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Original article

Transient elastography (FibroScan) is not useful in the diagnosis of schistosomal hepatic fibrosis

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Abstract:.
Transient Elastography (TE) is a widely-used noninvasive measure of liver stiffness. This study aimed to evaluate the diagnostic accuracy of TE in the diagnosis of schistosomal hepatic fibrosis (SHF). A total of 30 patients (Mean±SD age 42.1±8.8 years) with pure schistosomiasis were included. Abdominal ultrasound (US) and upper gastrointestinal endoscopy were performed to all patients to assess for signs of portal hypertension and the presence of varices as sequels of SHF. TE (FibroScan) was done to determine liver stiffness. A cutoff value of ≥10.1 Kpa indicates advanced fibrosis (F3-4). Splenomegaly was detected in 27(90 %) patients and was moderate to marked (≥15cm) in 19 (63.3 %). Esophageal and gastric varices were found in 25 (83.3 %) and 4 (13.3 %) cases respectively. TE was successful in all patients, and the mean ± SD liver stiffness was 9.4 ± 5.5 Kpa (Range: 3.5-30 Kpa).F3-4 by FibroScan was detected in 8/25 (32.0 %) and 9/27 (33.3 %) of patients with EV and splenomegaly respectively. Similarly, F3-4 was absent in 4/5(80.0 %) and3/3 (100 %) of those without EV and splenomegaly advanced fibrosis respectively (p=0.71 and p=0.27 respectively). To our knowledge, this study shows for the first time that TE is not useful in diagnosis of SHF and EV in patients with pure schistosomiasis. Whether this is applicable to other cases of pre-hepatic portal hypertension, such as portal vein thrombosis and congenital hepatic fibrosis, needs further investigation.

Keywords:

Non-invasive measures
liver fibrosis
bilharziasis
esophageal varices
Elastography

Abbreviations: *EV; esophageal varices. HCV; hepatitis C virus. IHA; indirect hemagglutination . Kpa; kilo Paskal. LB; liver biopsy. OR; odd ratio. PHT; portal hypertension. SHF; schistosomal hepatic fibrosis. TE; transient elastography. US; ultrasonography.*

1. Introduction

Schistosomiasis currently affects more than 250 million people per year worldwide and it is estimated that 20 million people suffer severe morbidity due to schistosomiasis globally [1]. The three major schistosome species known to infect

humans are *Schistosoma hemat-obium* (endemic in Africa and the eastern Mediterranean), *Schistosomamansoni* (endemic in Africa, the Middle East, the Caribbean and South America) and *Schistosomajaponicum* (endemic mainly in China, Japan and the Philippines) [2]. According to the largest survey conducted in Egypt, the prevalence of *S. hematobium* and *S. mansoni* infections is about 7.8 % and 36.4 % in Upper Egypt and Lower Egypt respectively [3]. *S. hematobium*, mainly affects the urinary tract, while *S. mansoni* and *S. japonicum* cause gastrointestinal and liver morbidities secondary to the passage of schistosome eggs from the lumen of the mesentric veins into adjacent tissues resulting in marked schistosomal hepatic fibrosis (SHF) known as pipestem fibrosis or Symmer's fibrosis. This subsequently leads to portal hypertension (PHT) and hepaticencephalopathy with their sequelae [2]. Despite availability and efficacy of praziquantel therapy, liver fibrosis, which is the most serious sequelae of chronic schistosomiasis develops in up to 20% of infected individuals [4]. The prognosis and management of advanced hepatic schistosomasis depends largely on the degree of liver fibrosis [5]. Despite being the gold standard in assessing hepatic fibrosis, use of liver biopsy (LB) is limited by poor patients' compliance, its associated morbidity, sampling error, poor intra- and inter-observer concordance, and by being unsuitable for dynamic surveillance [6,7]. Ultrasonography (US) has extensively been used to assess hepatic morbidity in patients with chronic schistosomiasis, but the associated inter-observer variations and the recent finding of only moderate correlation between US and LB findings makes US use in assessing HS-PPF inaccurate especially in non-severe case [8]. Moreover, only few studies have used serum biomarkers to assess the stage of hepatic fibrosis or esophageal varices (EV) in patients with schistosomiasis were reliable and sensitive markers for differentiating significant hepatic fibrosis in patients with advanced schistosomiasis japonica [9-11]. Transient elastography (TE; FibroScan) is a noninvasive, reproducible, user-friendly, and a well-established technique used in the initial assessment and follow up of hepatic fibrosis and cirrhosis [7,12]. The performance of TE in staging hepatic fibrosis was tested in a subgroup of Egyptian patients with positive schistosomiasis serology, but they were all coninfected with hepatitis C virus (HCV) [13]. However, it is well known that concurrent HCV and schistosomiasis infections result in an advanced and more severe liver disease than that observed with either disease alone [14]. To our knowledge, no previous study has used TE (FibroScan)as a non-invasive tool in the assessment of hepatic fibrosis in patients with pure chronic schistose-miasis, which is the aim of the present study.

2. Patients and Methods

2.1. *Patients*

A total of 30 Egyptian patients with mean ± SD age of 42.1 ± 8.8 (range: 18-60) years, with the diagnosis of pure Schistosoma mansoni were enrolled in the study. All patients were positive for indirect hemaggultination assay (IHA) for anti-schistosoma antibody with a titer

<1/160 and all have already received praziquantil therapy for schistosomiasis.

2.2.*Exclusion criteria*

Patients with any of the following conditions or characteristics were excluded from participation: Age <18 or >60 years; active alcohol consumption; pre-existing psychiatric condition, pregnant or breast feeding women; significant clinical co-morbidities; patients with co-existent liver disease, e.g. chronic hepatitis C, chronic hepatitis B, or autoimmune liver diseases; patients who were currently on anti-viral therapy or who had completed anti-viral therapy and those who had ascites or focal lesions by abdominal US.

2.3. *Approval and consent*

This study was performed in the Egyptian Liver Research Institute and Hospital (ELRIAH), Sherbin, Dakahliya, Egypt between December 2013 and December 2014. The study was approved by the local Ethics Committee and the institution's review board, conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines, and each participant gave an informed written consent before being enrolled in the study and before performing the upper endoscopy.

2.4.*Clinical and laboratory evaluation*

The patients were subjected to thorough history taking, clinical examination, routine pre-treatment laboratory work-up including complete blood count, international normalized ratio (INR), and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin, ferritin, and ceruloplasmin. Common terminology criteria Version 4.0 was used to grade the abnormal lab values [15]. Serum samples from all patients were also tested for serological tests including anti-HCV antibodies, HBsAg; HBcAb; anti-nuclear antibody (ANA); anti-smooth muscle antibody (anti-SMA), anti-liver kidney microsomal antibody (anti-LKM), and pregnancy test for female subjects of child bearing potential. Antischistosomal antibodies were tested by the indirect hemagglutination (IHA) test. Previous exposure to Schistosoma was identified by a history of previous contact with canal water and/or receiving antibilharzial therapy with a positive serology titer ≥1/160.

2.5.*Abdominal US and endoscopy*

Abdominal US was performed for all subjects using a Toshiba real time scanning device "*AplioM"* with a convex probe" to detect the presence of liver fibrosis and signs of portal hypertension (i.e., dilated portal vein >14 mm, dilated splenic vein >9 mm, presence of splenic hilar collaterals and splenomegaly >13 cm). Also, an upper gastrointestinal endoscopy was performed to all patients to assess for signs of PHT and the presence of EV as sequels of SHF.

2.6.*FibroScan*

TE (FibroScan) was done to determine liver stiffness using the ultrasound TE fibroscan device (Echosens, Paris, France), which consists of a 5-MHz ultrasound transducer probe mounted on the axis of a vibrator. Liver stiffness was measured on the same day as LB. TE measures liver stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 and 65 mm below the skin surface, and the technique was performed according to that described in previous studies [16]. A cutoff value of ≥10.1 Kpa indicates advanced fibrosis (F3-

F4).The classification used for grading liver stiffness by TE (FibroScan) was a modification from that described by Castera et al. [17]. F0–F1: 6-7 kPa, F2: 7.1–9.4 kPa, F3: 9.5–12.4 kPa and F4: >12.5 kPa.

2.7.*Statistical analysis*

Data were collected in a pre-formed data collection form prior to entery in a Microsoft Excel Sheet and then were transferred to SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows for analysis. The quantitative data were described with mean and standard deviation (SD) and compared by the Student's t-test. Qualitative variables were described by number and percent. They were compared by the chi-squared or Fischer's exact test, when appropriate. In all tests, a p value <0.05 was considered significant.

3. Results

A total of 30 patients were included in this study. Their mean ± SD age and body mass index (BMI) of all patients were 42.1 ± 8.8 years and 27.0 ± 4.7 kg/m^2 respectively, and 25 (83.3 %) of them were males. Characteristics of patients are listed in tab. (1).

Table (1) Patients' demographics and baseline characteristics (n = 30).

Variable	*Result*
Age	
- <40 years	9 (30.0)
- ≥40 years	21 (70.0)
Years	42.1 ± 8.8 (20-55)
Sex	
- Male	25 (83.3)
- Female	5 (16.7)
Body mass index	
- ≤25 Kg/m^2	18 (60.0)
- >25 Kg/m^2	12 (40.0)
- K/m^2	27.0 ± 4.7 (19-38)
Alanine transaminase IU/L	41.0 ± 33.9
Aspartate transaminase IU/L	39.0 ± 29.6
Serum albumin gm/dL	4.1 ± 0.5
Serum bilirubin mg/dL	1.0 ±0.3
Platelets x10^3	148.4 ± 76.1
FibroScan Kpa	9.4 ± 5.5 (3.5-30)
Splenomegaly*	
- Marked	8 (26.7)
- Moderate	7 (23.3)
- Mild	12 (40.0)
- No	3 (10.0)
Esophageal varices **** Yes	25 (83.3)
Gastric varices$^{\#}$ Yes	4 (13.3)
Fibrosis stage***	
- F0-2	22 (73.3)
- F3-4	8 (26.7)

*Data expressed as mean ± SD (range) or n (%) as appropriate. * by US scan.** by endoscopy. #; all 4 patients with gastric varices had esophageal varices, i.e., included in the 25 patients. n; number. SD; standard deviation.*** by FibroScan.*

Using US Scan, splenomegaly was detected in 27 (90 %) patients and was described as moderate to marked (≥15cm) in 19 (63.3 %). EV were found during

Upper Endoscopy in 25 (83.3 %) and 4/25 (16.0 %) patients had gastric varices together with the EV. FibroScan (TE) was successful in all patients and the mean ± SD liver stiffness in all patients (n=30) was 9.4 ± 5.5 Kpa (Range: 3.5-30 Kpa).Using FibroScan and a cutoff value of 10.1 Kpa, F0-F2 was detected in 22 (73.3 %) patients and F3-4 was detected in the remaining 8 (26.7 %). EV and splenomegaly were detected in 18/25 (81.8 %) and 19/27 (86.4 %) of cases with non-advanced fibrosis, and in 7(87.5 %) and 8(100 %) of cases with advanced fibrosis respectively (p=0.71 and p=0.27 respectively, tab. (2). It was identified by executing descriptive cross tabulation that 72.0% of variceal cases and 70.7 % of splenomegaly cases were diagnosed by FibroScan as F0-2, tab. (2). Overall it was noticed that out of 27 patients who had splenomegaly, only 8 were identified as F3 and F4 by FibroScan. Among variceal group, also only 7 were identified as F3-4 out of a total of 25 patients. It was interesting to see patients who have normal spleen were classified as F0-2, however, for the varices group (n=25), a single patient who did not have disease by Endoscopy was identified as F3 by FibroScan.

Table (2) Cross tabulation of hepatic fibrosis inpatients with varicesand splenomegaly as measured by FibroScan.*

FibroScan	***Splenomegaly***		**Varices**	
	No	***Yes***	***No***	***Yes***
F0-2	19 (70.4)	03 (100.0)	18 (72.0%)	04 (80.0)
F3-4	08 (29.6)	0 (0.0)	07 (28.0%)	01 (20.0)
Total	27 (100.0)	03 (100.0)	25 (100.0)	05 (100.0)

Data expressed an n (%). using a cutoff value of ≥10.1 Kpa indicates advanced fibrosis (F3-F4).*

As shown in tab. (3), the sensitivity, specificity, PPV, NPV and accuracy of fibroScan in detecting advanced fibrosis evidenced by presence of spenomegaly were 29.6 %, 100 %, 100 %, 13.64, and 36.7 %. Similarly, the corresponding performance characteristics of FibroScan in detecting advanced fibrosis evidenced by presence of varices are 28.0 %, 80.0 %, 87.5 %, 18.2 %, and 37.9 % respectively. Descriptive analysis was performed for the laboratory parameters AST, ALT and Bilirubin. Abnormal results for AST and ALT were compared with the Endoscopy, US and FibroScan findings. It was interesting to see only one patient had Grade II ALT results (clinically significant) whereas 7 patients had Grade I AST and ALT results. Grade I abnormality for bilirubin was also noted for 7 patients. There appears no specific pattern for abnormal laboratory results on FibroScan findings because out of these patients only one subject had F4 fibrosis stage, and the subject who had Grade II ALT results has F1 Fibrosis stage as summarized in tab. (4).

Table (3) Performance features of FibroScan in the detection of splenomegaly and varices cases.

Performance test	***Splenomegaly patients (n = 27)***	***Varices patients (n = 25)***
Sensitivity	29.6 (13.8 - 50.2)	28.0 (12.1 - 49.4)
Specificity	100 (29.2 - 100.0)	80.0 (28.4 - 99.5)
Positive Predictive Value	100 (63.1 - 100.0)	87.5 (47.4 - 99.7)

Negative Predictive Value	13.64 (2.9 - 34.9)	18.2 (5.2 - 40.3)
Accuracy	36.7	37.9

Data expresses as % and (confidence interval).

Table (4) Comparison of abnormal ALT and AST results with Endoscopy, US and Fibrosis stage

AST Grade*	***ALT Grade****	***Varices by Endoscopy***	***Splenomegaly by US***	***Fibrosis Stage***
Grade I	Grade II	EV	Mild	F1
Grade I	Grade I	EVs	Marked with PV = 22mm	F1
Grade I	Grade I	No EVs	Moderate with PV >13 mm	F2
Normal	Grade I	No EVs	Normal Spleen	F1
Grade I	Grade I	EVs	Mild	F1
Grade I	Grade I	Fundal varices	Mild	F3
Grade I	Grade I	No EVs	Mild	F0
Grade I	Grade I	EV	Marked	F4

PV; portal vein. ALT; alanine transaminase. AST; aspartate transaminase. EV; esophageal varices. According to Common terminology criteria Version 4.0i was used to grade the abnormal laboratory values

4. Discussion

This study shows for the first time that TE (FibroScan) is not useful in the diagnosis of SHF in patients with pure schistosomiasis. This is evidenced by the findings that almost one third of the patients who had proved by endoscopy to have varices by endoscopy were diagnosed by FibroScan as F0-2. Similarly, >70 % of patients who were diagnosed to have splenomegaly by US scan had F0-2 by FibroScan. These findings are consistent with the study conducted by Lebray et al in 2008, who showed that measuring liver stiffness is not a reliable marker of hepatic fibrosis in patients with congestive heart failure [18]. Simple noninvasive laboratory and US-based methods were utilized in the assessment of SHF. In a study by Wu et al, performed in 55 patients with advanced schistosomiasis japonica, utilizing LB as a gold-standard, HA and INR were reliable markers for differentiating significant liver fibrosis in patients with advanced schisto-somiasis japonica. The authors concluded that this new simple index can easily predict significant SHF with a high degree of accuracy [10]. Platelets count/spleen diameter ratio has been found useful in predicting the presence of EV in patients with advanced hepatosplenic schistosomiasis in upper endoscopy [11]. Liver stiffness measurement using TE (FibroScan) and reference needle LB were both done in 229 Egyptian patients with chronic HCV infection, 29 % of them had positive serology for Schistosoma mansoni infection. In this subgroup, the sensitivity of FibroScan in detecting fibrosis stages F2-3 was impaired. However, multivariate logistic regression showed that fibrosis stages F0-1 and F4

were the most independent factors associated with the agreement between TE (FibroScan) and LB (ORs: 3.4 and 7.12 and P<0.001 and P<0.001 respectively) [13]. However, these cases had concurrent HCV infection and none of them had pure schistosomiasis. In agreement with our findings, Shiha and Zalata 2001, demonstrated that the co-existence of schistosomiasis does not interfere with application of the Knodell score in patients with chronic HCV infection [19]. Also, Abdel-Rahman et al 2013 showed that positive schistosomal serology has no effect on hepatic fibrosis staging in patients with chronic HCV infection [20].This has also been shown by earlier studies in Egyptian patients with both chronic HCV infection and positive Schistosoma serology, which showed a lack of enhancement of the HCV-related pathology in the schistosomal patients [21]. FibroScan's sensitivity in detecting both varices and splenomegaly is low in our study (37.93 % and 36.66 % respectively). Although literature suggests FibroScan is a good non-invasive method to predict EV presence and possible grading with high sensitivity, but the different results can be due to difference in patients as our study is in pure schistosomal patients and Saad tested HCV patients [22]. Descriptive results for the laboratory data suggest that there is no specific pattern for abnormal laboratory results on FibroScan findings. The grade I abnormalities detected for AST and ALT values are shown in table 5 and these abnormalities are compared with FibroScan stage. Only one of the patients with abnormal grade one lab finding had F4 fibrosis stage. Unlike patients with cirrhosis, those with Schistosoma mansoni develop fibrosis that mainly involves the portal tracts (pipe-stem fibrosis), leading to a form of pre-hepatic PHT that leads to splenomegaly and varices with preserved liver functions. Advances or spread of the fibrosis process into the hepatic lobules occurs very late in the course of the disease and leads to liver cell failure. Therefore, LB and the METAVIR scoring system can't be considered as gold-standard in the evaluation of hepatic fibrosis in patients with schistosomiasis especially in early stages of the disease (prior to involvement of the whole lobule), which justifies the decision not to do LB for our patients. Indeed, the METAVIR, Ishak or Knoddle scoring systems were all developed and applied, for grading and staging inflammation and fibrosis respect-ively, in patients with parenchymal liver diseases of viral, metabolic, or alcoholic etiology, which involving the whole lobule rather the portal tracts as the case in schistos-omiasis and other causes of pre-hepatic PHT. In this study, we did not use LB as the gold-standard to assess SHF, and instead, we relied on endoscopy and ultrasound, in detecting varices and splenomegaly respectively as indicatives of advanced disease. Indeed, from 1991 to 2000, the WHO convened 3 Meetings on Ultrasonography in Schistosomiasis and establish a common grading system that include a qualitative assessment of liver parenchyma, height indexed measurements of portal branch wall thickening, portal vein enlargement, along with signs of portal hypertension (ascites, collateral vein enlargement) in a scoring matrix to define the presence of possible, probable, definite, or advanced schistosomiasis-related

periportal fibrosis and/or portal hypertension [23-27]. One of the potential limitations of this study is the small number of subjects included. However, given the decreasing prevalence of schistosmiasis secondary to the wide-spread use of preziquantil together with other control measure, and the high prevalence of chronic HCV infection in the whole country, especially among patients with schistosomiasis makes the finding and the inclusion of 30 patients with pure schistosomiasis a satisfactory number. Indeed, the previous nationwide use of the trivalent antimonial compounds in treatment of schistosome-infected patients is considered responsible for the current epidemic of HCV infection in Egypt, and makes the finding of pure schistosomiasis cases a difficult task. It is recommended that the results of FibroScan should always be interpreted by a qualified clinician according to the clinical context, taking into account the patient demographics, disease etiology, and laboratory parameters. There is strong need to plan future studies with carefully defined different cutoff values for fibrosis staging. Longitudinal cohort studies can be effective prior to implementing the FibroScan results for the detection of SHF in patients with and without associated viral or other parenchymal liver disease.

5. Conclusion

In conclusion, the present study shows for the first time that, TE is not accurately indicative of patients' with pure Schistosoma mansoni clinical condition, and is especially not useful in the diagnosis of SHF and EV in such patients. However, these findings need to be confirmed in a larger group of patients. Whether this is applicable to other patients with other causes of pre-hepatic PHT, such as portal vein thrombosis and congenital hepatic fibrosis, needs further investigation.

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