

**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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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	: α 1-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	: Daclatasvir
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
SOB	: Sofosbuvir
SVR	: Sustained virologic response
TE	: Transient elastography
TGFβ1	: Transforming growth factor β 1
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
VTQ	: 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 respectively). 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 $F \geq 2$, $F \geq 3$ 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