Value of PAPAS index as a marker in diagnosis of liver fibrosis in patients with chronic hepatitis C in comparison to FIB-4&FibroQ

Thesis

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Listof Abbreviations

Abbr.	*Full term*

AAR : Aspartate aminotransferase\ Alanine transaminase Ratio
AASLD :American association for thestudy of liver diseases
AFP : Alpha feto protein
AIDS :Acquired immune deficiency syndrome
ALD : Alcoholic liver disease
ALP : Alkaline phosphatase
ALT : Alanine transaminase
ANA : Anti-nuclear antibody
APGA : AST/platelet/gammaglutamyl transpeptidase (GGT)/a- fetoprotein
APRI : Aspartate aminotransferase\Platelet Ratio
ARFI : Acoustic radiation force impulse
AST : Aspartate aminotransferase
AUC : Area under the curve
BMI : Body mass index
CDS : Cirrhosis discriminate score
CHB : Chronic hepatitis B
CT : Computed tomography
CTGF : Connective tissue growth factor
ECM :Extracellular matrix
EGF : Epidermal growth factor
ELF : European Liver Fibrosis panel
ELISA : Enzyme-linked immunosorbent assay
GGT : Gamma glutamyl transferase
HBeAg : Hepatitis B envelope antigen
HCC : Hepatocellular carcinoma
HCV : Hepatitis C virus
HIV : Human immunodeficiency virus
HO-1 : Heme oxygenase 1

HSC : Hepatic stellate cell
HVPG : Hepatic venous pressure gradient
IGG : Immunoglobulin G
INR : International normalization ratio
KPa : Kilopascal
LR : Likelihood ratio
MMPs : Metalloproteinases
MRE : Magnetic Resonance Elastography
MRI : Magnetic resonance imaging
NADPH : Nicotinamide adenine dinucleotide phosphate H
NAFLD : Non-alcoholicfatty liver disease
NPV : Negative predictive value
PAPAS : 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
PPV : Positive predictive value
PSC : Primary sclerosing cholangitis
RF : Radio frequency
ROC : Receiving operator characteristics
TE : Transientelastography
TGF β1 : transforming growth factor β1
TIMPs : Tissue inhibitors of matrix metalloproteinases
TLC : Total leucocytic count
TLR : Toll-like receptor
ULN : Upper limit of normal
VCTE : Vibration controlled transient elastography
VEGF : vascular endothelial growth factor

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Introduction

Chronic hepatitis C has a significant prevalence worldwide reaching alarming levels at some regions such as Egypt where the prevalence is estimated at 15–20% ***(El-Zanatyet al.,2009)***. One of the mainstays of management of HCV is the detection of the stage of liver fibrosis.***Mitchellet al.,*** reported that the treatment of chronic hepatitis C should be initiated in patients with significant fibrosis (F≥2) ***(Mitchellet al.,2010)***. To date, the gold standard remains the liver biopsy, but is far from optimal. Although generally considered safe, complications such as bleeding and prolonged pain are reported***(Regevet al.,2002; (Seeffet al.,2010).***

Nearly 30% of patients report having substantial pain after liver biopsy, and some experience serious complications such as pneumothorax, bleeding, or puncture of the biliary tree ***(Rockeyet al.,2009).*** Another major issue with liver biopsy is that many patients are very anxious about the idea of having a liver biopsy ***(Regevet al.,2002)(Seeffet al.,2010),*** sampling error as only 1/50000th of the organ is sampled, intra- andinterobserver variability, and patient reluctance to undergo serial monitoring ***(Bedossaet al.,2003)***. Lastly, the cost of a liver biopsy is a major drawback especially in resource-limited areas.

Over the last 2 decades, there has been a relentless quest to develop an alternative that is less invasive, less costly and as accurate as a liver biopsy. A combination of advanced serum markers such as ‘Fibrotest’ and ‘Fibrometer’ have shown promising results as well as transient elastography. These tests, however, did not solve the problem of the cost as they all remain significantly expensive and unavailable in many developing countries***(Imbert-Bismutet al.,2001) (Caleset al.,2005),*** alsoTE cannot be used in individuals with ascites ***(Stasiet al.,2009) (Beaugrandet al.,2006),***expensive, liver stiffness values for TE may be 1.3–3 times higher in the setting of acute inflammation and/or moderate alanine aminotransferase (ALT) elevation ***(Tapperet al.,2012).***

Hence, several noninvasive tests have been proposed to assess the severity of hepatic fibrosisas an alternative to liver biopsy. As reported by***(Akkayaet al.,2007)***, alanine aminotransferase (ALT) levels in patients with hepatitis C virus (HCV) infection correlate with periportal bridging/necrosis, and***Luet al.(2006)***have reported that thrombocytopenia is a surrogate for cirrhosis.

One of these non-invasive tests isFibroQ, which is calculated from common laboratory test resultsthat include prothrombin time international normalized ratio(PT

INR),platelet count, AST, ALTand age**,** as(10 × age × AST × PT INR)/ (ALT × platelet count)isa novel noninvasive test, useful and easy tool to evaluate liver fibrosis in patients with chronic viral hepatitisand has better accuracy thanAPRI and is equal to AAR***(Hsiehet al.,2009)***.

Also, The FIB-4 index is another prediction value of liver fibrosis in chronic hepatitis C based on the standard biochemical values and age. The FIB-4 index has been reported to be markedly useful for the prediction of advanced liver fibrosis ***(Sterlinget al.,2006) (Vallet-Pichardet al.,2007).***

PAPAS (Platelet/Age/Phosphatase/AFP/AST) index is a new non-invasive test that canpredicts significant fibrosis in chronic hepatitis B**,** The negative predictive value to exclude significant fibrosis was 88.4%. This predictive power is superior to other non-invasive models using common parameters, including the AST/platelet/GGT/AFP (APGA) index, AST/platelet ratio index (APRI), and the FIB-4 index (AUROC of 0.757, 0.708 and 0.723 respectively). Using the PAPAS index, 67.5% of liver biopsies for patients being considered for treatment with ALT<2×ULN could be avoided***(Seto et al.,2011).***

In March 2015,***Ozelet al*** studied the PAPAS index as a novel index for prediction ofhepatitis C related fibrosis and

he reported that AUROCs for the PAPAS index for predicting significant fibrosis and cirrhosis were 0.71 (0.61–0.81) and 0.71 (0.61–0.81)respectively. At a cutoff value of 0.86 or less to exclude significant fibrosis, the PAPAS index has a PPV of 75.8% and an NPV of 52.1%. At a cutoff value of 1.33 or more to exclude cirrhosis, it has a PPV of 39.5% and an NPV of 83.8%***(Ozelet al.,2015).***

Ozel et al reported also thatthe PAPAS index was useful for differentiation of cirrhosis in patients with CHC withNPV83.8%***(Ozelet al.,2015).***

Aim of the Work

The aim of this work is to study the role ofPAPAS index as a marker in diagnosis of liver fibrosis in patients with chronic hepatitis C compared to FibroQ and FIB-4.