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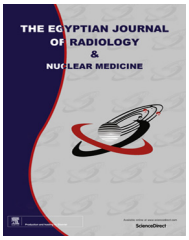

ORIGINAL ARTICLE

Fibroscan versus liver biopsy in the evaluation of response among the Egyptian HCV infected patients to treatment

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KEYWORDS

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Abstract *Background/aim:* Hepatitis C virus (HCV) infection usually progress to chronic infection with subsequent cirrhosis and cancer. Therapies aim to eradicate the virus and prevent further progression. Interferon is claimed to have anti-fibrotic effect. Histopathology is the gold standard in diagnosis and grading of hepatic fibrosis, but transient elastogram (Fibroscan) can be used as alternative non-invasive modality. This prospective study aimed to evaluate the accuracy of fibroscan in diagnosis of liver fibrosis, and assess the effect of antiviral therapy on fibrosis stages in HCV patients.

Patients and methods: The study was conducted from September 2012 to December 2014 as a project funded by Science and Technology Development Fund, Egypt, Grant No. 3448. It included 498 patients; 150 HCV cirrhotic patients as control, and 348 HCV naive patients grouped according to their liver biopsy into; mild (group I) and moderate (group II) fibrosis. They were examined using fibroscan (Echosens, Paris, France, device 502, M probe) before, 12, 24, and 48 weeks of therapy, with 300 patients (150 patients in each group) completed follow-up regardless of their response. The results of fibroscan were compared to each other and to liver biopsy.

Results: Fibroscan can diagnose F1 at 6 kPa with 26% sensitivity, 8% specificity, AUC = 0.037; F2 at level of 7 kPa with 84.6% sensitivity, 71.3% specificity, AUC = 0.692 and F3 at 9.5 kPa with 96% sensitivity, 97% specificity, AUC = 0.997. The fibrosis results had regressed significantly after 48 weeks of starting therapy of both patients' groups ($p < 0.05$). When categorized by response to therapy, responders showed significant decline in their fibroscan scores compared to non-responders of same fibrosis degree.

Conclusion: Fibroscan correlated with histopathology in moderate (F2–F3), but not mild (F1) fibrosis. The degree of fibrosis regresses significantly in HCV responders on anti-viral INF based therapy. Besides its accuracy as noninvasive device in detecting degree of fibrosis, fibroscan can be very useful in assessment of degree of fibrosis during and after therapy.

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1. Introduction

Infection with hepatitis C virus (HCV) is a common problem worldwide. Most cases progress to chronic infection with its complications. As a consequence of progressive HCV liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma may occur (1). Histological assessment of liver injury and fibrosis is the gold standard test. It is important for making treatment decisions, as well as for predicting prognosis and therapeutic outcome in chronic liver disease including HCV. However, liver biopsy is an invasive procedure, limited by cost, morbidity, and sampling errors. Moreover, it provides a static measure of fibrosis as its repetition is tedious (2,3).

As accurate noninvasive methods of monitoring changes in fibrosis would be helpful in following the natural history of the disease and monitoring potential anti-fibrotic responses to antiviral or other treatment modalities, several noninvasive predictive indices for hepatic fibrosis based on direct and indirect serum markers, or imaging modalities to measure liver stiffness, such as transient elastography (fibroscan) have been developed. Transient elastography (Fibroscan; Echosens, Paris, France) is a novel method for measuring liver stiffness as a surrogate of fibrosis. It has been validated in patients with various disorders including chronic viral hepatitis and has gained widespread use due to its simplicity, rapid results, and ease of incorporation into an outpatient setting (4,5).

The objective of this prospective study was to evaluate the accuracy of fibroscan in diagnosing liver fibrosis compared to liver biopsy in HCV patients, and to assess the effect of antiviral therapy on different stages of fibrosis.

2. Patients and methods

This study was performed on 498 patients, in the period from September 2012 to December 2014 as a project funded by Science and Technology Development Fund, Egypt, Grant No. 3448. Of them three hundred and forty eight (348) patients seek anti-HCV treatment through health insurance clinics or national anti-HCV program and accepted to take part in this study and signed the informed consent.

Patients were classified according to their liver biopsy results into group I: 163 patients with mild fibrosis (F0–F1), group II: 185 patients with moderate fibrosis (F2–3), and group III: 150 patients not fit for therapy as control (f4 or cirrhosis).

All treated patients (groups I and II) were homogenously collected according to Egyptian national protocol for treatment of HCV. All laboratory assessments of treated patients were performed centrally through the national or health insurance laboratories, with liver biopsy size of 15 mm at least, and all biopsies were evaluated by a single experienced liver histopathologist. The genotyping for HCV was not performed on the patients in our study, since approximately 90% of infections in Egypt are due to genotype 4 (6) and the Egyptian National Committee for Control of Viral Hepatitis does not recommend routine genotyping.

They all met the following inclusion criteria: age (18–60) years, positive anti-HCV antibodies, HCV-RNA level greater than 1000 IU/mL, body mass index (BMI) <30 calculated as (weight in kilograms/squared height in meters), normal α-fetoprotein, serum bilirubin <1 mg%, a liver biopsy specimen taken within one month prior to study entry, neutrophil and platelet counts of at least 2000 lL and 100,000 lL respectively, hemoglobin values of at least 12 g/dL for women and 13 g/dL for men, and creatinine levels less than 1.2 mg/dL. These were the same data needed for inclusion in standard of care therapy at this time (peg interferon + ribavirin).

Patients were excluded from this study if they had hepatitis B virus infection, human immunodeficiency virus infection, autoimmune disorders, clinically significant cardiac or cardiovascular abnormalities, evidence of malignant neoplastic diseases or concomitant immunosuppressive medication.

Liver biopsy specimens were obtained under complete aseptic procedures to retrieve 15 mm core. The specimen was processed and stained with hematoxline and eosine. Fibrosis was staged on a 0–4 scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis according to METAVIR scoring system (Bedossa P1996).

The patients on antiviral therapy were followed by PCR at weeks 12, 24, and 48 of therapy. Fibroscan examination (using fibroscan; Echosens, Paris, France, device 502, M probe) was parallel repeated in the same periods.

2.1. Fibroscan examination

After clinical and ultrasound examination, patient underwent fibroscan examination. Measurements were taken in the right lobe of the liver, through the intercostal spaces with the patient lying in the dorsal decubitus, and the right arm in maximum abduction. The tip of the probe transducer is covered with coupling gel and placed on the skin between the rib bones at the level of the right lobe. The operator, assisted by ultrasound time motion images, locates a portion of the liver that is at least 6 cm thick and free of large vascular structures. Once the area to be measured has been located, the operator presses the probe button to begin acquisition. Acquisitions that do not have the correct vibration shape or do not correctly follow the vibration propagation are automatically rejected by the software. The success rate is calculated as the number of successful acquisitions. Ten validated measurements were made on each patient. The results were expressed in kilopascals (kPa). Only examination with 10 validated measurements and a success rate of at least 70% (ratio of the number of successful acquisitions over the total number of acquisitions) were considered reliable. Shear wave propagation velocity depends on the severity of hepatic fibrosis. The elastic modulus E expressed as $E = 3\rho V2$, where V is the shear velocity and ρ is the mass density (constant for tissues); the stiffer the tissue, the faster the shear wave propagates. The median value of ten E results is automatically calculated by software. It was considered representative of the liver elastic modulus as previously described (7).

2.2. Statistical analysis

The collected data were analyzed using SPSS software statistical computer package version 16 (IBM Corp, Armonk, NY, USA). Data were summarized using mean, standard deviation (SD), and median for quantitative skewed variables. Kruskal–Wallis One Way Analysis of Variance on Ranks was used to

compare fibroscan results during follow-up in treated groups; if it was significant post hoc Tukey test was used for all pair wise comparison. Chi square was used to compare response rate among treated groups. Correlation between fibroscan results and liver fibrosis stage was done using spearman rank correlation test. Area under Receiver operator characteristic (ROC) curves was used to detect cutoff value to each hepatic fibrosis stage and detect its sensitivity and specificity for each stage. The results were considered statistically significant when $p < 0.05$ for all used tests.

3. Results

The study composed of 3 groups. Group I: started with 163 patients. Of them, 159, 154, and 150 stick to their follow-up at 12, 24, and 48 weeks respectively. Group II started with 185 patients. Of them, 169, 162, and 150 stick to their follow-up at 12, 24, and 48 weeks respectively. So, the data of 150 patients who completed their follow-up in each group were only included for analysis. Group III had 150 patients with cirrhosis without follow-up. Group I with mild fibrosis had mean age of 43.6 ± 8.9, group II with moderate fibrosis had mean age of 46.6 ± 8 and group III with advanced fibrosis and cirrhosis had mean age of 49.2 ± 7.5. There was no significant difference in age among all studied groups ($F = 2.81$ & $p = 0.061$) (Table 1).

Results of fibroscan and biopsy were available in 348 patients before therapy (163 in group I and 185 in Group II) and the biopsy correlated positively with fibroscan data in moderate fibrosis ($p < 0.001$), but not in mild or no fibrosis ($p = 0.12$) (Table 2).

According to standard of care, only groups I and II received treatment. Among group I, 81/150 (54%) were responders, while group II had 86/150 (57%) responders. There was no significant difference in response rate between the two groups ($x^2 = 0.642$). Genotyping for HCV was not performed in our study (Tables 3 and 4).

Among studied patients only 300 cases completed their follow-up during and after therapy (groups I and II); their data were tested using ROC curve with different cutoff values as follows: For stage F0, we have only 4 cases, so it was not tested. For F1, at level of 6 kPa to diagnose F1 fibroscan has sensitivity of 26% and specificity of only 8%, AUC was 0.037 (95%CI is 0.005–0.068), for F2 at level of 8.8 kPa to diagnose F2 fibroscan has sensitivity of 2% and specificity of 50%, but when we used elasticity of 7 kPa fibroscan has sensitivity of 84.6% and specificity of 71.3% with AUC = 0.692 (95%CI is 0.601–0.784) and for F3 at level of 9.5 kPa to diagnose F3 fibroscan has sensitivity of 96% and specificity of 97%. AUC was 0.997 (95%CI is 0.992–1.003) (Fig. 1).

Among 300 patients who received treatment, response rate was 54–57%. Changes in transient elastography during therapy were measured in 300 patients who completed their follow-up (150 patients in each group) at start, 12 weeks, 24 weeks, and 48 weeks of therapy. The clearance of the virus was associated with decline in liver stiffness measurements.

The Mean fibroscan scores were significantly changed in both groups I and II during and after therapy. When groups were stratified according to response the responders of both

Table 1 Demographic data of all studied groups.

	Group 1 $n = 150$	Group 2 $n = 150$	Group 3 $n = 150$
Age in years			
• Mean ± SD	43.6 ± 8.9	46.6 ± 8	49.2 ± 7.5
• Median	44	47	49
• Range	19–60	19–60	27–64
Sex			
• Female	55	44	33
• Male	95	106	117
METAVIR score			
• F0	4	0	0
• F1	146	0	0
• F2	0	63	0
• F3	0	87	0
• F4	0	0	150

Table 2 Correlation between liver biopsy and fibroscan results in studied groups.

Group	*r*	*p*
Group I	0.122	0.12
Group II	0.646*	< 0.0001

* Significant.

Table 3 Comparing fibroscan results before, during and after therapy in group I.

Group parameter	Before	12 w	24 w	48 w	*H*	*p*
Group I (n = 150)						
• Mean ± SD	5.713 ± 1.125	5.677 ± 1.171	5.584 ± 1.227	5.085 ± 0.819	40.072*	< 0.001
• Range	2.700–8.700	2.700–8.700	2.700–8.600	3.000–6.800		
• Median	5.900	5.800	5.000	5		
Responders of group I (n = 81)						
• Mean ± SD	6.193 ± 0.950	5.654 ± 1.128	5.596 ± 1.245	4.806 ± 0.734	73.117*	< 0.001
• Median	6.2	6.2	5.8	4.8		
• Range	3.200–8.700	2.800–8.400	2.700–8.600	3.00–7.00		
Non-responders of Group I (n = 69)						
• Mean ± SD	5.123 ± 1.055	5.710 ± 1.234	5.574 ± 1.218	5.275 ± 0.816	14.18*	0.003
• Median	5.100	5.800	5.800	5.300		
• Range	2.80–8.40	2.70–8.60	3.0–7.00	3.0–7.0		

* Significant.

Table 4 Comparing fibroscan results before, during and after therapy in group II.

Group parameter	Before	12 w	24 w	48 w	*H*	*p*
Group II (n = 150)						
• Mean ± SD	11.475 ± 6.252	11.315 ± 5.121	11.036 ± 4.595	9.841 ± 4.142	12.972*	0.005
• Range	2.200–48.000	2.400–42.200	2.200–41.600	3.100–36.000		
• Median	10.20	10.20	10.20	9		
Responders of group II (n = 86)						
• Mean ± SD	12.724 ± 7.585	11.681 ± 5.803	11.191 ± 5.393	8.748 ± 4.339	37.166*	< 0.001
• Median	10.500	10.300	10.250	8.000		
• Range	2.200–48.000	2.400–42.200	2.200–41.600	3.100–36.000		
Non responders of Group II (n = 64)						
• Mean ± SD	9.797 ± 3.135	10.823 ± 4.019	10.828 ± 3.259	10.259 ± 2.615	4.697	0.195
• Median	9.050	10.200	10.200	10.100		
• Range	4.400–22.000	4.30–31.60	4.40–19.30	4.50–18.20		

* Significant.

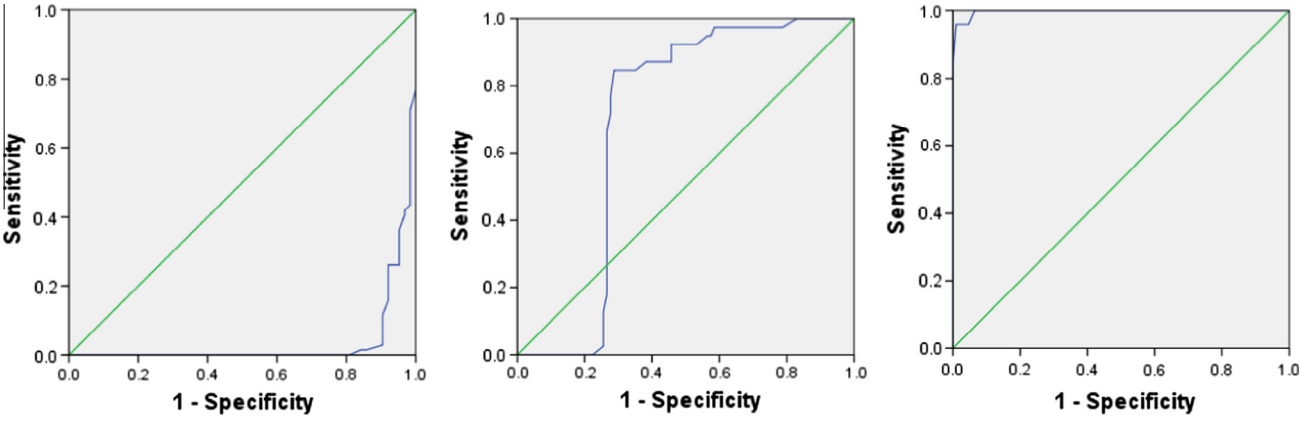

Fig. 1 ROC curve for grads of hepatic fibrosis as measured with fibroscan.

groups had significant lower scores throughout the course of therapy. Non-responders of both groups did not decline their fibroscan score. On the contrary, it was either significantly increased as in group I or non-significantly changed as in group II ($p = 0.19$) (Tables 3–5). Responders start fibroscan regression in week 12 and persist while non-responders showed fluctuation in their fibroscan scores during therapy (Figs. 2–5). A sample of group III was also available (Fig. 6).

Table 5 Comparison of treated patients at different intervals of therapy (Tukey test).

Group	Significant difference ($p < 0.05$)					
	Before Versus 12 weeks	Before Versus 24 weeks	Before Versus 48 weeks	12 weeks Versus 24 weeks	12 weeks versus 48 weeks	24 weeks versus 48 weeks
Group I ($n = 150$)	No	No	Yes	No	Yes	Yes
Responders of Group I ($n = 81$)	Yes	Yes	No	No	Yes	No
Non-responders of Group I (=69)	No	Yes	Yes	No	Yes	No
Group II ($n = 150$)	Yes	Yes	Yes	No	Yes	Yes
Responders of Group II ($n = 85$)	No	No	Yes	No	Yes	Yes
Non-responders of Group II	No significant difference in ANOVA					

Fig. 2 Fibroscan exam in group I responder at start, 12, 24, and 48 weeks (same patient).

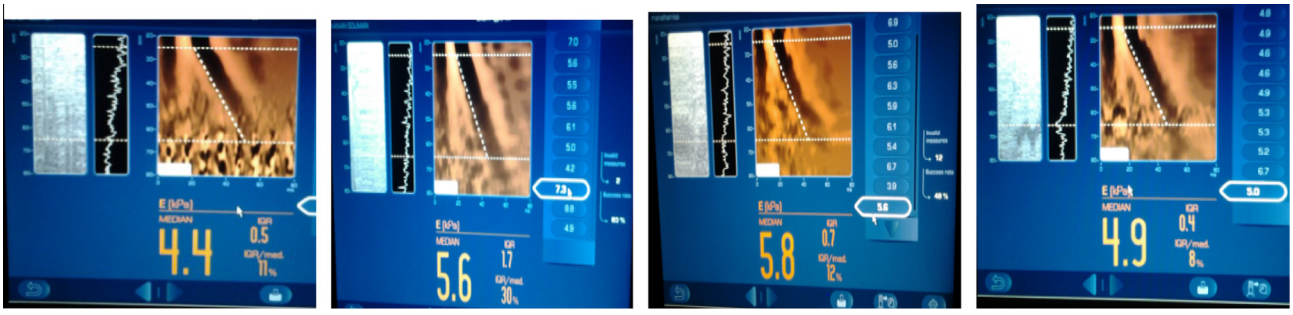

Fig. 3 Fibroscan exam in group I non-responder at start, 12, 24, and 48 weeks (same patient).

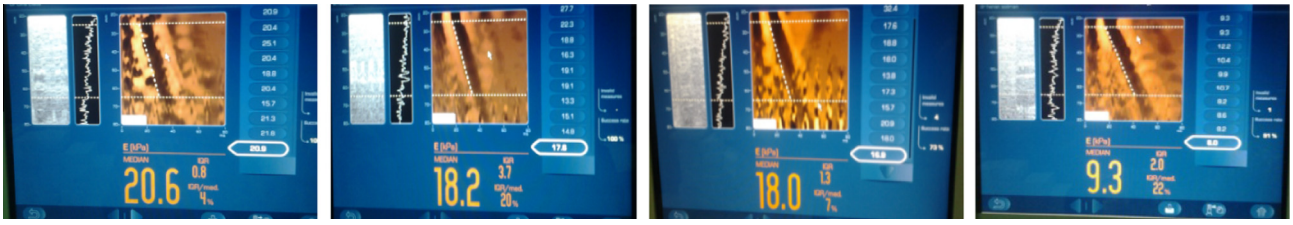

Fig. 4 Fibroscan exam in group II responder at start, 12, 24, and 48 weeks (same patient).

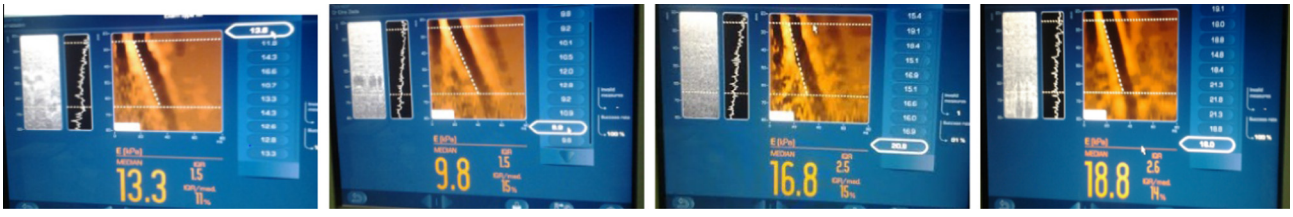

Fig. 5 Fibroscan exam in group II non-responder at start, 12, 24, and 48 weeks (same patient).

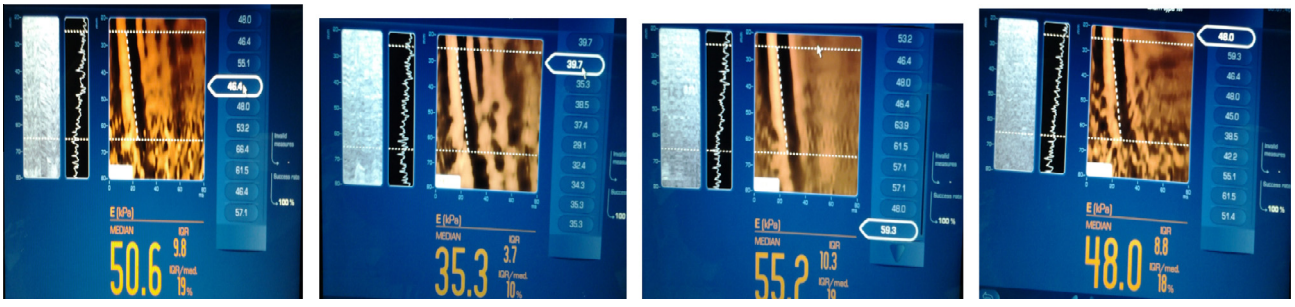

Fig. 6 Samples of fibroscan exam in group III (different patients).

4. Discussion

The diagnostic cutoffs for grades of fibrosis calculated in published studies are very heterogeneous (8). When we compare the results of liver biopsy cutoffs are provided by manufacture for correlating results in HCV patients using ROC curve and we find the following: for F1, at level of 6 kPa to diagnose F1 fibroscan has low sensitivity and specificity of only 8% and AUC was 0.037 (95%CI is 0.005–0.068), and for F2 at level of 8.8 kPa to diagnose F2 fibroscan has sensitivity of 2% and specificity of 50% which are very low parameters.

The data of our patients revealed 7 kPa as a cutoff for F2, with sensitivity of 84.6% and specificity of 71.3% with AUC = 0.692 (95%CI is 0.601–0.784). This cutoff was lower than that adopted by Ziol et al. (9) ($\geqslant$8.8 kPa for $F \geqslant 2$) and those specifically calculated for CHC in the meta-analysis of Stebbing et al. (10) ($\geqslant$8.5 kPa for $F \geqslant 2$). But it was in accordance with Castera et al. (11) who reported 7.1 kPa as a cutoff for $F \geqslant 2$.

In a recent study, Boursier et al. (12) studied the diagnostic accuracy of fibroscan at different cutoffs and stated that accuracy for diagnosing significant fibrosis ($\geqslant$F2) significantly decreased in patients with median $\geqslant$7.1 kPa. They find also that with IQR/M >0.30 may be considered "poorly reliable" in patients with median $\geqslant$7.1 kPa and "reliable" in patients with median <7.1 kPa. This is supporting our results which reflect level of 7 kPa as more reliable cutoff in F2 patients. According to the current definitions, all the following criteria have to be met to consider fibroscan result as reliable valid measurements, success rate >60%, and interquartile range/median (IQR/M) <0.30 (13–15). None of our patients had IQR/M >0.30 at any cutoff value in this work. So, we did not interpret examination results with IQR/M >0.30 as reliable result of fibroscan examination.

For patients with METAVARE F3, at level of 9.5 kPa fibroscan has sensitivity of 96% and specificity of 97% and AUC was 0.997 (95%CI is 0.992–1.003). Similar results were reported by Wong et al. (16) who reported 9 kPa as cutoff value of F3 in hepatitis B patients with normal ALT. But higher cutoff was adopted in HCV patients by Ziol et al. (9) and Castera et al. (11) who reported 12.5 and 14.8 kPa as cutoff values to diagnose fibrosis of F3 or more. However, they had 25% and 19.5% cirrhotic patients included in their studies respectively. So, their results may be overestimated by the results of F4 and cirrhotic patients included in the same group.

Among 300 patients who received treatment, response rate was 54–57%. This was much lower than El Khayat et al. (17) who reported end of therapy response (ETR) after 48 weeks of peg interferon + ribavirin in genotype 4 to be 80% (38/44 patients), and Shehab et al. (18) who reported 62% ETR in same genotype but, higher than that reported by Derbala et al. (19) who reported it to be 43.3%. These variations may be biased by small sample size used in these studies (44, 50 and 30 patients respectively). Despite genotyping for HCV was not performed on the patients in our study, yet approximately 90% of infections in Egypt are due to genotype 4, and previously mentioned studies were performed in Egypt suggesting no genotypic differences.

Changes in fibroscan during therapy were measured in 300 patients who completed their follow-up at start, 12 weeks, 24 weeks, and 48 weeks of therapy. The mean fibroscan scores were not significantly different at baseline between responders and non-responders. This was different from Patel et al. (20) who reported that among their 217 patients who perform fibroscan examination, responders had lower TE results compared to non-responders in same fibrosis degree. However, Vergniol et al. (21) tested 112 HCV patients receiving antiviral therapy, and did not find any significant differences in TE results at baseline between responders and non-responders, and similar results were obtained in French study by Hezode et al. (22), and Japanese's study by Ziol et al. (9).

It was interesting to observe that, regardless the degree of fibrosis, responders start fibroscan regression in week 12 and persist while non-responders showed fluctuation in their TE scores during therapy. Responders of both groups of fibrosis had significant lower scores throughout the course of therapy, while non-responders of both groups did not decline their fibroscan scores. This was in accordance with many previous studies which reported a decline in serum fibrosis marker indices or fibroscan measurements in patients with chronic HCV successfully treated with interferon based therapy (20,23–25).

In our work, the clearance of the virus was associated with decline in liver stiffness measurements. This was not clear in group I who had no or mild fibrosis (stages F0–1) prior to treatment. Thus, they were incapable of achieving a significant regression in fibrosis. Similar results were obtained by Patel et al. (20). On the other hand, patients in group II with moderate fibrosis (F2–3) allow for decline of degree of stiffness in fibroscan to be significant.

5. Conclusion

Fibroscan correlated with fibrosis degree in liver biopsy and can be used as noninvasive tool to diagnose moderate (F2–F3), but not mild (F1) fibrosis. Elastogram of 7 kPa is more accurate than 8.8 kPa in diagnosis of moderate fibrosis (F2). Responders showed significant decline in their fibroscan scores compared to non-responders of same fibrosis degree. Besides its accuracy as noninvasive device in detecting degree of fibrosis, fibroscan can be very useful in assessment of degree of fibrosis during and after therapy.

Conflict of interest

The authors declared that there is no conflict of interest.

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