Liver and Spleen Stiffness Measurements Based on Acoustic Radiation Force Impulse Elastography for Noninvasive Assessment of Esophageal Varices in HCV-Related Advanced Fibrosis.

Thesis submitted in partial fulfillment for
MSc degree in Infectious Disease and Endemic Hepatic and Gastrointestinal Diseases

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ABSTRACT

BACKGROUND: Upper gastrointestinal endoscopy (UGIE) screening for esophageal varices (EV) is expensive for the health system and invasive for the patients.

Aim: To identify the reliability of liver stiffness (LS) and spleen stiffness (SS) as noninvasive predictors of EV, and to compare them with other noninvasive parameters.

METHODS: Two hundred patients with HCV-related advanced fibrosis including liver cirrhosis were subjected to: Demographic, clinical, laboratory tests, abdominal ultrasound and Doppler, FIB-4 score, LOK index, platelets to spleen diameter ratio (PSR), LS measured by FibroScan®, LS and SS measured by acoustic radiation force impulse (ARFI) and finally UGIE.

RESULTS: Of the 200 patients (Mean age 54.9±8 years; Male 55.5%; CTP class A 72%; Fibrosis stage[F3] 4.5%), 90 patients had EV. For prediction of EV, spleen longitudinal diameter (SD) and splenic vein diameter (SVD) were the best parameters among all the ultrasonographic parameters. PSR, LOK index and FIB-4 score showed good diagnostic performance. Also, SS and LS showed good diagnostic performance, However, SS had diagnostic performance better than LS (AUROC: 0.760 and 0.70, 95% CI 0.69-0.83 and 0.63-0.77, respectively). The AUROC increased when LS and/or SS was combined with SD, SVD, PSR or FIB-4 score in a simple prediction model. The prediction model (SD×SVD×SS) showed the best diagnostic performance (AUROC: 0.85, 95% CI: 0.79-0.90). Followed by prediction model (LS×SS/PSR) (AUROC: 0.83, 95% CI: 0.77-0.88).

CONCLUSION: LS and SS are reliable predictive tools to presence of EV. Combination of LS and/ or SS with other parameters showed better diagnostic performance than LS or SS alone. These results could be used to reduce the need for routine upper gastrointestinal endoscopy screening.

Keywords: Noninvasive, ARFI, Liver Stiffness, Spleen Stiffness, Varices.

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ABBREVIATIONS

ADH	Antidiuretic Hormone
ALT	Alanine Transaminase
ARFI	Acoustic Radiation Force Impulse
AST	Aspartate Transaminase
ATII	Angiotensin II
AUROC	Area Under ROC Curve
bFGF	Basic Fibroblast Growth Factor
CCL21	Chemokine (C-C motif) Ligand 21
CCR5	Chemokine (C-C motif) Receptor 5
CDT	Carbohydrate Deficient Transferrin
CIx	Congestion Index
CO	Carbon monoxide
CPSS	Congenital Portosystemic Shunts
CT	Computed Tomography
CTGF	Connective Tissue Growth Factor
Cu	Copper
CVC	Cranial Vena Cava
CVP	Central venous pressure
ECM	Extracellular Matrix
EDHS	The Egyptian Demographic Health Survey
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
EGD	Esophagogastroduodenoscopy
EGF	Epidermal Growth Factor
ET	Endothelin
EV	Esophageal Varices
EVRS	Esophageal Varices Risk Score
FHVP	Free Hepatic Venous Pressure
FT	FibroTest
GI	Gastrointestinal
GOV	Gastroesophageal Varices
HBV/HCV	Hepatitis B/C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus

HSC	Hepatic Stellate Cells
HVPG	Hepatic Venous Pressure Gradient
kPa	Kilopascal
ICAM-1	Intercellular Adhesion Molecule-1
IGV	Isolated Gastric Varices
IHVR	Intrahepatic Venous Resistance
IQR	Interquartile Range
IVC	Inferior Vena Cava
LEV	Large Esophageal Varices
LS, LSM	Liver Stiffness, Liver Stiffness Measurement
M	Median
MAPSS	Multiple Acquired Portosystemic Shunts
MCP-1	Monocyte Chemoattractant Protein-1
MMPs	Matrix Metalloproteinases
m/s	Meter per second
MT1-MMP	Membrane-Type Matrix Metalloproteinase 1
MRE	Magnetic Resonance Elastography
mRNA	Messenger Ribonucleic Acid
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NE	Norepinephrine
NCPH	Noncirrhotic Portal Hypertension
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
NPV	Negative Predictive Value
pANCA	Perinuclear Neutrophil Cytoplasmic Antigen
PBF	Portal Blood Flow
PC	Prothrombin Concentration
PDGF	Platelet-Derived Growth Factor
PHG	Portal Hypertensive Gastropathy
PHT	Portal Hypertension
PPV	Positive Predictive Value
PSR	Platelet Count toSpleen Diameter Ratio
pSWE	Point Shear-Wave Elastography

PV	Portal Vein
PVD	Portal Vein Diameter
PVFV	Portal Vein Flow Volume
PVP	Portal Vein Pressure
PVR	Peripheral Vascular Resistance
PVV	Portal Vein Velocity
RAAS	Renin-Angiotensin-Aldosterone-Sympathetic System
RANTES	Regulated on Activation, Normal T Cell Expressed and Secreted
RLD	Right Lobe Diameter
RLD/Alb	Right Lobe Diameter to Albumin Ratio
ROI	Region Of Interest
ROS	Reactive Oxygen Species
SD	Splenic Longitudinal Diameter
Se	Sensitivity
SEC	Sinusoidal Endothelial Cell
SLA	Soluble Liver Antigen
SOS	Sinusoidal obstruction syndrome
Sp	Specificity
SPARC	Secreted protein acidic and rich in cystein
SS	Spleen Stiffness
SSI	Supersonic shear imaging
SV	Splenic Vein
SVD	Splenic Vein Diameter
SVFV	Splenic Vein Flow Volume
SVV	Splenic Vein Velocity
TE	Transient Elastography
TGF	Tissue Growth Factor
TIMPs	Tissue Inhibitors of Metalloproteinases
TIPS	Transjugular Intrahepatic Portosystemic Shunt
TNFa	Tumor Necrosis Factor alpha
US	Ultrasound
VEGF	Vascular Endothelial Growth Factor
VTTQ	Virtual Touch Tissue Quantification
WBC	White Blood Cell
WFUMB	World Federation for Ultrasound in Medicine and Biology

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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Chronic hepatitis C virus (HCV) infection represents a worldwide health concern, with 130–170 million chronically infected subjects, whose risk of developing cirrhosis within 20 years is estimated to be around 10% to 20% ***(Lavanchy, 2009; Shepard et al., 2005).***

The Egyptian Demographic Health Survey (EDHS), a cross sectional survey including hepatitis C virus (HCV) biomarkers, was conducted in 2008 on a large nationally representative sample, It estimated HCV prevalence among the 15–59 years age group to be 14.7% ***(El-Zanaty and Way, 2009)***. Accordingly, Egypt has the highest HCV prevalence in the world ***(Lavanchy, 2011).***

Today, HCV infection and its complications are among the leading public health challenges in Egypt ***(Miller and Abu-Raddad, 2010)***.

Portal hypertension (PH) is associated with the most severe complications of cirrhosis, such as ascites, hepatic encephalopathy, and bleeding from esophageal varices (EV). Gastroesophageal varices are present in approximately 50% of patients with liver cirrhosis ***(Sanyal et al., 2006).*** The most accurate method to evaluate PH is the measurement of the hepatic vein pressure gradient (HVPG). It has been demonstrated that a HVPG value higher than 10 mmHg predicts the presence of EV, while a value higher than 12 mmHg is predictive for variceal bleeding and a high HVPG > 20 mm Hg is associated with continued bleeding and medical therapy failure in acute variceal hemorrhage. However, the evaluation of HVPG is an invasive procedure, which is limited to highly specialized centers and experienced operators ***(Bosch et al., 2006; Moitinho et al., 1999)***.