Comparison of liver biopsy with fibroscan and other methods in predictivng fibrosis in chronic hepatitis B patients - a hospital based study

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Abstract

Introduction: Fibroscan is one of the recently introduced procedures in Bangladesh. It is used for assessing liver fibrosis non-invasively in liver diseases. The present study is done to assess its role as compared to other established methods in chronic hepatitis B patients. ***Methodology:*** Patients seeking treatment for chronic liver disease related to hepatitis B virus at outdoor or indoor of Department of Hepatology in Sir Salimullah Medical College Mitford Hospital were studied. These patients had compensated liver disease with no ascites, encephalopathy or jaundice. Here parameters of assessing liver fibrosis like liver biopsy, which is the gold standard, was compared with non-invasive tools like ultrasound, Fibroscan of liver, Aspartate Aminotransferase-to-Platelet ratio (APRI) index & Fibrosis-4 (FIB-4) scoring, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Hepatitis B virus (HBV) DNA level. ***Result:*** 23 patients of both sexes (Male 17, Female 6) having age range 18 -40 years were included in the study. All patients were suffering from compensated liver disease related to chronic hepatitis B infection. Almost all cases except one had HBeAg negative results. The study revealed AST to correlate most of factors like ALT, HBV DNA level, APRI and FIB-4 scores. Fibroscan value correlated with FIB-4 only. APRI correlated with AST, HBV DNA, FIB-4 whereas FIB-4 correlated with AST, Fibroscan, APRI and age. Histologic activity index did not correlate with any of the non-invasive markers. ***Conclusions:*** Though Fibroscan is an excellent tool for detecting cirrhosis of liver, its role in non-cirrhotic liver is limited. In these situations combination of other non-invasive tools may be more helpful.

Key words: Fibroscan, liver biopsy, fibrosis, APRI, FIB-4.

J Cox Med coll 2018;4(1): 16-20

Introduction

Chronic Hepatitis B (CHB) is a state of chronic necro-inflammation of the liver caused by persistent viremia with hepatitis B virus. It is a global health problem with considerable incidence in Bangladesh. It has been estimated that about 350 million people around the world are chronically infected with this virus[1]. Around 1 million liver related deaths worldwide each year are related to complications of chronic liver disease, cirrhosis or hepatocellular carcinoma[2]. Of these deaths, chronic hepatitis B is a predominant etiologic agent. In Bangladesh around 3.8-7.8% of general population are infected with this virus as revealed in many studies[3-8].

Critical part in decision making as regard to treatment is whom to treat and when to treat. There are several guidelines formulated by various associations, like Asia-Pacific, America and Europe Association for Study of Liver, to address these issues. Assessment of fibrosis before starting treatment is cornerstone in treatment decisions. Liver biopsy is gold standard in assessing necro-inflammation (Grading) and fibrosis (Staging), as it leads to direct visualization of liver histology in microscope. Besides assisting treatment strategy, it also helps in assessing treatment response and future decisions. However it is costly, invasive, with risks of morbidity (including hemoperitoneum, pneumothorax, and post-biopsy pain) occurring in 0.2- 2% of patients[9] and mortality, though rare, in expert hands. Various non-invasive markers are used to predict fibrosis non-invasively.

Several non-invasive serological markers and tests have been reported to predict the presence of significant fibrosis or cirrhosis in patients with chronic hepatitis C (HCV) with considerable accuracy, but most of these markers need complicated calculations, so less helpful to clinicians. So far, many studies have been done to evaluate the usefulness of readily available laboratory results to predict fibrosis or cirrhosis in chronic hepatitis C. Among these, AST and ALT, their ratio (aspartate aminotransferase to alanine aminotransferase ratio : AAR), AST to platelet ratio index (APRI), and age platelet count index (API) are routine laboratory based tools.

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Aspartate Aminotransferase-to-Platelet ratio index (APRI) :

The APRI is developed to calculate hepatic fibrosis or cirrhosis. It has been tested to detect fibrosis due to different etiologies like HCV related chronic hepatitis or cirrhosis or coinfection of HCV and HIV (Human Immunodeficiency Virus). APRI is calculated using the patient's AST level and platelet count, and the upper limit of normal aspartate aminotransferase AST level. A meta-analysis of 40 studies reveals APRI cutoff of greater than or equal to 0.7 has an estimated sensitivity of 77% and specificity of 72% in detecting of significant hepatic fibrosis (greater than or equal to F2 by METAVIR). A cutoff score of at least 1.0 has an estimated sensitivity of 61% to 76% and specificity of 64% to 72% indetecting of severe fibrosis/cirrhosis (F3 to F4 by METAVIR)[10]. In detecting cirrhosis of liver, a cutoff score of at least 2.0 is more specific (91%) but less sensitive (46%). However, APRI does not accurately differentiate intermediate fibrosis state from mild or severe fibrosis. APRI is recommended as non-invasive test in the recently published WHO guidelines for management of CHB in resource-limited settings[11].

FIB-4:

This is an inexpensive and easy to perform test for detection of liver fibrosis. It uses patient's age, AST, ALT, and platelet count. A value of less than 1.45 has a sensitivity of 74% and specificity of 80% in excluding significant fibrosis. A value of greater than 3.25 has a specificity of 98% in confirming cirrhosis. This model was good at excluding or confirming cirrhosis, but values between 1.45 and 3.25 do not fully discriminate fibrosis and need an additional method to predict liver fibrosis[12].

Transient Elastography (TE):

The ultrasound-based transient elastography is a painless, easy-to-perform ultrasound test to measure liver stiffness (liver stiffness measurment : LSM). Two transient elastography (TE) ultrasound systems are approved for assessement of liver fibrosis: these are TE or Fibroscan, and shear wave elastography (Shear Wave Elastography). Studies using transient elastography are reproducible. It examines a large mass of liver tissue (1 cm diameter by 5 cm in length) and thus provides a more representative assessment of the entire hepatic parenchyma. The test is performed using an ultrasound transducer probe that is mounted on the axis of a vibrator. Vibration is transmitted toward hepatic tissue, the vibrations are followed by pulse echo, and their velocities are measured which correlates directly with liver stiffness. Transient elastography has been validated in multiple studies for detection of advanced fibrosis and cirrhosis[13]. Multiple factors, such as hepatic inflammation, obesity, ascites, and elevated central venous pressure can influence the transient elastography results. Despite these limitations, transient elastography is a potentially very useful non-invasive method in quantifying liver fibrosis and cirrhosis[14]. Furthermore, TE has been shown to be a prognostic indicator in predicting complications such as hepatic decompensation or HCC[15]. The high cost of the Fibroscan machine limits its availability in resource-limited settings.

Methodology

A prospective randomized study was done in Department of Hepatology, Sir Salimullah Medical College Mitford Hospital, Dhaka, Bangladesh between January 2016 to June 2017. Adult patients (≥18 years) seeking treatment for chronic liver disease for hepatitis B infection were included in the study. These patients were clinically asymptomatic, were in compensated state with no ascites, encephalopathy or jaundice and had no associated comorbidity. Patients having associated fatty liver, chronic hepatitis C, decompensated cirrhosis of liver, uncontrolled diabetes mellitus and chronic kidney disease were excluded from the study as it might influence the values of the Fibroscan or have contraindication for liver biopsy. The study was approved by the Ethics Committee at Sir Salimullah Medical College Mitford Hospital beforehand. Written informed consent in English or Bengali language was obtained from each patient enrolled in this study. HBV infection was confirmed with HBsAg positive report on ELISA method and HBsAg positivity for at least 6 months was documented before enrolling the patients.

Liver stiffness measurement (LSM):

Fibroscan (Echosens, France, Model 402) was performed by a single skilled operator to assess LSM value. Ten LSM values were recorded and the median value calculated by the statistics analyze system was used as the final score. The liver stiffness cut-offs were staged on a scale of F0–F4 according to Fibroscan values given as F0-F1:1–7.2 kPa, F2: 7.2-8.3 kPa, F2-F3: 8.3-10.7 kPa, F3: 10.7-11.2 kPa, F3-F4: 11.2-18.4 and F4: 18.4-75 kPa in hepatitis B patients respectively. Here F0 indicated no fibrosis; F1 portal fibrosis without septa; F2 portal fibrosis with few septa; F3 numerous septa without cirrhosis; F4 cirrhosis respectively. These scores correlated to METAVIR score[16].

Surrogate serum markers:

Surrogate serum markers of liver fibrosis were estimated by routine blood specimens obtained for hematological and biochemical examinations.

Platelet count, AST and ALT levels were determined in the same laboratory. APRI and FIB-4 scores were calculated based on the following formulae[17,18].

APRI = ([AST/ULN]/platelet count) ×100

FIB 4 = (Age ×AST)/ (Platelet count × ALT)

Liver biopsy:

Liver biopsy was done using ultrasound guidance. Biopsy was taken by true cut needle. Grading and staging of biopsy specimen was done by Knodell's original Histologic Activity Index by a single expert[19]. Here Histologic Activity Index was calculated by summation of necro-inflammation and fibrosis scores.

Result

There was 23 patients of chronic hepatitis B. They were of both sexes (Male 17, Female 6), age range

Table1: Laboratory Parameters

Age	Range	18 – 40 years
	Mean±SD	27.9 ± 6.8
Sex	Male	17 (73.9%)
	Female	06 (26.1%)
ALT	Range	15 – 135 U/L
	Mean	38.35
AST	Range	18 -78 U/L
	Mean	34.35
HBeAg	Positive	1 (4.3%)
	Negative	22 (95.7%)
Ultrasound	Normal	12 (52.2%)
	Coarse liver	09 (39.1%)
	Missing data	02 (8.69%)
Fibroscan (LSM)	Range	3.4 -13.5
	Mean ± SD	7.61 ± 2.94
Histologic activity index (Necro-inflammation plus Fibrosis)	Range	3 – 11
	Mean ± SD	6.73 ± 2.33
APRI	Range	0.185 – 1.037
	Mean ± SD	0.416 ± 0.224
FIB 4	Range	0.32 – 2.32
	Mean ± SD	0.816 ± 0.446

Table-II : Correlations of different parameters

		ALT	AST	HBV DNA	USG	LSM	Necro inflam	Fibrosis	HAI	APRI	FIB_4	Age
ALT	Pearson	1	.552**	.288	-.213	-.035	-.096	-.110	-.113	.396	-.180	-.363
	Sig. (2-tailed)		.006	.194	.354	.873	.672	.628	.618	.061	.410	.088
	N	23	23	22	21	23	22	22	22	23	23	23
AST	Pearson	.552**	1	.578**	-.200	.184	.176	.271	.227	.860**	.483*	-.072
	Sig. (2-tailed)	.006		.005	.384	.401	.435	.222	.309	.000	.019	.743
	N	23	23	22	21	23	22	22	22	23	23	23
HBV_DNA	Pearson	.288	.578**	1	-.140	.036	.249	-.126	.173	.510*	.153	-.067
	Sig. (2-tailed)	.194	.005		.557	.875	.276	.588	.452	.015	.498	.767
	N	22	22	22	20	22	21	21	21	22	22	22
USG	Pearson	-.213	-.200	-.140	1	.065	-.059	-.147	-.089	-.311	-.233	-.209
	Sig. (2-tailed)	.354	.384	.557		.781	.800	.526	.700	.170	.310	.362
	N	21	21	20	21	21	21	21	21	21	21	21
LSM	Pearson	-.035	.184	.036	.065	1	.064	.167	.103	.354	.465*	.295
	Sig. (2-tailed)	.873	.401	.875	.781		.779	.457	.649	.097	.026	.171
	N	23	23	22	21	23	22	22	22	23	23	23
Necro inflammation	Pearson	-.096	.176	.249	-.059	.064	1	.436*	.963**	.207	.065	-.017
	Sig. (2-tailed)	.672	.435	.276	.800	.779		.043	.000	.356	.773	.939
	N	22	22	21	21	22	22	22	22	22	22	22
Fibrosis	Pearson	-.110	.271	-.126	-.147	.167	.436*	1	.662**	.290	.340	.149
	Sig. (2-tailed)	.628	.222	.588	.526	.457	.043		.001	.190	.122	.509
	N	22	22	21	21	22	22	22	22	22	22	22
HAI	Pearson	-.113	.227	.173	-.089	.103	.963**	.662**	1	.259	.156	.030
	Sig. (2-tailed)	.618	.309	.452	.700	.649	.000	.001		.244	.488	.894
	N	22	22	21	21	22	22	22	22	22	22	22
APRI	Pearson	.396	.860**	.510*	-.311	.354	.207	.290	.259	1	.712**	-.007
	Sig. (2-tailed)	.061	.000	.015	.170	.097	.356	.190	.244		.000	.974
	N	23	23	22	21	23	22	22	22	23	23	23
FIB_4	Pearson	-.180	.483*	.153	-.233	.465*	.065	.340	.156	.712**	1	.530**
	Sig. (2-tailed)	.410	.019	.498	.310	.026	.773	.122	.488	.000		.009
	N	23	23	22	21	23	22	22	22	23	23	23
Age	Pearson	-.363	-.072	-.067	-.209	.295	-.017	.149	.030	-.007	.530**	1
	Sig. (2-tailed)	.088	.743	.767	.362	.171	.939	.509	.894	.974	.009	
	N	23	23	22	21	23	22	22	22	23	23	23

USG score for analysis: Normal liver echotexture is marked as 1, coarse liver as 2 in analysis.

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

18 - 40 years, Mean±SD 27.9±6.8 [Table 1]. There were no stigmata of cirrhosis of liver on physical examination. Their ALT and AST levels were within normal limit (<40 U/L) or elevated (³40 U/L). Almost all cases except one case had HBeAg negative result. Majority (52.2%) of the patients had normal echotexture of liver on ultrasound, 39.1% had coarse echotexture. Fibroscan value ranged between 3.4 kPa and 13.5 kPa with mean 7.61 kPa. Pearson correlation analysis shown in Table 2 revealed AST to correlate to most of factors like ALT, HBV DNA level, APRI and FIB-4 scores [Table 2]. Fibroscan correlated with FIB-4 only. APRI correlated with AST, HBV DNA, FIB-4 whereas FIB-4 correlated with AST, Fibroscan, APRI and age. Histologic activity index did not correlate with any of the non-invasive markers. In Table 3, results of different fibrosis measuring tools of the study patients were compared. Patients' serum DNA values were mentioned at left column. Significant fibrosis results were given in bold letters in the table.

Discussion

Assessment of liver fibrosis is a major challenge in the management of patients with chronic hepatitis B patients. It is proven that liver biopsy is the gold standard in assessing liver fibrosis. But it has the risks of complications including rare instances of death, and other limitations like involvement of skilled personnels and costs. Non-invasive techniques were developed to detect fibrosis so that treatment can be done earlier without undertaking the risks of invasive techniques. Fibrosis has high negative predictive value (87.8%) in excluding cirrhosis of liver if a value of <8 kPa is considered as cut off value, as revealed in a number of studies. Thus, it has become part of hepatology practice in recent years. Ultrasound examination of liver has high sensitivity (87.8%) and positive predictive value (71.4%) indicating cirrhosis of liver, as seen in a study[20] done at our center on 320 patients of chronic hepatitis B and also in other studies in many centers. Our current study was done on patients having compensated liver disease. The study suggested that no single non-invasive method was sufficient to predict significant fibrosis (F3 or F4 stage). In this situation, a combination of at least two or more methods were needed to clear the dilemma. At some instances, invasive method like liver biopsy may have to be done. There are a number of factors which may effect in measuring fibroscan score and result in false positive or negative values. These are acute liver injury, platelet count, albumin, Body Mass Index (BMI), prothrombin activity[21]. These factors should be considered at the time of performing fibroscan in a patient. In stable state and in the absence of

Table-III : Comparison of results of different fibrosis measuring tools.

No. of Patients	HBV DNA	USG	LSM	NI	FIBROSIS	HAI	APRI	FIB-4
1	6870	**Coarse liver**	**8.9**	11	**3**	14	0.65	1.04
2	23600000	Normal echotexture	8	9	1	10	**0.975**	1.21
3	0	**Coarse liver**	**10.1**	7	1	8	0.313	0.42
4	206	**Coarse liver**	4.2	3	1	4	0.25	0.54
5	131	**Coarse liver**	7.2	5	1	6	0.417	0.98
6	929		12				0.185	0.72
7	744	Normal echotexture	3.4	7	**3**	10	0.223	0.4
8	394	Normal echotexture	3.7	9	1	10	0.313	0.86
9	2470	Normal echotexture	**13.3**	3	1	4	0.346	1.09
10	250	Normal echotexture	4.7	5	1	6	0.472	0.62
11	9180		**13.5**	7	**3**	10	**1.037**	**2.32**
12	663	Normal echotexture	7.6	7	1	8	0.422	0.57
13	740	Normal echotexture	5.9	3	1	4	0.527	0.34
14	111	Normal echotexture	6.4	7	1	8	0.25	0.61
15	149	**Coarse liver**	4.9	9	1	10	0.194	0.43
16		**Coarse liver**	6.9	3	0	3	0.296	0.86
17	842	Normal echotexture	**9.6**	7	1	8	0.529	**1.48**
18	0	**Coarse liver**	**10.1**	7	1	8	0.313	0.47
19	207	Normal echotexture	7.8	9	**3**	12	0.304	0.91
20	457	**Coarse liver**	5.1	5	1	6	0.333	0.93
21	221	Normal echotexture	4.2	7	1	8	0.405	1
22	3930000	**Coarse liver**	**8.4**	9	1	10	0.243	0.32
23	300	Normal echotexture	**9.2**	9	1	10	0.582	0.65

influencing factors, however, fibroscan score is fairly uniform.

Conclusions

The study suggests that, as a non-invasive technique, fibroscan alone can demonstrate the true extent of liver fibrosis in a limited number of cases, requiring in addition of other non-invasive methods to assess fibrosis more accurately. Nevertheless, till another non-invasive technique is developed, fibroscan may be combined with ultrasound or other tools to assess fairly accurate state of fibrosis. This study also highlights that further large scale study is needed to have more clear insight about the non-invasive techniques to assess liver fibrosis.

Acknowledgments

Thanks to Mr. Ibrahim Habib Rizwan (ibrahim.rizwan@gmail.com) for reviewing texts.

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