Impact of SVR to direct antivirals on liver stiffness in patients with chronic hepatitis C using Mac2 binding protein and PAPAS index compared to Fibro Scan

Thesis

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Marwan Mohammed Alhusseini Mohammed

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List of Abbreviations

Abbr.	Full-term
2D-SWE	**:** Real-time 2D shear wave elastography
AAR	**:** Aspartate aminotransferase and alanine aminotransferase ratio (AAR)
ACE	**:** Angiotensin-converting enzyme
ACEI	**:** Angiotensin converting enzyme inhibitors
ADC	**:** Apparent diffusion coefficient
AFP	**:** Alpha-feto protein
AGP	**:** α1-acid glycoprotein
AIDS	**:** Acquired immune deficiency syndrome
AIH	**:** Autoimmune hepatitis
ALD	**:** Alcoholic liver disease
ALT	**:** Alanine aminotransferase
APRI	**:** Aspartate aminotransferase-to-platelet ratio index
ARBs	**:** Angiotensin receptor blockers
ARFI	**:** Acoustic radiation force impulse
ASK1	**:** Apoptosis signal-regulating kinase 1
AST	**:** Aspartate aminotransferase
AUC	**:** Area under curve
AUROC	**:** Area under the receiving operating characteristics
BMI	**:** Body mass index
CB antagonist:	Cannabinoid antagonists
CDCA	**:** Chenodeoxycholic acid

CHC : Chronic hepatitis C infection

COI : Cut off index

CT : Computed tomography

CTGF : Connective tissue growth factor

CTL : Cytotoxic T lymphocytes

CVC : Cenicriviroc

DAAs : Direct acting antiviral agents

DAC : Dacltasvir

DAMPs : Damage-associated molecular patterns

DCE : Dynamic contrast enhanced

DCs : Dendritic cells

DTR : Diphtheria toxin receptor

DWI : Diffusion weighted imaging

EASL : European Association for the Study of the Liver

ECM : Extracellular matrix

EGF : Epidermal growth factor

EGFR : Epidermal growth factor receptor

ELF : European Liver Fibrosis

EMT : Epithelial-to-mesenchymal transition

EndoMT : Endothelial-to-mesenchymal transition

EOT : End of treatment

F/U : Follow-up

FIB-4 : Fibrosis-4 score

FXR : Farnesoid X receptor

GGT : γ glutamyl transferase

GR-MD-02 : Galactoarabino-rhamnogalaturonan

GT1 : Genotype 1

HA : Hyaluronic acid

HBV : Hepatitis B virus

HCC : Hepatocellular carcinoma

HCV : Hepatitis C virus

HIV : Human immunodeficiency virus

HO-1 : Heme oxygenase 1

HSCs : Hepatic stellate cells

HSP47 : Heat shock protein 47

HVPG : Hepatic venous pressure gradient

IQR : Inter quartile range

kPa : Kilopascals

KTA-HCM : Knowledge and technology association for hepatitis C management

LIF : Liver inflammation and fibrosis

LS : Liver stiffness

LSMs : Liver stiffness measurements

M2BPGi : Mac-2 Binding Protein Glycosylation isomer

MAPK : Mitogen-activated protein kinase

MBT : Methacetin breath test

MFAP-4 : Microfibril-associated glycoprotein 4

MFBs : Myofibroblasts

MMP : Matrix metalloproteinase

MMP-2 : Metalloproteinase 2

MMT : Mesothelial-to-mesenchymal transition

MRE : Magnetic resonance elastography

MRI : Magnetic resonance imaging

MRS : Magnetic resonance spectroscopy

NAC : N-acetylcysteine

NADPH : Nicotinamide adenine dinucleotide phosphate

NAFLD : Non-alcoholic fatty liver disease

NASH : Nonalcoholic steatohepatitis

OELF : Original European Liver Fibrosis

PAMPs : Pathogen-associated molecular patterns

PAPAS INDEX : (Platelet/Age/Phosphatase/AFP/AST) index

PBC : Primary biliary cirrhosis**.**

PDGF : Platelet-derived growth factor

PICP : Procollagen type I carboxy terminal peptide

PIIINP : Procollagen type III amino-terminal peptide

PON-1 : Paraoxonase 1

PPAR-γ : Peroxisome proliferator-activated receptor γ

PSC : Primary sclerosing cholangitis

pSWE : Point shear wave elastography

RANTS : Regulated upon activation normal T cell expressed and presumably secreted

RBV : Ribavirin

ROS : Reactive oxygen species

RTC : Randomized control trial

RTE : Real-Time Elastography

siRNA : Small interfering RNA

SOF : Sofosbuvir

SVR : Sustained virologic response

TE : Transient elastography

TGFβ1 : Transforming growth factor β1

TGR5 : G-protein-coupled membrane receptor 5

TIMPs : Tissue inhibitors of matrix metalloproteinases

TLR2 : Toll-like receptor 2

TNF : Tumor necrosis factor

UDCA : Ursodeoxycholic acid

ULN : Upper limit of normal

VEGF : Vascular endothelial growth factor

VTTQ : Virtual Touch™ Tissue Quantification

WFA+M2BP : Wisteria floribunda agglutinin-positive human Mac-2-binding protein

WHO : World Health Organization

α-SMA : α-smooth muscle actin

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ABSTRACT

Background: New direct-acting antivirals (DAA) has dramatically increased the cure rate in patients with chronic hepatitis C and result in improvement in liver stiffness measured by transient elastography (TE) in patients with sustained virologic response (SVR). Multiple non-invasive methods have been used successfully in the assessment of liver fibrosis. Mac-2 Binding Protein Glycosylation isomer (M2BPGi) is a novel serological glyco-biomarker for staging liver fibrosis. **Aim of the work:** We aimed to evaluate the impact of sustained virologic response (SVR) to direct antivirals on liver stiffness using the serum level of Mac-2 binding protein in patients with compensated chronic HCV who received direct acting antivirals (DAAs) according to National Committee for Combating Viral Hepatitis before (baseline) and after (sustained virologic response week 12) treatment, and to assess how this biomarker was correlated with another standard non-invasive methods of fibrosis assessment, FIB-4, PAPAS index and Fibro scan. **Patients and Methods:** Our cohort study consisted of 80 Egyptian patients with compensated chronic HCV who received direct acting antivirals (DAAs) (65 patients received sofosbuvir/ daclatasvir and 15 patients received sofosbuvir/ daclatasvir/ ribavirin) according to National Committee for Combating Viral Hepatitis. All patients were subjected to clinical evaluation, laboratory investigations, abdominal ultrasonography, transient elastography (Fibroscan) in addition to non-invasive indices (Mac-2bp, PAPAS index, and FIB-4). Fibroscan, Mac-2bp, FIB-4 and PAPAS index were measured in all patients at base line before treatment and 12 weeks after end of treatment (EOT) and achievement of SVR. **Results:** The current study showed that the mean value of LSM, FIB-4, PAPAS index and Mac-2bp at baseline were 11.4±9.5, 1.8±1.3, 2.2±0.5, and 9.0±8.8 and after achieving SVR 9.5±6.3, 1.3±0.7, 2.1±0.3 and 6.7±7.3 respectively with significant improvement in all parameters (P=0.002, <0.001, 0.010 and <0.001 respectivily). ALT, AST and ALP significantly decreased after achieving SVR 12 while Albumin and Platelets significantly increased after achieving SVR 12. Mac-2 bp levels increased with the progression of liver fibrosis. The areas under the curve (AUROC) of Mac-2bp at baseline in F≥2, F≥3 and F4 were 0.710, 0.569, and 0.801 respectively and after achieving SVR were 0.583, 0.893, and 0.844 respectively. (AUROC) of Mac-2bp for differentiating advanced fibrosis (F3-4) from non-advanced fibrosis (F0-2) at baseline and after achieving SVR were 0.730 and 0.891 respectively. Mac-2bp after achieving SVR12 had more favorable diagnostic accuracy for distinguishing advanced liver fibrosis (F3-4) from non-advanced fibrosis (F0–2) with an AUC 0.891.

Conclusion: Mac-2 binding protein (Mac-2bp) is a simple and reliable noninvasive marker for liver fibrosis assessment in patients with chronic hepatitis C. Liver stiffness measurements (LSM) evaluated using transient elastography (TE) significantly decreased overall in patients with chronic HCV infection who received direct-acting antivirals (DAAs) therapy and achieved sustained virologic response 12 weeks after end of treatment (SVR12).

Keywords: SVR, Mac-2bp, DAAs, LSM