Non Invasive Tools in Assessment Of Liver Fibrosis in Patients with Chronic Hepatitis B

Thesis

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List of Contents

List of Abbreviations

A	Necroinflammatory activity
AAR	ALT/AST ratio
AASLD	American Association for the Study of Liver Diseases
AFP	α-Foetoprotein
AIH	Autoimmune hepatitis
ALT	Alanine Aminotransferese
ANA	Antinuclear antibody
API	age/platelet index
APRI	AST to Platelet Ratio Index
ARFI	acoustic radiation force impulse imaging
ASH	Alcoholic steatohepatitis
AST	Aspartate Aminotransferese
BMI	Body Mass Index
CBC	Complete Blood Count
cccDNA	Closed circular DNA
CHB	chronic hepatitis B
CHC	Chronic Hepatitis C
CLD	chronic liver disease
CRS	the cirrhosis risk score
EASL	European Association of Study of Liver
ECM	Extracellular Matrix
F	Fibrosis
FRT	Fibrosis routine test
GUCI	Göteborg University Cirrhosis Index
HA	Hyaluronic acid
HAI	Histological activity index
HbcAg	Hepatitis B core Antigen
HBeAg	Hepatitis B e Antigen
HBIG	hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HCC	Hepato cellular carcinoma
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HDV	Hepatitis D virus
HIV	Human immunodeficiency virus
HVPG	hepatic-vein portal gradient
HS	Highly significant
IgG	Immunoglobulin G
IgM	immunoglobulin M
INR	International normalized ratio
IQR	Interquartile range
kPa	Kilopascals
MMP	matrix metalloproteinases
MR elastography	Magnetic resonance elastography
NAFLD	Nonalcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey
NS	Non-significant
ORFs	open reading frames
PBC	primary biliary cirrhosis
PCR	Polymerase Chain Reaction
PDGF	Platelet deriving growth factor
PICP	Procollagen type I carboxy-terminal peptide
PIIINP	Procollagen type III amino-terminal peptide
PIIINP or P3NP	Procollagen type III amino-terminal peptide
PT	Prothrombin Time
S	Significant
S.Cr	Serum Creatinine
SNP	single nucleotide polymorphisms
TE	Transient Elastography
TGF 1	transforming growth factor 1
TGFα	Transforming growth factor alpha

TGFβ	Transforming growth factor beta
The ELF group	The European Liver Fibrosis Group assay group
TIMP-1	Metalloproteinase 1
TIMPs	tissue inhibitors of metalloproteinases
TLR4	Toll-like receptor 4
TLR9	Toll-like receptor 9
VCTE	Vibration-Controlled Transient Elastography
VEGF	Vascular Endothelial Growth Factor

List of tables

(1) Tables in the review

(2) Tables in the results

List of figures

(1) Figures in the review:

(2) Figures in the results:

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Introduction

Chronic viral hepatitis B is a global public health problem leading to liver fibrosis and ultimately to cirrhosis, decompensated liver disease, and hepatocellular carcinoma ***(Stibbe et al., 2011).***

Approximately one third of the world's population has serological evidence of past or present infection with HBV and 350 million people are chronically infected. HBV- related end stage liver disease or HCC are responsible for over 1 million deaths per year and currently represent 5–10% of cases of liver transplantation ***(Patrick et al., 2009).***

An accurate assessment of liver fibrosis in patients with CHB is mandatory not only in predicting the long-term clinical course but also in determining whether and when to begin antiviral therapy. This is because maintenance of viral suppression can reduce liver-related complications in patients with significant fibrosis to cirrhosis ***(Lok and McMahon, 2007).***

Individuals with non-significant fibrosis are not likely to develop advanced fibrosis in the short term, even in the light of long-standing disease, and are typically monitored every 3–5 years. Individuals with significant fibrosis are at increased risk of developing cirrhosis and are usually treated ***(Manning and Afdhal, 2008)***.

Liver biopsy is still considered the gold standard for assessing liver fibrosis. This procedure is very useful because it provides information about the degree of liver fibrosis, as well as the severity and extent of inflammation. However, it is invasive and can lead to grave complications. Furthermore, its accuracy in

assessing fibrosis is questionable because of sampling errors and intra- and inter-observer discrepancies (***Lee et al., 2010).***

As liver biopsy is an invasive procedure, alternative, simple and non-invasive tests have been developed to reliably assess the stages of liver fibrosis ***(Skripenova et al., 2007).***

Ideally, non-invasive alternatives should be simple, cheap, easy to perform, safe, precise, reproducible and validated externally, and capable of differentiating patients in need of therapy ***(Omran et al., 2011).***

Non-invasive markers can be broadly divided into two major groups: radiological and serum-based markers ***(Rajasekhara et al., 2010).***

Fibroscan is a new, noninvasive approach to evaluate liver fibrosis by measuring liver stiffness. The FibroScan uses an ultrasound-based technique known as transient elastography (TE) to measure the speed of propagation of the shear wave through the liver. The wave is produced by a vibrator which is combined with an ultrasonic transducer probe. Each vibration pulse provides a liver stiffness measurement (LSM) measured in kilo Pascals (kPa) which is used to quantify the stiffness of the liver. The velocity of these waves is directly correlated with liver stiffness. The intra- and inter-observation coefficients of variation are 3.2% and 3.3%, respectively, indicating very good reproducibility. Recently, the measurement of liver stiffness by TE has been shown to be an accurate predictor of histological fibrosis in patients with various etiologies of liver disease ***(Marcellin et al., 2009).***