Evaluation of Spleen Stiffness Compared to Splenic Artery Resistive Index as Non Invasive Predictors for Esophageal Varices in Patients with Chronic Liver Disease

Thesis

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Mohamed Kamal Ismael Dewidar

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List of Abbreviations

Abb.	Full term

Ab ..... Antibody
AFP ..... Alpha Fetoprotein
ALD ..... Acute liver disease
ALP ..... Alkaline Phosphatase
ALT ..... Alanine Aminotransferase
AMA ..... Antimitochondrial antibodies
ANOVA ..... Analysis of Variance
AP ..... Arterial Portography
APRI ..... AST to Platelet Ratio Index
ASGE..... American Society of Gastroenterology
ASH ..... Alcoholic staeato Hepatitis
AST..... Aspartate Aminotranserase
AVP ..... Arginine vasopressin
BL..... Bleeding
BSG ..... British Society of Gastroenterology
BUN..... Blood Urea Nitrogen
CDUS ..... Color Doppler Ultrasonography
CI..... Congestion Index
CR..... Serum Creatinine
CRS ..... Cherry red spots
CSPH ..... Clinically Significant Portal Hypertension
CT..... Computed Tomography
CTA ..... Computed Tomography Angiography
D.BIL ..... Direct Bilirubin
DAAs ..... Direct-acting antivirals
DDU ..... Duplex Doppler ultrasound
DH ..... Dilutional Hyponatremia
DPAS..... Periodic acid-Schiff stain after diastase digestion
DR ..... Diffuse Redness
ECM ..... Extracellular Matrix
EEG..... Electro-encephalogram
EGD..... Esophagogastroduodenoscopy

List of Abbreviations (Cont...)

Abb.	Full term
EV	Esophageal Varices
EVBL	Esophageal Varices Band Ligation
EVL	Esophageal Varices Ligation
FDA	Food and Drug Administration
FT	Fibrotest
GABA	Gamma Amino Butyric Acid
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GOT	Glutamic oxaloacetic transaminase
HAART	Highly active antiretroviral therapy
HAPI	hepatic artery pulsatility index
HARI	hepatic artery resistive index
HBF	Hepatic blood flow
HBV	Hepatitis B Virus
HCC	hepatocellular carcinoma
HCV	Hepatitis C Virus
HE	Hepatic Encephalopathy
HGB	Hemoglobin
HIV	Human Immune deficiency Virus
HRS	Hepatorenal Syndrome
HSC	Hematocystic spots
HSCs	Hepatic Stellate Cells
HVPG	Hepatic Venous Pressure Gradient
INR	International Normalization Ratio
IVC	Inferior Venacava
K	Serum Potassium
KPa	kilopascals
LS	Liver stiffness
LSM	Liver stiffness measurement
LSPS	Spleen diameter to platelet ratio score
LT	Liver transplantation
MELD	Model of End Stage Liver Disease
MRI	Magnetic Resonance Imaging

List of Abbreviations (Cont...)

Abb.	Full term
Na	Serum Sodium
NAFLD	Non alcoholic Fatty Liver Disease
NASH	Non Alcoholic Steatohepatitis
NH3	Ammonia
NH4+	Ammonium
NO	Nitrous Oxide
NPV	Negative Predictive Value,
O.V	Oesophageal varices
PAS	periodic acid-Schiff stain
PBC	Primary biliary cirrhosis
PDGF	Platelet Derived Growth Factor
PGE 1	Prostaglandin E1
PH	Portal Hypertension
PHG	Portal Hypertensive Gastropathy
PHT	Portal hypertension
PPV	Positive Predictive Value
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PV	Portal vein
PVT	Portal Venous Thrombosis
PVV	portal vein velocity
QoL	quality of life
RBS	Random Blood Sugar
ROC	Reproducer Operating Characteristic Curve
RPF	Renal plasma flow
RWM	Red wall markings
S.Albumin.	Serum Albumin
SAPI	Splenic arterial pulsatility index
SARI	SplenicArtery Resistive Index
SBP	Spontaneous Bacterial Peritonitis
SBPD	Splenic Bipolar Diameter
SI	Splenic index

List of Abbreviations (Cont...)

Abb.	Full term
SIADH	Syndrome of inappropriate antidiuretic hormone
SP	Splenoportography
SPI	Splenoportal index
SRCR	Scavenger receptor cysteine- rich super
SS	Spleen Stiffness
SSM	Spleen Stiffness Measurement
SVR	Sustained virologic response
T.BIL.	Total Bilirubin
T.P.	Total protein
TE	Transient Elastography
TIPS	Transjugular intrahepatic portosystemic shunt
US	Ultrasound
V	Varices
VOD	Veno-occlusive Disease
WBC	White Blood Cells Count
WHVP	Wedge Hepatic Venous Pressure

INTRODUCTION

Liver cirrhosis (LC) is the final evolutive stage of any chronic liver disease and its outcomes are modulated by the degree and the consequences of portal hypertension (PH).Unfortunately, clinical investigation of PH is mainly invasive and implies either hepatic vein catheterization and hepatic vein pressure gradient (HVPG) measurement, or endoscopy for esophageal varices (EV) screening and grading. It was previously 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. Many efforts have been made to find a noninvasive surrogate marker for PH or for the presence or grade of EV, but until now, only a few biochemical markers (aspartate aminotransferase [AST] to platelets ratio index) or mixed indexes (platelets count tospleen diameter ratio) have been demonstrated to be partially correlated with the presence of EV ***(Stefanescu et al. 2011)***.

Portal hypertension (PHT) and development of esophageal varices (EV) are one of the major complications of liver cirrhosis. Bleeding from EV is a life-threatening event with 10 – 20 % mortality with each episode. Current guidelines recommend that all cirrhotic patients should undergo screening endoscopy at diagnosis to identify patients with varices ***(De Franchis, 2010)***. This approach increases burden upon endoscopy units, and the repeated testing over time may

decrease patient compliance. Upper gastrointestinal endoscopy (UGIE) is deemed to be the gold standard against which all other tests are compared, but is not without its limitations ***(Rye et al., 2012).***

Splenomegaly is a common finding in patients with cirrhosis and noncirrhotic PHT, and is commonly described because of blood congestion, increased portal pressure, augmented resistance to splenic vein outflow, and increased angiogenesis and fibrogenesis, These changes of spleen stiffness (SS) can be quantified by transient elasto graphy (TE) ***(Sharma et al., 2013).***

Portal hypertension is one of the complications of chronic liver diseases (CLD). Esophageal varices (EV) are the most relevant portosystemic collaterals resulting from clinically significant portal hypertension, and the presence of EV correlates with the severity of liver disease. As variceal hemorrhage is the most lethal complication of liver cirrhosis, patients with newly diagnosed cirrhosis in CLD are advised to undergo endoscopic screening for EV. However, endoscopy is an invasive and unpleasant procedure that sometimes requires sedation and carries rare, but serious, complications. Accordingly, several simple, non-invasive and accurate tests have been developed to identify EV. Transient elastography (TE) is a noninvasive tool that measures liver stiffness (LS) correlating to liver fibrosis stage. While TE also shows potential in the prediction of EV, its role is still under debate.

Moreover, the LS-spleen size-to-platelet ratio score (LSPS), which is a combination of three simple examination methods (LS, spleen size and platelet count) has been established to accurately predict EV in patients with compensated cirrhosis. To date, TE and LSPS have not been performed for the estimation of EV in chronic hepatitis C in Japan. The objective of this study was to determine the ability of LSPS in predicting the presence of EV ***(Shibata et al., 2016).***

Several serum and radiological parameters have been put forward for predicting EV, such as serum fibrosis markers, liver stiffness (LS), spleen stiffness (SS), LS-spleen diameter to platelet ratio score. Among them, it has been shown that both liver and spleen stiffness were more accurate in identifying EV and the degree of portal hypertension than other non-invasive parameters. LS has been largely accepted to reflect the degree of fibrosis and the presence of EV in CLD. Several studies have revealed that LS measured by elastography may represent a useful non-invasive tool for predicting EV, notably in combination with other non-invasive parameters. Current European Guidelines recommend to avoid screening EGD in patients with LS< 20kPa and platelet count >150, 000. While the role of LS alone in predicting varices is controversial due to unsatisfactory diagnostic accuracy and lack of consistent results, In the last few years, research emphasis has been placed on SS measurement in predicting EV and clinical significant portal hypertension. Portal hypertension leads to spleen

congestion and fibrosis, which is sufficient to increase organ stiffness ***(Xiaowen et al., 2016).***

Fibroscan (Transient Elastography- TE) is a type of ultrasound machine that designed for painless, immediate and non invasive liver stiffness measurements ***(Linda, 2008).***

In the evolution of chronic viral and non viral hepatitis, liver fibrosis is an important factor associated with prognosis. A precise evaluation of the severity of fibrosis is necessary in these patients for correct staging and, eventually, to take a decision regarding treatment ***(Christoph, 2012).***

Due to the limitations of liver biopsy, non invasive alternatives including FibroScan (Transient Elastography) have been developed. Transient elastography is an easy and quick clinical non invasive method to perform and it could be useful to evaluate liver fibrosis as to monitor liver disease progression ***(Yasser, 2009)***

Recently, more and more studies have attempted to clarify the utility of SS and LS for EV diagnosis in patients with CLD, but the results have been controversial. Research has shown that SS assessed by elastography was a more effective parameter with high diagnostic accuracy for identifying and grading EV than LS ***(Fraquelli et al., 2014).***

Splenomegaly is a possible consequence of portal hypertension. Contrary to other ultrasound (US) signs,