HEPATIC ELASTOGRAPHY AND FIB-4 SCORE VERSUS LIVER BIOPSY FOR ASSESSMENT OF LIVER FIBROSIS IN CHRONIC HCV PATIENTS

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ABSTRACT

Background: Chronic HCV infection is a major global health problem. Liver biopsy still the gold standard tool for assessment of hepatic fibrosis, however, real time hepatic elastography assessment and FIB-4 score calculation may be valuable alternatives. **Aim of the work**: Clarifying whether, hepatic elastography assessment and FIB4-score calculation are good and acceptable alternatives for Liver biopsy for assessment of liver fibrosis in patients with chronic HCV infection. **Patients and Methods:** The study was carried out through seven months duration on sixty-five HCV infected patients who were eligible for standard of care direct acting antiviral medications. Routine laboratory workup, abdominal US, transient hepatic elastography assessment, FIB-4 score calculation and liver biopsy were done for all participants. **Results:** ANOVA study of participant's age, Hb %, platelets count, albumin, ALT and AST among fibrosis stages diagnosed by LB showed no significant differences regarding participant's age and Hb%, while, a significant difference regarding serum albumin ($p = 0.05$) and highly significant difference were found regarding platelets count, serum ALT and AST ($p=0.001$, $<0.001$and <0.001 respectively). Post hoc study of the previous parameters between different fibrosis stages (Liver biopsy) showed no significant differences were found between F0 & F1, F0 & F2 and F1 & F2 regarding all parameters. No significant differences regarding Hb% and age but, highly significant differences were found between F0 &F3 as regard platelets count, albumin, ALT and AST. No significant differences regarding Hb% and age but, a significant difference and highly significant differences were found between F1 &F3 regarding serum albumin, platelets count, ALT and AST respectively. No significant differences regarding age and serum albumin but, highly significant differences were found as regard platelets count, ALT and AST between F2 &F3. Elastography readings agreed with liver biopsy in 4 out of 4 in F0, 26 out of 38 in F1, 9 out of 12 and 8 out of 11 in F3. Elastography readings in comparison to corresponding fibrosis stages readings by LB showed sensitivity (76.7%), specificity (100%), PPV (100%), NPV (96.7%) and accuracy rate (96.9%) with highly significant difference ($p = 0.001$). While FIB-4 score readings in comparison to corresponding fibrosis stage readings by liver biopsy showed sensitivity (35%), specificity (91.1%), PPV (63.6%), NPV (75 %) and accuracy rate (73.8%) with highly significant difference ($p = 0.001$). **Conclusion:** Hepatic elastography assessment and FIB-4 score calculation are rapid, accurate and sensitive tools for assessment of liver fibrosis in chronic HCV patients.

Key words: Hepatic elastography; FIB-4 score; Liver biopsy; Liver fibrosis; Chronic HCV

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INTRODUCTION

World Health Organization (WHO) has declared hepatitis C infection a global health problem with approximately 3~4 % of world's population (roughly 170-200 million people) infected with HCV. In US, approximately 3 million people are chronically infected, many of whom are still undiagnosed. [(1)] Egypt has the highest prevalence of hepatitis C seropositivity worldwide. The national Egyptian prevalence rate of HCV seropositivity has been estimated to be ~14.7%. [(2)]

Diagnosis of chronic HCV-induced liver fibrosis by liver biopsy (LB) is the most reliable method for assessing hepatic fibrosis, and apart from confirmation of fibrosis, much information on the extent of inflammation can be obtained. However, LB is an invasive procedure that may have some precautions and complications, in addition, sampling error may have occurred because only $1/50000^{th}$ of the liver is sampled. [(3)]

Quantitative hepatic elastography emerged as a tool to assess liver fibrosis noninvasively.

Nowadays, vibration-controlled transient elastography (VCTE) is by far, the most clinically validated quantitative elastography technique and with VCTE based device, fibroscan has emerged as the reference tool for liver stiffness assessment. [4]

FIB-4 score measurement is a noninvasive scoring system based on several laboratory tests that help to estimate the amount of liver scarring. This score has been studied in liver disease due to HCV infection and is calculated from the formula: (Age x AST) / (Platelets count x (Sqr (ALT)). For HCV mono-infection, FIB-4 score < 1.45 is corresponding to F0-F1 while FIB-4 score > 3.25 is corresponding to F3-F4. [5]

The use of noninvasive monitoring tools considered to be preferable to invasive testing, particularly in low- and middle-income countries especially with the era of new direct acting drugs, as LB is an expensive and invasive procedure that may associated with patient discomfort, a small risk of serious bleeding and requires specialist histological examination for accurate staging. On basis of the results of systematic review, it was considered that, FIB4-score and transient elastography are the most useful tests for assessing the stage of liver disease. [6]

PATIENTS AND METHODS

Study design and settings

This is a prospective comparative clinical study conducted in Internal Medicine, Tropical Medicine, Radiodiagnosis and Clinical Pathology departments in corporation with the advanced center for liver diseases, Zagazig university hospitals, Egypt, through seven months period from October 2014 to April 2015.

Ethics statement

All the patients received information on the study from their referring physician and were asked to sign an informed consent form. Standard management of HCV PCR-positive patients includes LB to determine if treatment is indicated. Needle biopsy of the liver was performed in the standard manner. The patients also underwent noninvasive (Elastography) and semi-invasive investigations (serum markers of fibrosis). The scientific and ethical committees in our faculty prepared an ethics statement that was signed by all participants in this research.

Target population and sampling

The study included sixty-five patient who were eligible for receiving standard of care direct acting antiviral medications for chronic HCV. Patients who had a history of Bilhariziasis were excluded from the study as well as patients who had visible granuloma on LB were not included in the analysis.

Patients classification and randomization

Patients fulfilled required inclusion and exclusion criteria for treatment of chronic HCV according to National Egyptian guidelines 2014 for treatment of chronic hepatitis C.

Methods and study tools

Complete history taking with special comments on age, sex, obesity, hypertension, history of diabetes, Bilhariziasis, drug intake, HCV and HBV infections. Full clinical examination was done aimed to exclude advanced cirrhotic patients (Child C). Routine laboratory investigation included CBC, Liver function, PT, PTT and INR, αFP, serum creatinine and blood urea, fasting blood glucose. Real time pelviabdominal ultrasound for detection of liver fibrosis and/or cirrhosis, splenomegaly, evidence of portal hypertension, presence or absence of ascites and/or focal lesions.

Liver histology

Liver biopsy was done by a trained interventive radiologist, with a 15-G Hepafix needle *(Braun Medical, Melsungen, Germany*). Samples were fixed in paraffin and stained with Sirius red and hematin-eosin. The stained slides were all read by two experienced pathologists, the second reader being unaware of the first reader's findings. Both readers were blinded to the results of the alternative methods of fibrosis assessment, and a consensus interpretation was reached if there was a discrepancy. Liver fibrosis and necroinflammatory activity were assessed with the METAVIR scoring from 0 to 4 (F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis and few septa, F3 = numerous septa without cirrhosis, F4 =

cirrhosis), and activity on a scale from 0 to 3 (A0 = none, A1 = mild, A2 = moderate, A3 = severe). [7]

Hepatic elastography assessment

Estimation of liver stiffness using realtime elastography was done by measuring the velocity of elastic shear waves in the liver parenchyma generated by the mechanical push (*using Phillips IU22*). The procedure was done in the *Advanced Centre for Liver Diseases*. The medium reading of the tissue elasticity was calculated and expressed in kPa. The success rate of the examination is calculated as the ratio between the number of measurements validated by the machine and the total number of attempted measurements during the same examination. The median value of the validated measurements is taken to represent liver stiffness. The interquartile range (IQR) represents the interval around the median that contains 50% of valid measurements. To be considered interpretable and valid, the examination must include at least 10 measurements with a success rate of at least 66%, and the IQR must not exceed 33% of the result of the examination. Hepatic elastography and laboratory workup were done in the same day. [8]

FIB 4- score calculation

All biochemical analyses were done in our hospital. AST and platelets count were measured with an ABX (*Pentra 60 automat Montpellier, France*). FIB-4 score was calculated according to of patient's age, serum AST and ALT level and platelets counts according to the formula: Age (years) × AST [IU/L]/ (PLT [10^9/L] × (ALT [IU/L]) ½). A 3.25 index was used as a threshold value for the diagnosis of advanced fibrosis and cirrhosis (F3 and F4) while 1.45 index was used as threshold value for no or early fibrosis (F0, F1). Serum AST and ALT were routinely measured in our hospital for all patients prior to evaluation, usual upper normal values were 45 IU/l for men and 40 IU/l for women and 65 IU/l for men and 50 IU/L for women, respectively. Platelets count was performed in the same hospital; normal values ranged between 150,000 and 450,000/mm3. [9]

STATISTICAL ANALYSIS

Collected data imported into Statistical Package for the Social Sciences (SPSS version 20). Differences between frequencies and percentages in groups were compared by Chi-square test., KAPPA AGREEMENT to test agreement between two different diagnostic tools. Differences between means (quantitative variables) in multiple parametric quantitative by ANOVA. P value was set at <0.05 for significant results & <0.001 for highly significant results.

RESULTS

The participant's age and sex were matched with no significant difference. Males accounted 60 % while females accounted 40% of the participants number (*Table 1*). F0 was the least reading recorded by hepatic elastography, while F1 was the common findings, in contrary to FIB-4 score readings in which F0-F1 was the common reading followed by F2 while F3 was the least recorded reading in both. Liver elastography readings were near to that of LB especially in F1 and in F3 (*Table 2*).

ANOVA study of participant's age, Hb %, platelets count, albumin, ALT and AST among fibrosis stages diagnosed by LB showed no significant differences regarding participant's age and Hb%, while, a significant difference regarding serum album (p =0.05) and highly significant difference were found regarding platelets count, serum ALT and AST (p=0.001, <0.001and <0.001 respectively). Post hoc study of the previous parameters between different fibrosis stages (LB) showed no significant differences were found between F0 & F1, F0 & F2 and F1 & F2 regarding all parameters. No significant differences regarding Hb% and age but, highly significant differences were found between F0 &F3 as regard platelets count, albumin, ALT and AST. No significant differences regarding Hb% and age but, a significant difference and highly significant differences were found between F1 &F3 regarding serum albumin, platelets count, ALT and AST respectively. No significant

differences regarding age and serum albumin but, highly significant differences were found as regard platelets count, ALT and AST between F2 &F3 (*Table 3 and 4*).

Hepatic elastography readings agreed with LB in 4 out of 4 in F0, 26 out of 38 in F1, 9 out of 12 and 8 out of 11 in F3 (table 5). cross-tab Elastography readings in comparison to their corresponding fibrosis stage readings by LB showed the following characteristic: In F0 stage: elastography readings showed sensitivity (66.7%), specificity (100%), positive predictive value (100%), negative predictive value (96.7%) and accuracy rate (96.9%) with highly significant difference (p =0.001). In F1 stage: Elastography readings showed sensitivity (89.7%), specificity (93.7%), positive predictive value (75%), negative predictive value (79.2%) and accuracy rate (78.4%) with highly significant difference (p =0.001). In F2 stage: elastography readings showed sensitivity (45%), specificity (100%), positive predictive value (100%), negative predictive value (96.7%) and accuracy rate (96.9%) with highly significant difference (p =0.001). In F3 stage: elastography readings showed sensitivity (80%), specificity (94.5%), positive predictive value (72.7%), negative predictive value (96.2%) and accuracy (92.3%) with highly significant difference (p =0.001) (*Table 5 and 7*).

Cross-tab of FIB-4 score readings in comparison to their corresponding fibrosis stage readings by LB showed the following calculated results; in F0-F1 stage, FIB-4 score readings showed sensitivity (35%), specificity (91.1%), positive predictive value (63.6%), negative predictive value (75 %) and accuracy rate (73.8%) with highly significant difference (p =0.001). In F2 stage: FIB-4 score readings showed sensitivity (89.7%), specificity (93.7%), positive predictive value (75%), negative predictive value (79.2%) and accuracy rate (78.4%) with highly significant difference (p =0.001). In F3 stage, FIB-4 score readings showed sensitivity (60%), specificity (100%), positive predictive value (100%), negative predictive value (93.2%) and accuracy rate (93.8%) with highly significant difference (p =0.001) (*Table 6*).

Table (1): Demographic data of the participants

Variable		**Mean ± SD**
Age (years)		40.8± 9.25
Sex	**No.**	**%**
Male	39	60
Female	26	40
Total	65	100%

Table (2): Frequency and percentage of fibrosis stages among different assessment tools

Fibrosis Stage	**Elastography**		**FIB-4 score**		**Liver biopsy**	
	NO	**%**	**NO**	**%**	**NO**	**%**
F0	4	6.3	47	72.3	6	9.2
F1	38	58.4			29	44.6
F2	12	18.4	12	18.5	20	30.8
F3	11	16.9	6	9.2	10	15. 4
Total	65	100%	65	100%	65	100%

Table (3): Means ± SD of participant's age and some laboratory values in different fibrosis stages (LB)

Variable	F0 Mean ± SD	F1 Mean ± SD	F2 Mean ± SD	F3 Mean ± SD	p
Age(years)	32.3 ± 7.6	41.8± 9.2	40.4 ± 8.5	43.9± 9.9	0.084
PLT count(10^9/L)	221.2 ± 24.9	207 ± 1.5	133 ± 1.9	138 ± 33.9	0.001
Hb %(g/dL)	13.3 ± 1	13.1 ± 1.5	13 ± 0.9	12.9 ± 1.3	0.925
Albumin (g/dL)	3.9 ± 0.5	4 ± 0.5	3.9 ± 0.3	3.5 ± 0.2	0.05
ALT(u/L)	22 ± 5	24± 9.2	31.9 ± 18.9	62 ± 30.8	<0.001
AST(u/L)	24.5 ± 3.4	26.4 ± 6.6	29.3 ± 14.8	63.2 ± 35.2	<0.001

Table (4): Post Hoc study of age and some laboratory parameters in different fibrosis stages (LB)

Fibrosis Stages		Parameters					
		Age	**Hb%**	**PLT**	**ALT**	**AST**	**Albumin**
F 0	**F1**	0.22	0.68	0.30	0.70	0.78	0.55
	F2	0.06	0.63	0.06	0.21	0.49	0.97
	F3	0.15	0.50	0.0001	0.0001	0.0001	0.001
F1	**F0**	0.22	0.68	0.30	0.70	0.78	0.55
	F2	0.57	0.88	0.11	0.16	0.51	0.28
	F3	0.53	0.50	0.0001	0.0001	0.0001	0.02
F2	**F0**	0.06	0.63	0.06	0.21	0.49	0.97
	F1	0.57	0.88	0.11	0.16	0.51	0.28
	F3	0.31	0.75	0.0001	0.0001	0.0001	0.14
F3	**F0**	0.15	0.50	0.0001	0.0001	0.0001	0.001
	F1	0.53	0.66	0.0001	0.0001	0.0001	0.02
	F2	0.31	0.75	0.0001	0.0001	0.0001	0.14

Table (5) Hepatic elastography in different fibrosis stages in comparison to liver biopsy (METAVIR system)

Fibrosis stages			Liver biopsy				Total	X2	p
			F0	F1	F2	F3			
Elastography	F0	Count	4	0	0	0	4	91	0.001
		%	66.7%	0.0%	0.0%	0.0%	6.2%		
	F1	Count	2	26	10	0	38		
		%	33.3%	89.7%	50%	0.0%	58.5%		
	F2	Count	0	1	9	2	12		
		%	0.0%	3.4%	45%	20%	18.5%		
	F3	Count	0	2	1	8	11		
		%	0.0%	6.9%	5.0%	80%	16.8%		
Total		Count	6	29	20	10	65		
		%	100%	100%	100%	100%	100%		

Table (6) FIB-4 score in different fibrosis stages in comparison to liver biopsy in (METAVIR system)

			Liver Biopsy				Total	X2	p
			F0	F1	F2	F3			
FIB-4 score	F0- F1	Count	6	26	12	3	47	46	0.001
		%	100%	89.7%	60. 0%	30.0%	72.3%		
	F2	Count	0	3	8	1	12		
		%	0.0%	10.3%	40.0%	10.0%	18.5%		
	F3	Count	0	0	0	6	6		
		%	0.0%	0.0%	0.0%	60%	9.2%		
Total		Count	6	29	20	10	65		
		%	100%	100%	100%	100%	100%		

Table (7): Elastographic negative and positive cases in each fibrosis stage in comparison to LB

Elastography			Liver biopsy stag e			X2	p
			-ve	+ve	Total		
F0	-ve	Count	59	2	61	41.9	0.001
		%(Within)	100%	33.3%	93.8%		
	+ve	Count	0	4	4		
		%(Within)	0%	66.7%	6.2%		
Total		Count	59	6	65		
		%(Within)	100%	100%	100%		
F1	-ve	Count	24	3	27	20.9	0.001
		%(Within)	66.7%	10.3%	41.5%		
	+ve	Count	12	26	38		
		%(Within)	33.3%	89.7%	58.5%		
Total		Count	36	29	65		
		%(Within)	100%	100%	100%		
F2	-ve	Count	42	11	53	13.5	0.001
		%(Within)	93.5%	55%	81.5%		
	+ve	Count	3	9	12		
		%(Within)	6.7%	45%	18.5%		
Total		Count	45	20	65		
		%(Within)	100%	100%	100%		
F3	-ve	Count	52	2	54	33.4	0.001
		%(Within)	94.5%	20%	83.1%		
	+ve	Count	3	8	11		
		%(Within)	5.5%	80%	16.9%		
Total		Count	55	10	65		
		%(Within)	100%	100%	100%		

DISCUSSION

Up to near time, liver biopsy had been considered as the gold standard tool for assessment of necroinflammatory activity and fibrosis staging in patients with chronic liver diseases and is still the reference method and final court for assessing the fibrosis. [10]

Despite its diagnostic utility, LB has several limitations, including patient reluctance, adverse events, accessibility, effective cost, sampling error, intra- and interobserver variability. [11]

Recently, transient hepatic elastography, a morphological method of that measures liver stiffness has been evaluated. Other biochemical tests such as Fibrometer (*BioLiveScale, Angers, France*) and Hepascore, which combine several variables like FibroTest, are under development. [12]

All these noninvasive tools have a rather good predictive positive value for diagnosis of nil or minimal fibrosis and extended fibrosis. Despite being potential alternatives to LB, routine use of these noninvasive tests is hampered by the cost of the device (FibroScan and Elastography), false negative or false positive results (FIB-4 score), or the need for standardization assays to perform the test. [13]

The recorded elastography readings in our study were accurate and sensitive when

compared to those of LB; in F0 (identical 100%), in F1 and F2 (highly near), and in F3 (almost identical). Real time elastography assessment of liver fibrosis were sensitive and specific with high accuracy rate in different fibrosis stages in comparison to LB. (66.7%/100%,89.7%/66.7%, 45%/93.3% and 80% /94.5%) in F0, F1, F2 and F3 respectively. *Shinya Fujiwara et al.,* [14] reported that measurement of hepatic elastography confirmed to be a very useful and specific noninvasive tool for assessment of the hepatic fibrosis especially in chronic HCV infection where heaptic inflammation and fibrosis markers are correlated very well with the progression of the hepatic fibrosis. In the same direction, *Castera et al.,* [9] also confirmed the previous results and found that combining hepatic elastography and Fibrometer (a blood test that measures hyaluronate, prothrombin time, platelets count, AST, α2 macroglobulin, urea, and age) can provide an 87% accuracy rate. However, *Ferraioli et al.,* [10] reported that hepatic elastography isn't 100% accurate and has been shown to have a high degree of accuracy for predicting mild fibrosis, severe fibrosis and cirrhosis, but, it is less likely to distinguish the difference between no or minimal fibrosis.

At CI = 95 %, AUROC of our elastography readings were (0.75, 0.78 and 0.80) in F1, F2 and F3 respectively when compared to that of LB (METAVIR score). Our results and conclusions are slight near to a similar study conducted by *Sporea et al.,* [15] on 274 patients with HCV infection where AUROC were calculated retrospectively to be (0.89, 0.90 and 0.93) to predict fibrosis stages F1, F2, and F3 respectively. High values more than our readings were reported in a metaanalysis carried by *Friedrich-Rust et al.,* [16] which included 518 patients with chronic HCV disease, AUROC were calculated retrospectively to be (0.87, 0.91 and 0.93) to diagnose fibrosis stages. Elastography can be considered an adequate diagnostic technique for the assessment of hepatic fibrosis, particularly in chronic HCV. *Rizzo et al.,* had shown similar findings and concluded that hepatic elastography perform equal to LB in accurate assessment of liver fibrosis regardless of the fibrosis stage. [17]

Similar results were found in other diseases such as chronic hepatitis B, alcoholic hepatitis and HIV-HCV coinfection but, it appears however, that the performance of the hepatic elastography is slightly poorer; in alcoholic cirrhosis, (AUROC = 0.88) when compared to viral cirrhosis (AUROC = 0.94). AUROC values in chronic HCV cirrhosis ranged from (0.81 to 0.95) for METAVIR fibrosis scores of F ≥ 2 and from (0.80 to 0.98) for the diagnosis of cirrhosis while, AUROC values ranged from 0.72 to 0.87 for METAVIR fibrosis scores of F ≥ 2 and from 0.87 to 0.99 for the diagnosis of cirrhosis in HIV-HCV coinfection. [18]

In patients with chronic HCV infection when compared to LB, liver fibrosis measurement by elastography can differentiate between significant fibrosis and absent or mild fibrosis. In a retrospective study carried by *González Guilabert et al.,* [19] found that a cut-off value of 6.8 kPa is the one that best differentiates absence or mild fibrosis (F < 2 METAVIR) from significant fibrosis (F ≥ 2 METAVIR), with PPV of 98%, NPV of 30.1%, sensitivity of 59.6%, specificity of 93.3% and a diagnostic performance of 77.3%. In another cohort study done by *Castera et al.,* a cut-off value of 6.8 kPa had been used for presence of significant fibrosis; more than 80% of the LB would have been avoided. [9]

In most of the world, LB is still considered the reference test to determine liver fibrosis stages. As a result, all diagnostic technique performance studies for liver fibrosis staging have compared the noninvasive test results to LB histological score. A diagnostic tool is defined as being perfect if AUROC is 100%, excellent if the AUROC is over 90% and good if the AUROC is over 80%, however, the diagnostic performance of LB in significant fibrosis is only moderate (AUROC approximately 0.8). It is therefore difficult to precisely determine the performance of the noninvasive markers to diagnose significant fibrosis, as the reference test (LB) itself is less

than perfect. In chronic HCV fibrosis staging studies, AUROC of the hepatic elastography ranged from 0.77 to 0.90 for the assessment of significant fibrosis (F ≥ 2), and from 0.90 to 0.97 for assessment of cirrhosis respectively. [20]

Ziol et al., found a significant positive correlation between hepatic elastography and fibrosis stages in patients with chronic HCV. [21] This observation is consistent with our findings because stiffness of tissues largely depends on their collagen content and on the microscopic structural organization of these blocks (septa). Significant AUROC curves for F 3 and F 2 (0.97) and (0.91) for the whole studied population and 0.95 and 0.99 for the larger biopsy specimens, respectively), distinct cut-off values were (14.5 kPa and 9.6 kPa) with high total sensitivity and specificity, and high likelihood ratios suggest that liver elastography is a reliable method for the diagnosis of hepatic fibrosis (F2 and F3).

In our study, when FIB-4 score was put at a cut off <1.45(F0 and F1); sensitivity, specificity, PPV, NPV and accuracy rate were: (91.4 %, 50%, 68%, 83 % and 72%) respectively in comparison to LB. While, at cut-off >3.25(F3), sensitivity, specificity, PPV, NPV and accuracy rate were: (60 %, 100%, 100%, 93 % and 93%) respectively. We detected a good NPV (83%) value for FIB-4 for exclusion of advanced fibrosis and very high PPV (100%) in cut-off value>3.25 for diagnosis of sever fibrosis. Like our work, *Rizzo et al.*, examine FIB-4 score for HCV infected patients. A cut-off value of < 1.45, FIB-4 had a NPV (90%) for the exclusion of advanced fibrosis, while a cut-off value > 3.25 has a PPV (65%) for the diagnosis of extended fibrosis. [17] Moreover, *Vallet-Pichard et al.*, observed and reported that at a cut-off value of < 1.45, a high NPV (94.7%) with a sensitivity of (74.3%) is needed to exclude severe fibrosis. Whereas, for confirming the presence of advanced fibrosis at cut-off value > 3.25, FIB-4 score had a PPV (82.1%) with specificity of (98.2%). [22]

A persistent problem is that the noninvasive markers and tools used for assessment of hepatic fibrosis are usually compared with LB results, which remains the gold standard for fibrosis evaluation, however, LB also over or under- estimate the degree of hepatic fibrosis. It had been suggested that discordances between LB and hepatic elastography results could be explained by the technical difficulties involved in the examination of LB samples, which makes it unreliable. *Poynard et al.*, observed that FIB-4 score discordances in 29% of patients that were due to marker failure and LB failure in 2.4% and 18% of cases, respectively. They showed that LB diagnostic failures were seven times more common than diagnostic failures due to markers. Furthermore, to evaluate diffuse liver diseases in a reliable manner, a specimen sample measuring at least 15 mm is needed. [23] *Bedossa et al.*, showed that only 65% of liver biopsies relying on 15 mm samples led to correct diagnoses (using the METAVIR score), whereas 75% of biopsies relying on 25-mm samples were correct. Because there were no benefits to taking bigger samples, the investigators suggested that 25-mm samples are necessary to evaluate fibrosis accurately. [24]

The use of noninvasive monitoring tools and markers is preferable to invasive testing in assessment of liver fibrosis, particularly in low- and middle-income countries like our country, as LB is an expensive and invasive procedure associated with patient discomfort, too much laboratory work, a small risk of serious bleeding and requires specialist histological examination for accurate staging. Based on results of the systematic review discussed above, it was considered that FIB4-score and hepatic elastography are the most useful and convenient tests for assessing the stage of liver fibrosis. The advantage of FIB-4 is that it is validated for the diagnosis of stages >F3 fibrosis and would thus be useful for identifying persons at greatest risk of morbidity who, therefore, could be prioritized for treatment. It was also recommended that persons who tested negative for significant fibrosis and/or cirrhosis could be retested

periodically and could thus be tightly followed if their FIB-4 indices increased. [5]

In conclusion, combining FIB-4 score and hepatic elastography which is superior to FIB-4 score, may be of great value with the devolvement of new effective direct acting antiviral drugs being rapid, accurate and sensitive tools for assessment of liver fibrosis in patients who are eligible for receiving these medications. Upgrading and increase the sensitivity of the hepatic elastography devices and technique may add more benefits and advances for better assessment and increase accuracy that can push LB back and keep it reserved for debated cases.

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