ORIGINAL PAPER

Surg. Gastroenterol. Oncol. 2023, vol. 28, eCollection March 31 DOI: 10.21614/sgo-eC-397

DAADs Improve Liver Fibrosis, Myth or Truth?

Abdel Naser Abdel Atty Gadallah[1]*, Elsayed Ibrahim Elshayeb[1], Shimaa El-Shafey Soliman[2], Muhammad Elsayid Ahmad Abulfadl[1], Ahmed Ezz El-Arab Abd El-Alim[1]

[1]Internal medicine department, faculty of medicine, Menoufia University, Shebeen Elkom, Menoufia, Egypt
[2]Medical Biochemistry and Molecular Biology, Menoufia University, Shebeen Elkom, Menoufia, Egypt

***Corresponding author:**
Abdel Naser Abdel Atty Gadallah, MD
Menouf, Menoufia, Egypt
Telephone: +2-01005207873
E-mail: ahmed_Naser2004@yahoo.com

ABSTRACT

Background: Hepatitis C is a worldwide problem. The hepatitis C virus (HCV) is a major cause of both acute and chronic hepatitis. The World Health Organization (WHO) estimates about 71 million people globally have chronic hepatitis C accounting for 1% of the population.
Objectives: This study aims to investigate the response of liver fibrosis to direct-acting antiviral drugs (DAADs) used in the treatment of chronic hepatitis C infection in different stages of fibrosis regarding several non-invasive biochemical markers.
Methods: This retrospective study was conducted on Five hundred and twelve patients were enrolled in this study.
Results: Patients with significant liver fibrosis had regressions in liver fibrosis regarding FIB-4, APRI, and King's score. The only liver fibrosis worsening, within this group of patients, was noted in Lok index values that increased from 0.35±0.01 to 0.39±0.2 in patients with significant P-value. Patients with no cirrhosis showed a statistically significant decrease in liver fibrosis values regarding APRI, GUCI, and King's score. On the other hand, there were mild increases in the Lok index and API values. FIB-4 and CDS had no statistically significant changes.
Conclusion: Reversal of liver fibrosis was achieved in a significant number of patients who received direct antiviral agents
Key words: Direct-acting antiviral drugs, Hepatitis C, Liver fibrosis

INTRODUCTION

Hepatitis C is a worldwide problem. The hepatitis C virus (HCV) is a major cause of both acute and chronic hepatitis. The World Health Organization (WHO) estimates about 71 million people globally have chronic hepatitis C accounting for 1% of the population. There are still 1.75 million new HCV infections (global incidence rate: 23.7 per 100 000) with approximately 399,000 dying from this infection primarily due to cirrhosis and hepatocellular carcinoma (HCC) (1).

Previously pegylated interferon was the main treatment for HCV with unsatisfying results. The development of direct-acting antiviral agents (DAA)

Received: 29.09.2022
Accepted: 18.11.2022

against HCV was a revolutionary step in the management of chronic hepatitis C (2,3).

In Egypt, sofosbuvir-based regimens are the cornerstone for the management of HCV. Sofosbuvir 400 mg plus daclatasvir 60 mg ± weight-based ribavirin doses are the most widely used protocol of HCV treatment in Egypt.

HCV nonstructural protein 5A (NS5A) is inhibited by daclatasvir, and HCV ribonucleic acid (RNA) polymerase (nonstructural protein 5B (NS5B) is inhibited by sofosbuvir, two proteins that play critical roles in HCV RNA replication (4).

Liver fibrosis assessment for patients with HCV is a must due to the fact that 5 -20% of patients with HCV develop liver cirrhosis (5). Also, diagnosis of the stage of liver fibrosis is essential for making a prognosis regarding the development of cirrhosis and hepatocellular carcinoma; and deciding on antiviral therapy and follow-up both during treatment and after cessation of treatment (6).

Extracellular matrix (ECM) proteins, such as collagen, accumulate excessively in the liver, causing fibrosis. Transforming growth factor (TGF)-β, the most potent fibrogenic cytokine, is produced in its high molecular weight latent form and partly activated through the proteolytic cleavage of its propeptide region, termed latency-associated protein (LAP), by serine proteases, plasmin, and plasma kallikrein (7).

Although liver biopsy is still considered as the gold standard for identifying liver histological stages, an assessment of the disease development based on non-invasive clinical findings is an acceptable method for assessment of liver fibrosis degree due to their clinical and economic advantages as they are much less costly with much fewer complications (8).

To estimate fibrosis and detect cirrhosis, simple laboratory tests such as albumin, total bilirubin, platelet count, prothrombin time, and serum aminotransferase levels are often used. The degree of hepatic fibrosis has been estimated using various combinations of these measurements (9).

Aim of work

This study aims to look at how liver fibrosis responds to direct-acting antiviral medications used to treat chronic hepatitis C infection in different stages of fibrosis regarding several non-invasive biochemical markers.

PATIENTS AND METHODS

This is a retrospective study conducted on 512 chronic HCV patients at Menoufia University Outpatients Clinic over the period from March 2019 to December 2019. The study was approved by the Ethical Committee of Faculty of Medicine, Menoufia University.

Inclusion criteria

Age above 18 years old, Patients with chronic hepatitis C virus infection, Positive PCR for HCV RNA.

Exclusion criteria

Patients who received DAAs treatment and failed to achieve 12 weeks sustained virological response. Patients with non-HCV-related causes for liver disease. Pregnant or breastfeeding females. Patients who are ineligible for available treatment of hepatitis C.

Patient classifications

Patients were divided according to their laboratory findings and therapeutic protocols into two groups: 1- Dual therapy group who were classified as “easy to treat group”. This group received sofosbuvir 400 mg plus daclatasvir 60 mg once daily for 12 weeks. 2- Triple therapy group who were classified as “hard to treat group”. This group received sofosbuvir 400 mg plus daclatasvir 60 mg once daily plus ribavirin 600-1200 mg daily for 12 weeks.

Patients were divided according to fibrosis scores as follows (9,10,11): a) No cirrhosis or significant fibrosis: Aspartate aminotransferase-to-platelet ratio index (APRI)less than or equal to 0.5, Fibrosis-4(FIB-4)score less than 1.45, Lok index less than 0.2, King’s score less than or equal to 12.2, Göteborg university cirrhosis index(GUCI)scores less than 1, Age-platelet (AP) index less than 6. Cirrhosis discriminant score (CDS) less than 8. b) Significant fibrosis level: APRI more than 0.5 and less than or equal to 2, FIB-4 more than or equal to 1.45 and less than or equal to 3.25, Lok index more than or equal to 0.2 and less than 0.5, King’s score more than 12.2 and less than or equal to 16.6. c) Cirrhosis or significant fibrosis: APRI more than 2, FIB-4 more than 3.25, Lok index more than or equal to 0.5, King’s score more than 16.6, CUGI score more than or equal to 1, AP index more than or equal to 6, CDS more than or equal to 8.

Statistical analysis

The data were collected, tabulated, and analyzed by

SPSS (statistical package for social science) version 17.0 on IBM compatible computer (SPSS Inc., Chicago, IL, USA). A P-value of <0.05 was considered statistically significant.

RESULTS

The mean age and gender percentages. The age varied from 19 to 89 years old with mean age 51.7 ± 14.6. The triple therapy group of patients was older than the dual therapy group of patients with mean ages 56.11±13.81 and 50.78±14.58 respectively. Female patients were 334 representing 65.3% of total studied cases, 282 (66.7%) of the dual therapy group, and 52 (58.9%) of the triple therapy group with no statistically significant difference between groups of patients (*table 1*).

AST, ALT, Bilirubin showed a highly statistically significant increase after treatment when compared to before treatment levels P-value < 0.001. Hemoglobin (Hb) showed a highly statistically significant decrease after treatment when compared to before treatment levels P-value < 0.001. INR showed a highly statistically significant decrease after treatment when compared to before treatment levels P-value < 0.001 (*table 2*).

FIB-4, APRI, GUCI, King's score showed highly significant regression after treatment when compared to before treatment levels P-value <0.001 (*table 2*).

Regarding FIB-4 scoring system prevalence of patients with cirrhosis was statistically lower after treatment (N=29, 5.7%) when compared to before treatment (N=59, 11.5%). Also, the prevalence of significant fibrosis was lower after treatment (N=154, 30.1%) when compared to before treatment (N=205, 40.0%). Prevalence of patients with no fibrosis or cirrhosis was statistically higher after treatment (N=329, 64.3%) when compared to before treatment (N=248, 48.5%), P-value <0.001 (*table 3*).

Regarding APRI prevalence of patients with cirrhosis was statistically lower after treatment (N=3, 0.6%) *(table 3)*.

Regarding GUCI prevalence of patients with cirrhosis was statistically lower after treatment (N=17, 3.3%). Regarding King's scoring system prevalence of cirrhotic patients were statistically lower after treatment (N=30, 5.9%) (*table 3*).

Four hundred twenty-three patients received a dual therapy regimen resembling 82.6% of total patients' count while 89 patients received triple therapy regimen resembling 17.4% of total patients' count (*fig. 1*).

FIB-4, APRI, GUCI, King's score showed highly significant regression after treatment when compared to before treatment levels, P-value <0.001 (*table 4*).

FIB-4 score, APRI, Lok index, GUCI, King's score, and CDS showed highly significant regression after treatment when compared to before treatment P-value <0.001. API showed significant regression after when compared to before treatment levels P-value 0.03 (*table 5*).

Regarding FIB-4 scoring system, patients who were sorted as cirrhotic patients (n=59, 11.5%) showed marked regression in the degree of fibrosis after treatment in comparison to before treatment, P-value <0.001. Also, patients with significant fibrosis showed regression in the degree of fibrosis after treatment in comparison to before treatment, P-value <0.001 (*table 6*).

Regarding API, non-cirrhotic patients showed an increase degree of fibrosis after treatment in comparison to before treatment, P-value 0.01. Cirrhotic patients showed no statistically significant relation between before and after treatment regarding API with P-value 0.37. Regarding CDS, patients showed no statistically significant relation between before and after treatment with P-value 0.51 for non-cirrhotic patients and 0.06 for cirrhotic patients (*table 6*).

DISCUSSION

The World Health Organisation (WHO) has called for the elimination of hepatitis C virus (HCV) infection by 2030 (12). HCV prevalence in Egypt was known to be

Table 1 - Age and sex among the studied cases

	Treatment modalities			Test	P-value
	Dual therapy N = 423	Triple therapy N = 89	Total N = 512		
Age (years)				t-test	
Mean ±SD	50.78±14.58	56.11±13.81	51.71±14.56	3.17	0.002
Range	19 – 89	25 – 88	19 – 89		
Sex				χ^2	
Male	141 (33.3%)	37 (41.1%)	178 (34.7%)	1.98	0.16
Female	282 (66.7%)	52 (58.9%)	334 (65.3%)		

Table 2 - Statistical comparison between studied patients before and after treatment regarding laboratory tests

	The studied patients		Test	P-value
	Before treatment	After treatment		
ALT (IU/L)			W	
Mean ± SD	21.83±9.26	49.53±36.46	17.65	<0.001
Range	2 – 115	4 – 421		
AST (IU/L)			W	
Mean ± SD	24.83±9.09	46.82±28.94	17.44	<0.001
Range	4 – 78	2 – 378		
Total bilirubin (mg/dl)			W	
Mean ± SD	0.54±0.35	0.69±0.28	12.16	<0.001
Range	0.11 – 4.2	0.1 – 3.4		
Albumin (g/dl)			Paired t	
Mean ± SD	4.31±0.46	4.03±0.53	9.53	<0.001
Range	2.9 – 5.5	2.07 – 5.3		
Creatinine (mg/dl)			Paired t	
Mean ±SD	0.93±0.28	0.91±0.21	2.04	0.04
Range	0.2 – 2.04	0.31 – 1.82		
Hb (g/dl)			Paired t	
Mean ±SD	13.62±1.53	12.76±1.5	15.12	<0.001
Range	7.9 – 17.5	7.4 – 17.2		
Total leucocytes (10^3/mm^3)			Paired t	
Mean ±SD	7.21±2.38	7.0±2.18	2.1	0.037
Range	2.9 – 19.8	2.5 – 18.6		
Platelets (10^9/L)			W	
Mean ±SD	224.71±76.31	218.76±66.65	1.78	0.08
Range	60 – 591	37 – 499		
INR			Paired t	
Mean ±SD	1.15±0.18	1.09±0.17	5.55	<0.001
Range	0.96 – 2.7	0.88 – 3.27		
FIB-4			W	
Mean ±SD	1.87±1.37	1.50±1.08	8.57	<0.001
Range	0.10 – 11.83	0.11 – 8.09		
APRI				
Mean ±SD	0.62±0.50	0.35±0.36	14.83	<0.001
Range	0.03 – 5.43	0.03 – 5.0		
Lok index				
Mean ±SD	0.45±0.23	0.43±0.21	1.64	0.10
Range	0.03 – 1	0.03 – 1		
GUCI				
Mean ±SD	0.70±0.53	0.41±0.36	13.89	<0.001
Range	0.05 – 4.41	0.05 – 4.17		
King's score				
Mean ±SD	15.33±18.85	8.81±21.06	15.14	<0.001
Range	0.34 – 322.6	0.35 – 321.5		
CDS				
Mean ±SD	4.82±1.57	4.75±1.37	1.07	0.29
Range	0 – 9	0 – 9		
API				
Mean ±SD	4.12±2.36	4.06±2.32	0.83	0.41
Range	0 – 10	0 – 10		

the highest among all countries that were mainly due to mass schistosomiasis treatment campaigns and reusing non-disposable syringes during the period 1960s through the early 1980s (13). There is a predominance of genotype 4 that represents more than 90 % of all cases (14). A national campaign for HCV elimination took place in Egypt called "100 Million Seha" aimed at the treatment of millions of patients to prevent developing complications as well as preventing further spread of the infection.

Table 3 - Statistical comparison between studied patients before and after treatment regarding the prevalence of cirrhosis

	The studied cases				Test	P-value
	Before treatment		After treatment			
	No	%	No	%	χ^2	
FIB-4						
No fibrosis	248	48.5	329	64.3	28.84	<0.001
Significant fibrosis	205	40.0	154	30.1		
Cirrhosis	59	11.5	29	5.7		
APRI						
No fibrosis	259	50.6	454	88.7	175.61	<0.001
Significant fibrosis	241	47.1	55	10.7		
Cirrhosis	12	2.3	3	0.6		
Lok index						
No fibrosis	81	15.8	82	16.0	4.39	0.11
Significant fibrosis	223	43.6	253	49.4		
Cirrhosis	208	40.6	177	34.6		
GUCI						
No cirrhosis	411	80.3	495	96.7	67.58	<0.001
Cirrhosis	101	19.7	17	3.3		
King's score						
No fibrosis	290	56.6	448	87.5	127.15	<0.001
Significant fibrosis	73	14.3	34	6.6		
Cirrhosis	149	29.1	30	5.9		
CDS						
No cirrhosis	493	96.3	497	97.1	0.49	0.49
Cirrhosis	19	3.7	15	2.9		
API						
No cirrhosis	381	74.4	387	75.6	0.19	0.67
Cirrhosis	131	25.6	125	24.4		

HCV generally and particularly genotype 4 infection is responsible for developing many hepatic and extra-hepatic complications. HCC and liver cirrhosis are considered the most serious hepatic complications (10) (15). The rapidity of fibrosis progression caused by HCV infection widely varies from one patient to another (16).

Before the era of DAAs, there were very limited choices available for HCV treatment. Pegylated interferon-based therapy represented the backbone line of treatment and standard of care at that time. Between 2006 and 2014, a significant national initiative to combat HCV in Egypt did not achieve a durable virological response in more than 60% of patients treated with Pegylated interferon-based therapy (2).

In December 2013, FDA approved sofosbuvir as an oral direct antiviral drug to be used in a combination with other antiviral drugs for the treatment of chronic hepatitis C infection since when SOF-based therapies are the novel standard of care with high anti-viral activity, broad genotypic coverage, and a high barrier to resistance (3).

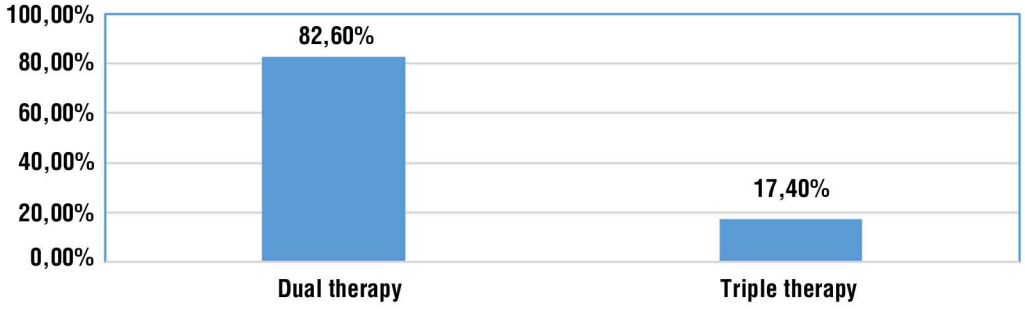

Figure 1 - Frequency of different treatment modalities

Table 4 - Statistical comparison between dual therapy group patients before and after treatment regarding non-invasive liver fibrosis scores

	Dual therapy patients (N= 423)				Test	P-value
	Before treatment		After treatment			
FIB-4					W	
Mean ±SD	1.70±1.18		1.41±0.97		7.28	<0.001
Range	0.10 – 9.91		0.11 – 8.0			
APRI						
Mean ±SD	0.56±0.39		0.34±0.38		13.54	<0.001
Range	0.03 – 3.94		0.03 – 5.0			
Lok index						
Mean ±SD	0.41±0.20		0.42±0.21		0.66	0.51
Range	0.03 – 1		0.03 – 1			
GUCI						
Mean ±SD	0.63±0.45		0.39±0.32		11.99	<0.001
Range	0.05 – 4.41		0.05 – 2.74			
King's score						
Mean ±SD	12.86±10.64		7.91±17.68		13.52	<0.001
Range	0.34 – 91.73		0.35 – 321.5			
CDS						
Mean ±SD	4.58±1.45		4.63±1.33		0.56	0.57
Range	0 – 9		0 – 9			
API						
Mean ±SD	3.78±2.13		3.80±2.20		0.22	0.82
Range	0 – 10		0 – 10			
FIB-4						
No fibrosis	223	52.7	287	67.8	21.46	<0.001
Significant fibrosis	171	40.4	122	28.8		
Cirrhosis	29	6.9	14	3.3		
APRI						
No fibrosis	231	54.6	386	91.3	144.4	<0.001
Significant fibrosis	184	43.5	34	8.0		
Cirrhosis	8	1.9	3	0.7		
Lok index						
No fibrosis	75	17.7	72	17.0	0.38	0.83
Significant fibrosis	208	49.2	217	51.3		
Cirrhosis	140	33.1	134	31.7		
GUCI						
No cirrhosis	362	85.6	411	97.2	36.0	<0.001
Cirrhosis	61	14.4	12	2.8		
King's score						
No fibrosis	259	61.2	385	91.0	104.7	<0.001
Significant fibrosis	68	16.1	21	5.0		
Cirrhosis	96	22.7	17	4.0		
CDS						
No cirrhosis	415	98.1	414	97.9	0.06	0.81
Cirrhosis	8	1.9	9	2.1		
API						
No cirrhosis	336	79.4	338	79.9	0.03	0.86
Cirrhosis	87	20.6	85	20.1		

Developing DAA medications was a great leap in the management of HCV showing very felicitous results in reaching viral clearance and a good chance for patients to achieve SVR. More than 97% and 88% of non-cirrhotic and cirrhotic patients respectively achieved SVR at 12 weeks (17,18).

When given to mono-infected patients with HCV for 12 weeks with or without ribavirin, the combination of daclatasvir and sofosbuvir has been linked to high rates of sustained virologic response and a benign side-effect profile (19-21).

Before starting anti HCV therapy, liver assessment is mandatory for the detection of liver fibrosis, cirrhosis, or HCC. Percutaneous liver biopsy used to be the

Table 5 - Statistical comparison between triple therapy group of patients before and after treatment regarding non-invasive liver fibrosis scores

	Triple therapy patients (N= 89)				Test	P-value
	Before treatment		After treatment			
FIB-4					W	
Mean ±SD	2.72±1.85		1.96±1.40		4.58	<0.001
Range	0.37 – 11.83		0.43 – 8.09			
APRI						
Mean ±SD	0.92±0.77		0.40±0.23		6.70	<0.001
Range	0.09 – 5.43		0.11 – 1.2			
Lok index						
Mean ±SD	0.64±0.24		0.50±0.22		4.33	<0.001
Range	0.03 – 1		0.05 – 0.96			
GUCI						
Mean ±SD	1.07±0.71		0.48±0.48		6.93	<0.001
Range	0.12 – 4.0		0.11 – 4.17			
King's score						
Mean ±SD	27.06±36.77		13.08±32.47		6.71	<0.001
Range	1.4 – 322.6		1.04 – 308.48			
CDS						
Mean ±SD	5.97±1.58		5.31±1.45		3.54	<0.001
Range	1 – 9		2 – 9			
API						
Mean ±SD	5.74±2.69		5.26±2.53		2.18	0.03
Range	1 – 10		1 – 10			
FIB-4						
No fibrosis	25	28.1	42	47.2	9.37	0.009
Significant fibrosis	34	38.2	32	36.0		
Cirrhosis	30	33.7	15	16.9		
APRI						
No fibrosis	28	31.5	68	76.4	37.28	<0.001
Significant fibrosis	57	64.0	21	23.6		
Cirrhosis	4	4.5	0	0.0		
Lok index						
No fibrosis	6	6.7	10	11.2	15.48	<0.001
Significant fibrosis	15	16.9	36	40.4		
Cirrhosis	68	76.4	43	48.3		
GUCI						
No cirrhosis	49	55.1	84	94.4	36.43	<0.001
Cirrhosis	40	44.9	5	5.6		
King's score						
No fibrosis	31	34.8	63	70.8	38.69	<0.001
Significant fibrosis	5	5.6	13	14.6		
Cirrhosis	53	59.6	13	14.6		
CDS						
No cirrhosis	78	87.6	83	93.3	1.63	0.20
Cirrhosis	11	12.4	6	6.7		
API						
No cirrhosis	45	50.6	49	55.1	0.36	0.54
Cirrhosis	44	49.4	40	44.9		

gold standard method for assessment of liver histology and determination of hepatic fibrosis degree. Performing liver biopsy has many drawbacks as it is invasive, costly, requires experienced personnel to perform, and develops many complications including pain, hemorrhage, and hemobilia (22).

In addition to the costs of the therapy, the pre-enrollment investigations add to the financial burden, so the development of non-invasive markers to predict liver fibrosis degree instead of liver biopsy with almost the same accuracy (sensitivity and specificity) was a must (23).

This study aims to look at how liver fibrosis responds to direct-acting antiviral medications used to treat

Table 6 - Progress of cases after treatment in terms of non-invasive fibrosis scales measurements

	N (%)	Before	After	Test	P value
		Mean ±SD	Mean ±SD	W	
FIB-4					
No fibrosis	248 (48.5%)	0.96±0.32	1.01±0.66	0.46	0.64
Significant fibrosis	205 (40.0%)	2.15±0.50	1.81±1.09	4.46	<0.001
Cirrhosis	59 (11.5%)	4.79±1.65	2.52±1.36	6.24	<0.001
APRI					
No fibrosis	259 (50.6%)	0.33±0.09	0.28±0.13	3.06	0.002
Significant fibrosis	241 (47.1%)	0.83±0.31	0.43±0.50	5.97	<0.001
Cirrhosis	12 (2.3%)	2.79±1.02	0.47±0.21	13.8	<0.001
Lok index					
No fibrosis	81 (15.8%)	0.13±0.05	0.35±0.18	7.24	<0.001
Significant fibrosis	223 (43.6%)	0.35±.008	0.39±0.20	2.65	0.008
Cirrhosis	208 (40.6%)	0.68±0.14	0.50±0.22	8.78	<0.001
GUCI					
No cirrhosis	411 (80.3%)	0.37±0.24	0.26±0.11	10.7	<0.001
Cirrhosis	101 (19.7%)	0.56±0.39	0.37±0.37	8.34	<0.001
King's score					
No fibrosis	290 (56.6%)	7.04±2.75	5.54±8.01	8.66	<0.001
Significant fibrosis	73 (14.3%)	14.16±1.33	12.10±35.5	6.24	<0.001
Cirrhosis	149 (29.1%)	32.03±28.2	13.58±27.3	9.77	<0.001
CDS					
No cirrhosis	493 (96.3%)	4.73±1.5	4.69±1.34	0.67	0.51
Cirrhosis	19 (3.7%)	7.05±1.65	6.10±1.41	1.91	0.06
API					
No cirrhosis	381 (74.4%)	3.09±1.58	3.28±1.85	254	0.01
Cirrhosis	131 (25.6%)	7.14±1.51	6.31±2.07	0.90	0.37

chronic hepatitis C infection in different stages of fibrosis regarding several non-invasive biochemical markers.

The patients were classified according to eligibility for treatment therapy into dual therapy groups who received sofosbuvir/daclatasvir regimen without ribavirin and triple therapy group who receive sofosbuvir /daclatasvir in addition to ribavirin.

In the current study the mean age of patients was above 50 in correspondence to Louie V et al., and Elsharkawy A et al., (24,25). Also, patients who received triple therapy are older than patients who received dual therapy which is against Abdel-Aziz A et al., (26). This difference could be due to the wide difference in the number of studied patients.

By studying the effect of DAAs on biochemical laboratory tests in our study, there was significant regression in AST and ALT. These results were consistent with the previously performed study by Mohamed M et al., on 374 Egyptian patients with HCV infection that revealed significant regression in AST and ALT after receiving a peg-interferon free regimen of sofosbuvir/ daclatasvir ± ribavirin (27). Another study performed by Miyaki E et al. concluded that achieving viral eradication by DAAs could lead to liver function parameters improvement and liver fibrosis markers reductions (28). Also, Lanini S et al. concluded significant improvement of ALT levels in HCV patients after receiving DAAs (29). This could be explained by the removal of irritative factor, HCV, which resulted in decreased hepatic cells damage and release of transaminases.

Regarding our results, there is a mild decrease in albumin levels. This was in contrast to Mohamed M et al., who defined improvement in albumin levels in chronic hepatitis C patients after eradication of HCV using DAAs (27). This could be explained by selection bias as at the time of DAAs initiation it was not possible to treat all patients immediately due to the large amount of HCV infected patients and the decision was made to start with those patients who had advanced liver fibrosis (F3-F4) as recommended by EASL 2014 and AASLD 2015.

In our study, bilirubin levels showed a mild increase while hemoglobin levels showed about 1 g/dl decrease after treatment when compared to baseline laboratory data. These results were consistent with Deterding K et al., (30). Both of these changes could be explained by the fact that ribavirin causes hemolysis which in turn increases bilirubin levels and decrease hemoglobin.

In our study, platelets count showed no statistically significant changes after treatment when compared to

baseline values. This goes against Bruno G et al., findings which looked at the efficacy and safety of a 12-week course of SOF + SMV±RBV in HCV monoinfected and HIV/HCV co-infected people (26). This contrast could be due to the involvement of HIV/HCV co-infected patients in Bruno G et al., study and the fact that HIV affects bone marrow that might result in decreased platelet count at baseline laboratory test.

Non-invasive liver fibrosis parameters depending on biochemical laboratory profile were used and certified as efficient tools for categorizing patients regarding liver fibrosis degrees (31). Gökcan H et al. declared that APRI, FIB-4, King's score, and GUCI can be used to discriminate patients with mild fibrosis with a high negative predictive value and in the differentiation of severe/significant fibrosis from mild to moderate fibrosis (32).

The use of these indices is of benefit as they do not add more cost or burden to the patient's routine workup of the pre-treatment. Further assessment and investigations would be performed for those patients with suspected significant fibrosis or cirrhosis like upper endoscopy as screening for oesophageal varices.

In the present study, assessment of 7 non-invasive liver fibrosis parameters was performed at baseline and at 12 weeks after the end of treatment. These parameters included FIB-4, APRI, Lok index, GUCI, CDS, API, and King's score.

According to our study, the treatment of HCV patients with DAAs resulted in significant regression in liver fibrosis regarding FIB-4, APRI, GUCI, and king's score. On the other hand CDS, API and Lok index revealed no statistically significant relation.

Noting that patients in this study who received triple therapy group showed a statistically significant decrease in all seven non-invasive liver fibrosis parameters and also there were much more regressions in fibrosis markers values in a triple therapy group of patients than in dual therapy one. This could be explained by the potency of the additive effect of ribavirin to the treatment and also the patients who received the triple therapy group had worse baseline laboratory results and liver fibrosis scores than dual therapy one.

The decline in the estimated liver fibrosis assessed by biochemical profile-based fibrosis scores (FIB-4 and APRI) after HCV treatment goes with similar results in a retrospective study performed by Elsharkawy A et al., in 2017 on 337 genotypes 4 HCV infected Egyptian patients (25). Bachofner J et al., also reported a decline in APRI and FIB-4 after treatment of 392 CHC patients (33).

Elsharkawy A et al., 2017 and Bachofner J et al., 2016 studies were among the first studies evaluating the impact of sofosbuvir-based regimens without interferon on the changes of liver fibrosis measurement by transient elastography (TE) and liver biochemical profile based fibrosis scores as determined by FIB-4 and APRI. They reported a significant decline 12 weeks after the end of treatment for liver fibrosis measurements and validated fibrosis scores as FIB-4 and APRI. In analogy to TE measurements, the fibrosis scores APRI and FIB-4 displayed a significant decrease when assessed in all patients undergoing DAAs treatment in Bachonfer J et al., study. The decrease in fibrosis scores reached the significance level of $p < 0.01$ in patients achieving SVR that could explain the role of DAAs in improving liver fibrosis scores in the current study (33).

Thirty genotype 2 HCV infected individuals were included in a trial to evaluate the efficacy of sofosbuvir-based treatment on patients with hepatitis C virus who were treated with a combination of sofosbuvir and NS5A inhibitor treatments. Regardless of treatment methods or degree of liver fibrosis, all patients obtained SVR. The severity of liver fibrosis improved after treatment according to scores APRI (2.27±2.14 vs. 0.89±0.77, P=0.003) and FIB-4 (1.17±1.22 vs. 0.42± 0.25, P 0.013) were both significantly lower than those before treatment (154). Also Tao Y et al., reported significant regression in APRI and FIB-4 score following DAAs used in treatment of recurrent HCV infections in post-liver transplant patients (2.7±0.3 vs. 0.4±0.05, $p<0.0001$) and (4.6±0.5 vs. 2.5±0.2, $p<0.0001$) respectively (155). Another study was conducted on 102 Chinese patients with HCV genotype 3 chronic infections showed significant high efficacy of sofosbuvir-based DAAs in fibrosis remission regarding APRI and FIB-4 scores (34).

These scores are affected by the reduction of AST, ALT, and platelet count denoting significant improvement of liver fibrosis (platelets) and necroinflammation (AST and ALT) following the sofosbuvir-based regiment which was taken by our study population. This early reduction in liver fibrosis measurement following DAAs treatment remains questionable as this reduction represents an actual improvement in liver fibrosis or as a result of a reduction in liver inflammation because of antiviral treatment, however, the influence of inflammation on the liver fibrosis assessment is controversial as reported by Bachofner J et al., and Chekuri S et al., (33,35).

Patients with liver cirrhosis showed marked regression in fibrosis score when compared to patients with no cirrhosis or significant fibrosis regarding FIB-4, APRI, Lok, GUCI, and King's score. This could be due to more suppression of liver enzymes, improvement of platelet

count, and more decrease in INR in this category of patients. Abdel-Aziz A et al. studied DAAs effect on FIB-4 in patients with HCV genotype 4 chronic infections and detected an increase in the percentage of patients with mild fibrosis and a significant decrease in the percentage of patients with severe fibrosis that goes with our results (26).

Studies supporting the benefit of GUCI in determining the severity of fibrosis and predicting the outcome of treatment in chronic hepatitis C were delivered by Westin J et al., in 2008 (31).

Despite their approved capacity for liver fibrosis assessment, CDS, Lok and AP indices are not well investigated as responders to HCV treatment and available data lacks information about the effect of DAAs as well as Peg-interferon as a treatment of HCV chronic infection on CDS, GUCI, Lok and AP indices.

Non-invasive, simple, and easily calculated liver fibrosis parameters can be used as a good predictor of liver fibrosis in a patient with chronic hepatitis C virus infection that can minimize the need for liver biopsy, especially when it is contraindicated or the patient is reluctant to perform it.

The use of these indices is of benefit as they do not add more cost or burden to the patient's routine workup of the pre-treatment. The future combination of the previously mentioned serum non-invasive predictors of fibrosis and the FibroScan may offer better results and performance which needs to be confirmed.

The routine pre-treatment workup of patients with chronic HCV may be helpful to predict fibrosis and also be used as a predictor of response to treatment. Ribavirin included regimens should be considered for all HCV patients who are a candidate for DAAs treatment once they are fit and have no contraindications for ribavirin.

Summary

Enrolled patients were also categorized according to the degree of liver fibrosis regarding non-invasive markers into patients with no fibrosis (FIB-4≤ 1.45, APRI< 0.5, Lok index< 0.2, King's score≤ 12.2, GUCI< 1, API< 6, CDS <8), patients with significant fibrosis (FIB-4>1.45 but ≤3.25, APRI >0.5 but ≤ 2, Lok index≥0.2 but< 0.5, King's score >12.2 but ≤ 16.6) and patients with liver cirrhosis (FIB-4 >3.25, APRI> 2, Lok index ≥ 0.5, King's score > 16.6, GUCI ≥ 1, API ≥ 6, CDS ≥ 8).

Apart from CDS and API, all patients with liver cirrhosis had significant improvement in liver fibrosis parameters. CDS and API also showed mild improvement in liver fibrosis but this improvement does not mount to statistical significance.

Patients with significant liver fibrosis had regressions in liver fibrosis regarding FIB-4, APRI, and King's score. The only liver fibrosis worsening, within this group of patients, was noted in Lok index values that increased from 0.35±0.01 to 0.39±0.2 in patients with significant P-value.

Patients with no cirrhosis showed a statistically significant decrease in liver fibrosis values regarding APRI, GUCI, and King's score. On the other hand, there were mild increases in the Lok index and API values. FIB-4 and CDS had no statistically significant changes.

CONCLUSION

1. Non-invasive liver fibrosis parameters are of high value in detection and follow-up liver fibrosis and/or cirrhosis at low cost and wide availability.
2. DAAs could be used safely as a treatment of HCV regardless of the degree of liver fibrosis.
3. Achieving SVR after HCV treatment with DAAs could be of benefit in liver fibrosis reversal in patients with liver fibrosis and/or cirrhosis regarding widely used highly reliable biochemical non-invasive liver fibrosis parameters.
4. Ribavirin has an additive effect on liver fibrosis regression when used in combination with DAAs for HCV treatment.

Recommendations

1. More studies are needed for the evaluation of King's score, GUCI, API, and CDS response to direct-acting antiviral drugs.
2. Try to discover new scores using the routine biochemical markers that have higher diagnostic accuracy for the prediction of fibrosis and validate the already present scores. This could be achieved by using a combination of two or more non-invasive liver fibrosis parameters.
3. Further studies should examine the association between liver fibrosis improvement and risk reduction of decompensated cirrhosis, HCC, and death in chronic HCV patients who receive DAA therapy and achieve SVR.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests

All Authors declare no conflict of interests.

Acknowledgments

Authors thank all the clinicians' part of the study staff of our Units collected from patients.

REFERENCES

1. World Health Organization. Global hepatitis report 2017. World Health Organization; 2017.
2. El Kassas M, Elbaz T, Elsharkawy A, Omar H, Esmat G. HCV in Egypt, prevention, treatment and key barriers to elimination. Expert Rev Anti Infect Ther. 2018/03/11. 2018;16(4):345–50.
3. Asselah T. Sofosbuvir for the treatment of hepatitis C virus. Expert opinion on pharmacotherapy. 2014;15(1):121-30.
4. Bifano M, Hwang C, Oosterhuis B, Hartstra J, Grasela D, Tiessen R, et al. Assessment of pharmacokinetic interactions of the HCV NS5A replication complex inhibitor daclatasvir with antiretroviral agents: ritonavir-boosted atazanavir, efavirenz, and tenofovir. Antivir Ther. 2013;18(7):931–40.
5. Singh T, Allende DS, McCullough AJ. Assessing liver fibrosis without biopsy in patients with HCV or NAFLD. Clevel Clin J Med. 2019;1;86(3):179-86.
6. van der Meer AJ, Feld JJ, Hofer H, Almasio PL, Calvaruso V, Fernández-Rodríguez CM, et al. Risk of cirrhosis-related complications in patients with advanced fibrosis following hepatitis C virus eradication. J Hepatol. 2017;66(3):485-493.
7. Akita K, Okuno M, Enya M, Imai S, Moriwaki H, Kawada N, Suzuki Y, Kojima S. Impaired liver regeneration in mice by lipopolysaccharide via TNF-alpha/kallikrein–mediated activation of latent TGF-beta. Gastroenterology. 2002;123(1):352-64.
8. Alboraie M, Khairy M, Elsharkawy A, Asem N, El Kassas M, Elgendy AA, et al. Role of liver biopsy versus non-invasive biomarkers for diagnosis of significant fibrosis and cirrhosis: a web-based survey. Egyptian Liver Journal. 2021;11(1):1-8.
9. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotic. Hepatology. 2007;46(1):32-6.
10. Cross TJ, Rizzi P, Berry PA, Bruce M, Portmann B, Harrison PM. King's Score: an accurate marker of cirrhosis in chronic hepatitis C. Eur J Gastroenterol Hepatol. 2009;21(7):730-8.
11. Udell JA, Wang CS, Tinmouth J, FitzGerald JM, Ayas NT, Simel DL, et al. Does this patient with liver disease have cirrhosis? Jama. 2012; 307(8):832-42.
12. World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. World Health Organization; 2016.
13. Kandeel A, Genedy M, El-Refai S, Funk AL, Fontanet A, Talaat M. The prevalence of hepatitis C virus infection in Egypt 2015: implications for future policy on prevention and treatment. Liver International. 2017;37(1):45-53.
14. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45-57.
15. Colecchia A, Colli A, Casazza G, Mandolesi D, Schiumerini R, Reggiani LB, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. J Hepatol. 2014;60(6):1158-64.
16. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci. 2006;3(2):47-52.
17. El Kassas M, Alboraie M, Omran D, Salaheldin M, Wifi MN, ElBadry M, et al. An account of the real-life hepatitis C management in a single specialized viral hepatitis treatment center in Egypt: results of treating 7042 patients with 7 different direct-acting antiviral regimens. Expert Rev Gastroenterol Hepatol. 2018;12(12):1265-1272.
18. Gentile I, Borgia F, Buonomo AR, Castaldo G, Borgia G. A novel promising therapeutic option against hepatitis C virus: an oral nucleotide NS5B polymerase inhibitor sofosbuvir. Curr Med Chem. 2013;20(30):3733-42.
19. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370(3):211-21.
20. Everson GT, Sims KD, Rodriguez-Torres M, Hézode C, Lawitz E, Bourlière M, et al. Efficacy of an interferon-and ribavirin-free regimen of daclatasvir, asunaprevir, and BMS-791325 in treatment-naive patients with HCV genotype 1 infection. Gastroenterology. 2014; 146(2):420-9.
21. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, et al. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet. 2014;384 (9954):1597-1605.
22. Midia M, Odedra D, Shuster A, Midia R, Muir J. Predictors of bleeding complications following percutaneous image-guided liver biopsy: a scoping review. Diagn Interv Radiol. 2019;25(1):71-80.
23. Khairy M, Abdel-Rahman M, El-Raziky M, El-Akel W, Zayed N, Khatab H, et al. Non-invasive prediction of hepatic fibrosis in patients with chronic HCV based on the routine pre-treatment workup. Hepat Mon. 2012;12(11):e6718.
24. Louie V, Latt NL, Gharibian D, Sahota A, Yanny BT, Mittal R, et al. Real-world experiences with a direct-acting antiviral agent for patients with hepatitis C virus infection. Perm J. 2017;21:16-096.
25. Elsharkawy A, Alem SA, Fouad R, El Raziky M, El Akel W, Abdo M, et al. Changes in liver stiffness measurements and fibrosis scores following sofosbuvir based treatment regimens without interferon. J Gastroenterol Hepatol. 2017;32(9):1624-1630.
26. Abdel-Aziz AM, Ibrahim MA, El-Sheikh AA, Kamel MY, Zenhom NM, Abdel-Raheim S, et al. Effect of sofosbuvir plus daclatasvir in hepatitis c virus genotype-4 patients: promising effect on liver fibrosis. J Clin Exp Hepatol. 2018;8(1):15-22.
27. Mohamed MS, Hanafy AS, Bassiony MA, Hussein S. Sofosbuvir and daclatasvir plus ribavirin treatment improve liver function parameters and clinical outcomes in Egyptian chronic hepatitis C patients. Eur J Gastroenterol Hepatol. 2017;29(12):1368-1372.
28. Miyaki E, Imamura M, Hiraga N, Murakami E, Kawaoka T, Tsuge M, et al. Daclatasvir and asunaprevir treatment improves liver function parameters and reduces liver fibrosis markers in chronic hepatitis C patients. Hepatol Res. 2016;46(8):758-64.
29. Lanini S, Scognamiglio P, Mecozzi A, Lombardozzi L, Vullo V, Angelico M, et al. Impact of new DAA therapy on real clinical practice: a multicenter region-wide cohort study. BMC Infect Dis. 2018;18(1):223.
30. Deterding K, Höner Zu Siederdissen C, Port K, Solbach P, Sollik L, Kirschner J, et al. Improvement of liver function parameters in advanced HCV-associated liver cirrhosis by IFN-free antiviral therapies. Aliment Pharmacol Ther. 2015;42(7):889-901.
31. Westin J, Ydreborg M, Islam S, Alsiö Ţ, Dhillon AP, Pawlotsky JM, et al. A non-invasive fibrosis score predicts treatment outcome in chronic hepatitis C virus infection. Scand J Gastroenterol. 2008; 43(1):73-80.
32. Gökcan H, Kuzu UB, Öztaş E, Saygılı F, Öztuna D, Suna N, et al. The predictive value of noninvasive serum markers of liver fibrosis in patients with chronic hepatitis C. Turk J Gastroenterol. 2016;27(2): 156-64.
33. Bachofner JA, Valli PV, Kröger A, Bergamin I, Künzler P, Baserga A, et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int. 2017;37(3):369-376.
34. Tao YC, Deng R, Wang ML, Lv DD, Yuan M, Wang YH, et al. Satisfactory virological response and fibrosis improvement of sofosbuvir-based regimens for Chinese patients with hepatitis C virus genotype 3 infections: results of a real-world cohort study. Virol J. 2018;15(1):150.
35. Chekuri S, Nickerson J, Bichoupan K, Sefcik R, Doobay K, Chang S, et al. Liver stiffness decreases rapidly in response to successful hepatitis C treatment and then plateaus. PLoS One. 2016 21;11(7): e0159413.