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Impact of Liver Stiffness on Hepatitis C Virus Relapse after Treatment with Direct Acting Antiviral Drugs

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ABSTRACT
Background: Unexplained hepatitis C virus (HCV) relapse after treatment by DAAs (sofosbuvir and daclatasvir) is due to several factors, one of them is liver stiffness. We studied this factor trying to avoid relapse of HCV after treatment in the future and assess the treatment role on liver stiffness regression.
Aim: Prevention of HCV relapse after treatment by direct acting antiviral drugs.
Patients and methods: This cohort research was conducted at Alahrar Teaching Hospital (Zagazig City, Sharkia Governorate). Patients with age > 18 years old with HCV infection (diagnosed by HCV PCR), after received treatment (relapsers) by (sofosbuvir and daclatasvir) were included in the study. All cases underwent full history taking, laboratory investigations, thorough physical examination and liver fibrosis evaluation by fibroscan.
Results: Liver stiffness measurement (LSM), fibrosis 4 (FIB 4), and AST to Platelet Ratio Index (APRI) scores were significantly different between SVR and non-SVR groups before and after treatment. **Conclusion:** Improved liver fibrosis measures (LSM, FIB 4, and APRI scores) are associated with the successful treatment of chronic HCV with novel direct-acting antivirals. In addition, elevated LSM prior to therapy can be predictive of non-response.
Keywords: Liver stiffness, HCV, Relapse, Direct acting antiviral drugs.

INTRODUCTION

Infection with the Hepatitis C virus (HCV) is one of the primary global causes of chronic liver disease. The estimated number of chronically infected individuals globally is roughly 180 million, although the majority are ignorant of their affliction **[1,2].**

It is considered a significant endemic health issue in Egypt. 14.7 % of the Egyptian population have been infected based on an Egyptian demographic health survey performed in 2008 **[3].**

HCV treatment has evolved recently with the direct acting antiviral (DAA) therapies development, that have been introduced into the clinical practice in 2014/2015. They predicted a potential future for HCV treatment and few adverse effects from therapy [4].

By using usual regimens of (sofosbuvir and daclatasvir) there was about 96% of patients have SVR and only about 4% have been relapsed [5]**.** For decades, reversal of liver fibrosis has been the focus of research and discussion among liver specialists. Recent studies have demonstrated the incidence of fibrosis regression in a wide array of chronic liver disorders, including chronic viral hepatitis **[6].** Numerous research demonstrated that liver fibrosis regression in chronic hepatitis C (CHC) patients treated with effective antiviral agents could be accomplished by slowing the progression in relapsers and by necroinflammation enhancement and damage mitigation in sustained responders **[7].**

Guidelines for CHC treatment recommend liver fibrosis assessment, which assists in treatment alternatives selection and appropriate length [8]**.** Even in patients with severe fibrosis and cirrhosis, fibrosis regression is associated with sustained virological response **[9].** Currently, in HCV patients, transient elastography (TE) is a validated, non-invasive approach for hepatic fibrosis evaluation, offering the benefits of high accuracy and reproducibility **[6].** Several noninvasive laboratory techniques, involving APRI and FIB-4, have been shown to be accurate in chronic liver disease staging prior to antiviral therapy and hepatic fibrosis prediction in HCV patients **[10].**

The aim of the study to prevent HCV relapse after treatment by direct acting antiviral drugs.

PATIENTS AND METHODS

This cohort research was performed at Alahrar Teaching Hospital (Zagazig City, Sharkia Governorate) during the period from April 2021 to April 2022 and involved patients with age > 18 years old with HCV infection (diagnosed by HCV PCR), after received treatment (relapsers) by (sofosbuvir and daclatasvir).

The exclusion criteria were patients with age < 18 years old, achieved sustained virological response (SVR) following treatment, with renal impairment, with HIV, with combined HBV and HCV with decompensated liver cell failure, complicated by hepatocellular carcinoma (HCC) or portal vein thrombosis.

All cases underwent full history taking, thorough physical evaluation, laboratory investigations (CBC, serum creatinine, prothrombin time (PT), INR, serum albumin, total and direct serum bilirubin, ALT, AST, random blood sugar, HbA1 C, hepatitis B surface antigen (HBsAg), anti-HCV and serum alpha fetoprotein).

Estimation of liver fibrosis by fibroscan:-

It was done for all patients and was repeated after treatment in patients with f3 and f4. The Fibroscan device (Echosens) was used to assess liver stiffness, it acts by

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shear wave velocity measuring. In this method, a small transducer on the end of an ultrasound probe transmitted a 50-MHz wave into the liver. The transducer can evaluate the shear wave velocity (m/s) while that wave crossing the liver. The shear wave velocity can then be changed into liver stiffness, that was measured in kilopascals. In essence, the technology measured the sound wave velocity travelling through the liver and then changed that measurement into a liver stiffness measurement; the whole process was commonly known as liver ultrasonographicelastography.

Ethical considerations:

Tha researh was approved by Institutional Review Board (IRP) Zagazig University. All the participants gave their written consent after being fully provided with all the necessary information regarding the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

SPSS v.20 (Armonk, NY: IBM Corp) was utilized for data analysis. Student t-test, Mann Whitney test and chi-square tests were utilized. Chi-square test, student t-test and Mann Whitney test were used.

RESULTS

The basic characteristics of the studied patients are shown in table 1.

Table (1): Baseline characteristics of the studied sample

	Number	Percent
Age (years)		
Range	43-70	
Mean±S.D.	57.97±7.423	
Gender		
Male	62	62.0
Female	38	38.0
BMI		
Range	22.40-33.10	
Mean±S.D.	26.65±2.902	
Medical Comorbidity		
HTN	18	18.0
DM	28	28.0
Cirrhosis	22	22%
Splenomegaly	27	27%
	Mean ± SD	
PV diameter (mm).	9.60±2.238	
Pulse	78.10±8.482	
SBP	122.79±16.220	
DBP	79.89±11.110	

As shown in table 2, platelets, RBS, AFP and liver enzymes (ALT, AST, ALP) were significantly different between before and after treatment, while other laboratory tests were insignificantly different after treatment.

Table (2): Comparison of laboratory tests between before and after treatment

	Before	After	P value
Hb	11.96±1.432	11.99±1.486	0.900
WBCs	5.31±1.381	5.46±1.451	0.451
Platelet	158.86± 38.067	177.27± 41.623	<0.001 *
ALT	60.11± 15.677	33.82± 15.668	<0.001 *
AST	63.65± 16.917	34.20± 14.134	<0.001 *
Albumin	3.63±0.580	3.63±0.566	0.998
Bilirubin	0.84±0.252	0.84±0.253	0.962
Direct Bilirubin	0.19±0.084	0.20±0.110	0.736
Indirect Bilirubin	0.65±0.205	0.65±0.188	1
ALP	101.12± 22.955	94.66± 23.811	<0.001 *
Prothrombin time	12.06± 0.941	12.20± 0.964	0.217
INR	1.13±0.074	1.13±0.101	0.537
Serum creatinine	0.95±0.182	0.92±0.180	0.184
Urea	22.18±8.818	22.75±9.751	0.676
RBS	168.66± 74.426	136.95± 37.492	<0.001 *
AFP	6.18±1.961	5.23±1.725	<0.001 *

*: Significant

As shown in table 3, 91.0% of studied patients achieved SVR.

Table (3): Distribution of studied sample according to SVR

SVR	Number	Percent
No	9	9.0
Yes	91	91.0
Total	100	100

SVR = sustained virologic response.

As shown in table 4, in all patients, LSM, FIB 4, and APRI were significantly decreased after treatment compared to before treatment.

Table (4): Comparison of LSM, FIB 4 and APRI scores between before and after treatment

	Before	After	P value
LSM			
Range	2.1-24.5	2.1-25.1	<0.001 *
Mean ±S.D.	10.28±5.881	8.97±5.535	
FIB 4	**Before**	**After**	**P value**
Range	1.31-7.52	0.82-5.34	<0.001 *
Mean ±S.D.	3.26±1.344	2.13±1.042	
APRI			
Range	0.40-2.45	0.20-2.12	<0.001 *
Mean ± S.D.	1.08±0.446	0.55±0.399	

LSM = liver stiffness measurement, *: Significant.

As shown in table 5, age, gender, BMI and medical hypertension were insignificantly different between who achieved SVR and patients who did not. Meanwhile, diabetes frequency was significantly higher in patients who achieved SVR than who did not. Frequency of liver cirrhosis and splenomegaly in PAUS were significantly higher in cases who did not achieve SVR than who were successfully treated, while PV diameter was comparable between both groups.

Table (5): Relation between response to treatment and the baseline data of studied patients

	SVR				P value
	No (n = 9)		Yes (n = 91)		
	No.	%	No.	%	
Age (**Mean ±S.D)**	57.00±8.631		58.07±7.341		0.713
BMI (Mean ±S.D)	27.46±2.516		26.57±2.937		0.386
Gender (Male)	5	55.6	57	62.6	0.055
Medical Comorbidity					
HTN	3	33.3	15	16.5	0.209
DM	6	66.7	22	24.2	0.007*
Cirrhosis					
No	2	22.2	76	83.5	<0.001*
Yes	7	77.8	15	16.5	
PV diameter					
Range	10-14		7-14		0.386
Mean± S.D.	12.89±1.364		9.27±2.039		
Splenomegaly					
No	1	11.1	72	79.1	<0.001*
Yes	8	88.9	19	20.9	

SVR = sustained virologic response, *: Significant.

Hb, platelets, ALT, AST, Albumin, prothrombin time, RBS, and AFP before and after treatment, and bilirubin, direct bilirubin, indirect bilirubin and alkaline phosphatase after treatment were significantly different between SVR and non-SVR groups. WBCs and INR were insignificantly different. SVR group showed significant improvement in platelets, ALT, AST, ALP, RS and AFP while non-SVR group showed no change in mostly all lab results except for slight improvement in platelets and RBS and significant worsening in ALP (Table 6).

Table (6): Relation between SVR and all laboratory tests

		SVR		P value
		No (n = 9)	Yes (n = 91)	
Hb	Before	10.78±1.131	12.1±1.408	0.003*
	After	10.73±1.042	12.12±1.469	0.011*
	P value	0.799	0.932	
WBCs	Before	5.57±1.552	5.28±1.37	0.608
	After	5.27±1.74	5.48±1.429	0.555
	P value	0.374	0.284	
Platelet	Before	113.11±13.29	163.38±36.719	<0.001*
	After	103.67±14.283	184.55±35.948	<0.001*
	P value	0.011*	<0.001*	
ALT	Before	80.11±12.129	58.13±4.605	<0.001*
	After	78.33±11.079	29.42±6.433	<0.001*
	P value	0.477	<0.001*	
AST	Before	73±9.381	62.73±7.244	0.045*
	After	74±9.028	30.36±6.86	<0.001*
	P value	0.953	<0.001*	
Albumin	Before	3.06±0.159	3.69±0.576	0.002*
	After	3.12±0.113	3.69±0.562	0.003*
	P value	0.928	0.986	
Bilirubin	Before	0.92±0.253	0.84±0.252	0.317
	After	1.05±0.152	0.82±0.252	0.010*
	P value	0.200	0.472	
Direct Bilirubin	Before	0.2±0.087	0.19±0.085	0.617
	After	0.26±0.053	0.19±0.013	0.013*
	P value	0.059	0.816	
Alkaline phosphatase	Before	112.44±23.346	100±22.739	0.132
	After	119.67±20.688	92.19±22.736	0.002*
	P value	0.050*	<0.001*	
PT	Before	13.44±0.527	11.92±0.859	<0.001*
	After	13.56±0.527	12.07±0.892	<0.001*
	P value	0.655	0.233	
INR	Before	1.14±0.054	1.12±0.076	0.708
	After	1.13±0.158	1.13±0.095	0.510
	P value	0.575	0.721	
AFP	Before	8.22±2.15	5.98±1.833	0.003*
	After	7.49±1.729	5.01±1.564	<0.001*
	P value	0.092	<0.001*	
RBS	Before	256.67±106.351	159.96±65.089	0.017*
	After	195±57.075	131.21±29.772	0.003*
	P value	0.021*	<0.001*	

SVR = sustained virologic response, *: Significant.

LSM, FIB 4, and APRI scores before and after treatment were significantly different between SVR and non-SVR groups. Also, SVR group showed significant difference in the same parameters before and after treatment while non-SVR group showed no difference in FIB 4 and APRI, while LSM was significantly increased (Table 7).

Table (7): Relation between SVR and LSM, FIB4, and APRI

		SVR		P value
		No (n = 9)	Yes (n = 91)	
LSM	Before	18.24±5.262	9.5±5.349	<0.001*
	After	19.76±5.294	7.91±4.293	<0.001*
	P value	**0.011***	**<0.001***	
FIB 4	Before	4.16±0.544	3.17±1.368	0.002*
	After	4.58±0.454	1.89±0.72	<0.001*
	P value	0.086	<0.001*	
APRI	Before	1.58±0.185	1.03±0.433	<0.001*
	After	1.73±0.194	0.43±0.135	<0.001*
	P value	0.058	<0.001*	

SVR = sustained virologic response LSM= liver stiffness measurement, *: Significant.

ROC curve analysis to predict response for treatment according to LSM showed that at cut off value of ≤9.6 it can predict treatment response with sensitivity and specificity of 63.7% and 100% respectively (Table 8).

Table (8): ROC curve analysis to predict SVR according to LSM

	Cut off value	Sensitivity	Specificity	PPV	NPV	AUC	P value
LSM	≤9.6	63.7	100	100	21.4	0.875	<0.001*

AUC= area under curve, PPV=positive predictive value, NPV= negative predictive value, LSM= liver stiffness measurement, *: Significant.

DISCUSSION

This is, to our knowledge, one of the first studies assessing the changes in liver stiffness measurement as measured by TE and fibrosis scores (FIB-4 and APRI) after retreatment of relapsed individuals (presented with compensated cirrhosis who did not achieve SVR after DAAs therapy). Limited research of HCV recurrence has clarified the changes in liver stiffness measurement by TE as well as ARFI elastography and fibrosis scores following DAAs therapy; nevertheless, liver transplantation recipients with HCV recurrence have demonstrated these alterations [11].

In the current research, the mean participants' age was 57.97 years with male predominance (62.0%), this was in consistent with **Ghweil *et al.*** [12] who demonstrated a male predominance (69%) and the mean age of their patients was 45±12 years. Also, male predominance (64.4%) was reported by **Elsharkawy *et al.*** [13] and the mean age of studied cases was 50.8 ± 11.3 years. In contrast other recent studies reported female predominance in their studied cohort [14,15].

In our study 18 (18.0%) had hypertension and 28 (28.0%) had DM as medical comorbidity with mean BMI of 26.65±2.902 kg/m^2. Similarly, hypertension in 13.6% of patients and DM was found in 27.1% in a study conducted by **Agwa *et al.*** [14]. Also, **Petta *et al.*** [16] found that 41.8% were hypertensive and 20% of patients were diabetics.

In the present study all of the included patients showed relapse after treatment of HCV treatment by SOF/DAC regimen; none of them showed any signs of cellular or vascular decompensation and ultrasound for all patients showed that 22 patients had cirrhosis, 27 had splenomegaly. PV diameter was with mean value of 9.60±2.238 mm. The primary objectives of CHC treatment with DAAs are to increase SVR rates and liver function enhancement. SVR results in the resolution of liver inflammation, which minimizes the risk of liver fibrosis and associated consequences as HCC, variceal hemorrhage and hepatic decompensation [17,18].

In the present study after retreatment by DAAs our results showed that 91(91.0%) of studied patients achieved SVR. Furthermore, there was marked improvement in liver enzymes (ALT, AST, ALP), platelets, RBS, and AFP as platelets, RBS, AFP and liver enzymes (ALT, AST, ALP) were significantly different between before and after treatment (p<0.001), while other laboratory tests were insignificantly different after treatment. In accordance with our result, **Ghweil *et al.*** [12] reported that all patients were responsive at the end of treatment, and 12 weeks after the end of treatment, 94% of patients attained SVR whereas 6% of patients relapsed. There was considerable improvement in platelets count, ALT, AST, APRI and serum fibronectin level from baseline to SVR 12 with significant difference in noncirrhotic patients and at SVR 12 (p<0.001).

In accordance with **Rusman *et al.*** [19] study who reported that, 12 weeks after DAAs therapy, 90.7% (78/86) of patients had undetectable HCV-RNA. These findings indicate that the SVR12 for CHC in patients treated with DAAs can exceed 90%. Multiple studies demonstrate a high SVR12 with DAA therapy. The SVR12 reached 100% in **Pott-Junior *et al.*** [20] study on 65 cases receiving daclatasvir and sofosbuvir therapy, additionally, there was a 98% SVR12 with sofosbuvir and daclatasvir in **Charatcharoenwitthaya *et al.*** [21] study. Similarly, the SVR12 ranged from 89–97% of genotypes 1–4 in CHC patients treated with sofosbuvir and daclatasvir as was reported by **Zoratti *et al.*** [22] in their metanalysis.

In the present study SVR group showed significant improvement in platelets, ALT, AST, ALP, RBS and AFP while non-SVR group showed no change in mostly all lab results except for slight improvement in platelets and RBS and significant worsening in ALP. This is in agreement with **Miyaki *et al.*** [23] who examined 30 chronic HCV patients, 26 achieved SVR and 4 did not, and reported that only in SVR patients, serum liver fibrosis indicators, AFP, ALT and albumin were significantly improved with DAA therapy.

In agreement with our findings, **Elsharkawy *et al.*** [13] reported that all patients in their study, cirrhotic or not, exhibited a significant decrease in ALT and AST, as well as a significant improvement in platelet count in cirrhotic patients compared to baseline SVR12 among naive patients and those who had previously received antiviral therapy.

Our findings demonstrated significant differences in age, gender, BMI, or medical hypertension between individuals who achieved SVR and those who did not. This is in accordance with **Rusman *et al.*** [19] whose gender correlation analysis in their study revealed insignificant association between men and women. In contrast to gender-dependent interferon therapy, DAA therapy is still very effective in both genders. In the period of interferon, there were disparities in virological responses between males and females due to hormonal activity particularly estrogen levels and faster viral clearance in females than in males can lessen this gap. Then, in the present DAA era, this discrepancy is diminishing, likely as a result of superior antivirus efficacy, which is able to reduce this difference [24,25]**.**

In the current investigation, the proportion of diabetic patients who obtained SVR was considerably higher than that of those who did not, and there was no association between BMI and virological response. **Rusman *et al.*** [19] also demonstrated that there is insignificant association between BMI and virological response; nevertheless, 75 % of the participants who did not attain SVR12 were obese or overweight. This is believed to be a result of the insulin resistance observed in obese and diabetic people. In addition, certain comorbidities (as diabetes) appear to directly influence viral clearance rates [26,27]**.**

In the current research, LSM was significantly decreased after treatment compared to before treatment (8.97±5.535 vs. 10.28±5.881, P<0.001). LSM improves early after therapy (12 weeks after EOT), regardless of treatment outcome, because a transient reduction in viral replication may be sufficient to lower LSM. This early reduction in LSM following treatment with DAAs is disputed, as it may indicate a real improvement in liver fibrosis or a reduction in liver inflammation due to antiviral medication; however, the effect of inflammation on LSM is debatable. Some studies suggested that LSM increased with increasing hepatic necroinflammatory activity and that the resolution of liver necroinflammatory activity was associated with normalization of transaminases after antiviral treatment [28, 29]**.** While other research found that LSM wasn't affected by inflammatory activity [30,31].

Our data revealed that LSM was significantly increased in non-SVR group than SVR group. In accordance with our findings, **Bachofner *et al.*** [32] reported considerable regression of TE values in patients with SVR after DAA therapy. In the study by **Agwa *et al.*** [14], 42.7% of F4-treated patients showed improvement and were reclassified as 220 F1, 90 F2 and 190 F3. In addition, 40 of 60 F3 patients improved, becoming 10 F2 and 30 F1. 28.4% of the treated patients underwent a transition to non-significant fibrosis (F2) from substantial fibrosis (≥F3) following treatment.

In line with our findings, **Elsharkawy *et al.*** [13] observed that in terms of LSM, 29.1% had non-significant fibrosis, 17.2% had mild to substantial fibrosis, 8.6% had advanced fibrosis and 45.1% of the examined population had cirrhosis. Their investigation revealed a significant drop in LSM 12 weeks after EOT.

In the current research, SVR was related with a decrease in fibrosis indices, since FIB-4 and APRI scores before and after treatment were significantly different between SVR and non-SVR groups. After treatment, the non-SVR group exhibited no difference in FIB 4, APRI. According to **Abdelkader *et al.*** [33], the non-invasive fibrosis serum biomarker APRI reduced significantly in both research groups, and a significant decrease of Fib4 was observed in advanced stages. They found that the percent of change of Fib4 is correlated with AST and the percent of change of APRI is correlated with that of AST and ALT; consequently, this improvement of serum biomarkers may be due to normalization of liver enzymes alone and may not represent fibrosis regression, particularly since the percent of change of liver stiffness is not correlated with that of liver enzymes, APRI, or Fib4. Therefore, the authors suggested that TE is a more trustworthy approach for detecting substantial fibrosis in

the setting of post-HCV treatment follow-up since it is not impacted by changes in liver enzymes. In addition, high pre-treatment LSM scores are likely to continue following therapy, even if a reduction was achieved.

In addition, **Bachofner *et al.*** [32] published comparable findings, revealing that APRI and FIB-4 are verified fibrosis scores. Similarly, to TE values, these fibrosis scores decreased substantially within weeks of HCV elimination. The drop was only significant in individuals who achieved SVR, while SVR was not a condition for reduced APRI and FIB-4 scores 12 weeks following treatment.

Our finding revealed that LSM can significantly predict the treatment response at cut off value of ≤9.6 Kpa with 63.7% sensitivity and 100% specificity. Because of the excellent response rates of DAA-based regimens, few investigations have reported the effect of liver stiffness (LS) on DAA regimen relapse rates. Based on our findings, high LS was able to predict recurrence among DAA-treated patients at cutoff value of 9.6 Kpa, corroborating **Neukam *et al*.** [34] assertion that the degree of LS influences the relapse rate to DAA-based therapy in clinical practice. Although, in the study by **Neukam *et al.*** [34] LS values greater than 2.1 kPa were related with relapse, that can be attributed to the large number of cirrhotic patients enrolled in the research.

CONCLUSION

Successful treatment of chronic HCV with novel DAAS is associated with improvements in liver fibrosis indices (LSM, FIB4, APRI scores). In addition, elevated LSM prior to therapy may be predictive of non-response.

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