection.

HCV

HCV infection is globally one of the main blood-borne causes of chronic liver disease that affects almost 3% of the world's population, with morbidity and mortality rates that are second to HIV among the emerging infections. About 160 million people worldwide are known to be chronically infected, although most are unaware of their infection. HCV infection consequences -on the long run- ranges from minimal histological changes to advanced fibrosis with or without HCC HCV infection is a global disease ***(Lavanchy, 2011).***

Egypt has the highest HCV infection prevalence in the world, estimated at 15% among 15- to 59-year-olds. This unparalleled level of prevalence HCV infection appears to reflect an epidemic at national level. It has been supposed that the epidemic has been caused by parenteral anti-schistosomal therapy mass-treatment campaigns making it the biggest example of extensive iatrogenic transmission. 70–90% of Egyptian patients with chronic hepatitis, cirrhosis, or HCC have HCV infections ***(El-Zanaty and Way, 2009).***