Noninvasive Assessment of Liver Fibrosis By Transient Elastography and FIB4/APRI for Prediction of Treatment Response in Chronic Hepatitis C—An Experience from a Tertiary Care Hospital

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Background: **Liver fibrosis and its sequel cirrhosis represent a major health care burden, and assessment of fibrosis by biopsy is gradually being replaced by noninvasive methods. In clinical practice, the determination of fibrosis stage is important, since patients with advanced fibrosis have faster progression to cirrhosis and antiviral therapy is indicated in these patients.** ***Aims:*** **To assess the role of transient elastography (TE) and compare it with APRI and FIB4 for predicting liver fibrosis and assessing the effect of host and viral factors on fibrosis and treatment outcome in CHC patients.** ***Methods:*** **In a retrospective analysis, 330 CHC patients underwent liver stiffness measurement (LSM) by TE and tests needed for calculating APRI and FIB4 scores at baseline. 228 patients received a combination of Pegylated IFN-based antiviral therapy and were analyzed for therapeutic response.** ***Results:*** **The study included 330 patients (median age 39 years [range 18–67]), predominantly males (*n* = 227, 68.8%) with baseline LSMs. The median liver stiffness was 7.8 kPa (range 3.2–69.1 kPa). LSMs and its thresholds for severe fibrosis progression (≥9.5 kPa) and cirrhosis (≥12.5 kPa) were significantly higher in patients with age ≥40 years, diabetes mellitus, and patients with significant alcohol intake (*P* = 0.003 to *P* < 0.001). By taking TE as a reference, the diagnostic accuracy of FIB4 scores for predicting cirrhosis (AUROC 0.896) was good (+LR 13.4) compared to APRI (AUROC 0.823) with moderate likelihood ratio (+LR 6.9). Among 228 treated patients the SVR rate in genotype 3 was 70% versus 57.8% in genotype 1. Fibrosis score F4 (*P* = 0.023) and HCV genotype (*P* = 0.008) were independent predictors of SVR.** ***Conclusion:*** **The study shows that LSM by TE and fibrosis assessment by FIB4/APRI scores can be used with fair reliability to predict fibrosis and treatment response in patients with CHC infection. (J Clin Exp Hepatol 2016;6:282–290)**

Liver fibrosis

Liver fibrosis and its sequel cirrhosis represent a major health care burden.[1] Progressive liver fibrosis is a characteristic feature of chronic liver diseases, and its implication is evolution toward cirrhosis, liver failure, and hepatocellular carcinoma with advancement of the primary disease with time.[2] The major causes of liver fibrosis are chronic hepatitis C (CHC) and chronic hepatitis B (CHB), autoimmune liver disease, alcohol and non-alcoholic steatohepatitis.[3] Approximately, 170 million people are infected with CHC worldwide and most of these patients generally show an asymptomatic onset and slow progression of fibrosis.[4,5] The mechanisms of fibrogenesis in CHC infection have not been explored in great detail; however, there is a possible direct profibrogenic and pro-carcinogenic mechanisms of certain HCV proteins.[6] As the degree of fibrosis affects both prognosis and treatment, the prediction of fibrosis is critical for management decisions in patients with CHC.

Liver biopsy (LB) still remains the gold standard for the diagnosis of liver fibrosis; however, it is invasive and has a finite risk of major complications.[7] Hence, many noninvasive tests for assessment of liver fibrosis have been proposed and have been used in the past.[8] These tests rely on distinct but complementary approach and include a biologic method, which quantifies serum levels of biomarkers,

Keywords: noninvasive markers, transient elastography, chronic hepatitis C, liver fibrosis, liver biopsy
Received: 8.02.2016; *Accepted:* 11.08.2016; *Available online:* 18 August 2016
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Abbreviations: LF: liver fibrosis; HCV: hepatitis C; TE: transient elastography; LSM: liver stiffness measurement; APRI: AST to Platelet ratio index; FIB4: fibrosis-4 score; kPa: kilopascals; IQR/M: interquartile range/median; LB: liver biopsy; CHB: chronic hepatitis B; CLD: chronic liver disease; PEG INF: Pegylated Interferon; RBV: Ribavarin; BMI: body mass index; RVR: rapid virological response; EVR: early virological response; ETR: end of treatment response; SVR: sustained virological response; RGT: response guided treatment; DM: diabetes mellitus; AST: aspartate transaminases; ALT: alanine transaminases; ROC: receiver operating characteristic; PPV: positive predictive value; NPV: negative predictive value
http://dx.doi.org/10.1016/j.jceh.2016.08.001

and a physical method that measures liver stiffness by ultrasound or magnetic resonance imaging.[9] Although no single noninvasive test or model developed to date can match the information obtained from actual histology, combination of two modalities can be used to reduce the need for liver biopsy. Liver stiffness measurement (LSM) by transient elastography (TE) is a new upcoming, noninvasive and attractive alternative for staging of fibrosis by noninvasive tests. Several studies have assessed the diagnostic performance of TE for significant fibrosis and cirrhosis in CHC patients and confirmed the excellent diagnostic performance for advanced fibrosis and cirrhosis.[9] In light of its accuracy, simplicity and rapid results, TE has gained widespread use in many countries.[10] APRI and FIB4 are other widely used first-line tests for the prediction of significant fibrosis and cirrhosis. There is a sparse literature on fibrosis assessment by noninvasive methods and prediction of response to Pegylated Interferon and Ribavarin in CHC from India. Hence this study was carried out to assess the role of TE and compare it with APRI and FIB4 to predict liver fibrosis and assess the effect of host and viral factors on fibrosis and treatment outcome in CHC patients.

PATIENTS AND METHODS

Study Design and Assessments

In a retrospective analysis from January 2011 to December 2012, a total of 432 patients with CHC were consecutively screened; in whom baseline LSM and APRI/FIB4 for liver fibrosis assessment was indicated. HCV infection was diagnosed by the presence of serum antibodies against HCV and detectable HCV RNA by quantitative real-time polymerase chain reaction (RT-PCR) assay (Roche Diagnostic), with a limit of detection of ≥15 IU/ml. The exclusion criteria used were: a co-infection with hepatitis B virus (n = 7) or human immunodeficiency virus (n = 17), Hepatocellular carcinoma (17), ALT flare [value five fold the upper limit normal (45 U/ml)] (n = 12), and a failed or unreliable LSM (n = 23). Four patients with genotype 2, nineteen patients with genotype 4 and three patients co-infected with more than one HCV genotype were also excluded because of small number for analysis. Therefore the total number of patients enrolled in the study was 330 as shown in flow Diagram 1.

The study was approved by institutional ethics committee for assessing the anonymous routine clinical data without written informed consent from patients. A detailed clinical history using a precoded questionnaire and biochemical parameters were taken from liver clinic file database. BMI was considered normal within range of 18.5–22.9, overweight from 23 to 24.9, and obese ≥25 according to Indian guidelines for obesity [11]. Alcoholics were defined as those who were consuming ≥30 g of alcohol per day in the last year or more.

TE and Serum Biomarkers Assay

TE was carried out with a Fibroscan (Echosens, Paris, France), which provides a quantifiable estimate of liver stiffness in kilopascals (kPa). Measurements of liver stiffness was performed on the right lobe of liver through intercostal space while the patients was lying in the dorsal decubitus position with the right arm in maximum abduction. Ten successful measurements were performed on each patient and the median value was considered representative of elastic module of the liver. LSM was considered reliable when it included ≥10 valid measurements with success rate ≥60% and IQR/M < 0.3 as per usual definition.[12] In most of studies in CHC, the proposed cut-off for cirrhosis ranged from 11.9 to 14.8 kPa. However a recent study by Bousier et al.[12] have shown that cut off published by Castera et al.[13] provided highest accuracy for significant fibrosis and LSM classification. So LSM were classified in the METAVIR system according to validated cutoffs published by Castera et al.[13] for no or minimal fibrosis [F0–F1] < 7.1 kPa, moderate fibrosis [F2] = 7.1–9.4 kPa, severe fibrosis [F3] = 9.5–12.4 kPa, and for cirrhosis [F4], cutoff of ≥12.5 (Figure 1).

Serum biomarker scores were calculated for APRI (AST to platelet ratio) and FIB4 by using standard formulae as described: APRI = AST (/ULN)/platelet (10^9/L) × 100 with AST (ULN) taken as 35 in our study population. FIB4 = age (years) × AST (U/L)/platelets (10^9/L) × ALT (U/L)$^{1/2}$. The recommended cut-offs[14] for significant fibrosis and cirrhosis (APRI—0.5 and 2, FIB4—1.25 and 3.25, respectively) were used to define the positive tests.

Treatment Outcomes

Amongst 330 CHC patients in whom LSM was assessed at baseline, 228 (69.1%) patients received Pegylated IFN-based antiviral therapy. Genotype 1 was present in 64 (28%) whereas 164 (72%) patients were having genotype 3. Antiviral therapy was prescribed as per the response guided therapy guidelines,[15] and the patients were assessed on an outpatient basis as described in our previous study.[16] Patients were evaluated for treatment response during therapy (e.g. rapid virological response [RVR], early virological response [EVR], and end of treatment response [ETR]) and sustained virological response [SVR] at 6 months after stopping therapy. Patients with undetectable HCV RNA at 4 and 12 weeks after the commencement of treatment were considered to have RVR and EVR respectively. As SVR was the primary outcome in this study, patients with relapse were considered along with nonresponders who were patients who experienced suboptimal virological response during therapy period.

Statistical Analysis

The statistical analysis was carried out using the Statistical Package for Social Sciences version 16 for Windows (SPSS