ORIGINAL ARTICLE

Effects of direct acting antiviral therapy on liver stiffness measured by using fibro scan in Egyptian patients with chronic hepatitis C

Abdel Naser Abdel Atty Gadallah[1], Abdullah Abdulaziz Bahnasi[1], Waleed Abdelfattah[2], Mousa, Mohammed Shafiek Mohammed Elsayaad[3], Hany Abdelbary Abdelaziz Elbasyouni[1]

[1]Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine, Menoufia University, Menoufia, [2] Radiology, Faculty of Medicine, Menoufia University, Menoufia, [3]Internal Medicine, Benha University, Benha: Egypt

ABSTRACT

Aim Egypt has the highest incidence of hepatitis C virus (HCV) infection in the world. Fibrosis development is common in HCV cases, and it is important in disease prediction. The aim of this study was to demonstrate the role of fibro scan in assessment of changes in hepatic stiffness in patients with chronic HCV infection following direct acting antiviral treatment (DAAT).

Methods This prospective observational research included 120 patients with compensated HCV infection. All patients were subjected to fibro scan before and after receiving DAAT. Patients' history, clinical examination, laboratory parameters (red – RBCs, and white blood cells - WBCs, hepatic function test, renal function test, coagulation profile, HBsAg, AFP - alpha feto protein, HbA1C, HCVAb) and fibro scan were done for all patients.

Results Stiffness may differentiate F0-2 minimal fibrosis from F3-4 massive fibrosis using ROC-curve analysis, with 77.5% sensitivity, 90% specificity, 88.57% positive predictive value (PPV), and 80% negative predictive value (NPV). With sensitivity, specificity, PPV, and NPV of 71.4%, 44.5%, 43.48%, and 71.43%, respectively, the APRI-score can discriminate F0-2 from F3-4 at cutoff of 0.314. At a cutoff of 1.18, Fib4 calculation can discriminate F0-2 from F3-4, with sensitivity, specificity, PPV, and NPV of 78.6%, 64.1%, 63.04%, and 78.57%, respectively.

Conclusion Hepatic fibrosis measurements such as fibro scan and non-invasive fibrosis scores (FIB-4) and aspartate aminotransferase (AST) to platelet ratio index (APRI) showed a significant improvement after direct-acting antiviral therapy. Improvements in hepatic function tests, serum creatinine level, and platelet count are also seen.

Key words: HCV, hepatic fibrosis progression, liver stiffness

Corresponding author:
Abdel Naser Abdel Atty Gadallah
Internal Medicine,
Gastroenterology and Hepatology,
Faculty of Medicine
Shebin El Koom – 13829 Menoufia, Egypt
Phone: +20 48 206 697 170;
E-mail: abdelnaser.abd@med.menofia.edu.eg
ORCID ID: https://orcid.org/0000-0003-2835-0486

Original submission:
27 October 2022;
Revised submission:
10 January 2023;
Accepted:
06 February 2023
doi: 10.17392/1553-23

Med Glas (Zenica) 2023; 20(2):188-195

INTRODUCTION

Hepatitis C virus (HCV) infection has affected 71.1 million persons globally. Chronic hepatitis C (CHC) is a significant cause of mortality among patients with chronic hepatitis, cirrhosis, and hepatocellular cancer (HCC) (1). HCV infection prevalence is higher in Egypt comparing to other countries ranging from 6%- 40%, with an average of 14% (2) of HCV, causes massive hepatic damage that takes a decade or more to manifest liver cirrhosis eventually leading to HCC or hepatic failure. Hepatitis C was responsible for 40 000 deaths per year in Egypt by 2015 (3).

Liver biopsy has been used to diagnose hepatic cirrhosis, but it has a number of drawbacks, including invasiveness, sample mistakes, and diagnostic variations amongst pathologists (4). It became feasible to evaluate hepatic elasticity by the use of fibro scan by the transient elastography (5). For prediction and surveillance, assessment of the grade of hepatic fibrosis is required (6).

Direct-acting antivirals (DAAs) had a high cure rate (90%) (7) . However, it is still unclear if novel DAAs can improve liver stiffness and, if so, what risk factors would hinder this (8). We argue that alternations of the fibro scan and the reduction of fibrosis regression may have a therapeutic importance in the assessment of chronic HCV cases, indicating that hepatic fibrosis is a process with the possibility for recovery and restoring function (9).

The aim of this research was to investigate changes in fibro scan measurements of hepatic stiffness after DAAs medication in the patients with chronic HCV infection.

PATIENTS AND METHODS

Patients and study design

Over the course of two years, this investigation was conducted as a randomized controlled trial (from May 2019 to May 2021). Patients were randomly chosen from outpatient clinics and inpatients at the Menoufia University hospital's Internal Medicine Department and the National Institute's Hepatology and Gastroenterology Department, Shebin el Kom, Egypt. All procedures were authorized by the Ethics Committee of Menoufia University's Faculty of Medicine, Shebin el Kom, Egypt (ID: 2/2020INTM48).

The study comprised 120 treatment-naive compensated chronic liver disease patients above 18 years of age with HCV infection confirmed by immunoassay and quantitative PCR. Exclusion criteria included patients with hepatocellular carcinoma (HCC), renal impairment, bilirubin more than 3 mg/dL, serum albumin less than 2.8 mg/dL, international normalized ratio (INR) >1.8, platelets <50x103, uncontrolled diabetes mellitus as HbA1C >9, prior antiviral therapy with interferon or immunosuppressive therapy, hepatic transplantation, portal vein or splenic vein thrombosis, and HBsAg (+) patients.

Demographic data (age, gender, occupation, residence, medical history, drug intake), general and abdominal examination, laboratory investigations, and non-invasive fibrosis scores (FIB-4) and aspartate aminotransferase (AST) to platelet ratio index (APRI) were recorded.

According to the Egypt's National Committee for Combating Viral Hepatitis, all patients were given sofosbuvir-based therapy protocol.

Patients were examined for HCV RNA at baseline, EOT (end of treatment) and following sustained virologic response (SVR)12 by PCR.

Methods

Laboratory parameters such as complete blood count (CBC), haemoglobin (Hb), white blood cells (WBCs), and platelets, liver function test including albumin level, aspartate aminotransferase (AST(, alanine aminotransferase (ALT), total and direct bilirubin, alkaline phosphatase (ALP), kidney function test including urea, creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR) coagulation profile (prothrombin time - PT), partial thromboplastin time (PTT), international normalized ratio (INR), HBsAg, AFP (alpha feto-protein), HbA1C, HCVAb, and HCV RNA by quantitative PCR were analysed.

Regarding transient elastography results (10) the patients were classified into four groups: F0-1 - non-significant fibrosis (less than 7.1 KPa), F2 - significant fibrosis (7.1 -9.5 KPa), F3 - advanced fibrosis (9.5 -12.5 KPa), and F4 - cirrhosis (>12.5 KPa) (11). Aspartate aminotransferase (AST) to platelet ratio index (APRI) in order to measure liver fibrosis was calculated predicting accurately mild fibrosis in patients with a value <0.42 and those with a value >1.2 with a significant grade of fibrosis (12).

Fibro scan (Echosens, 502 Touch, Paris, France) was used to assess liver size, echo pattern, amount of ascites, spleen enlargement, and to exclude HCC and portal vein thrombosis; it was carried out by an experienced examiner in all patients (fasting at least six hours) and at least ten valid values were determined and median of liver stiffness (LS) expressed in kilopascals (kPa) was recorded. Only examinations with success rate more than 60% and interquartile range (IQR) less than 30% were considered.

The non-invasive fibrosis score (FIB-4) was calculated automatically using the formula: age (years) X AST (U/l)/(platelets (109/l) X (ALT (U/l))1/2), in which the age of the patient was the age at the time of the presentation. The FIB-4 index delineates patients with no or moderate fibrosis (F0-F1- F2-F3) when the score is <1.45 from those with extensive fibrosis or cirrhosis (F4-F5-F6) when the score is >3.25 (in the ISHAK classification of fibrosis) (13). Regarding abdominal ultrasound (Mindray, DP-5, China) was done for all patients.

Statistical analysis

The Shapiro Walk test was used to determine distribution normality. Frequencies and relative percentages were used to depict qualitative data. The $\chi 2$ test was employed to evaluate the difference between qualitative variables. The mean and SD (standard deviation) were used to represent quantitative data. For parametric and non-parametric variables, the student t test was employed to calculate the difference between quantitative variables before and after the treatment. All statistical comparisons were done with a two-tailed significance level.

RESULTS

The average age of patients was 49.7±12.03 years. Regarding gender, 59 (49.2%) were male and 61 (50.8%) were female (ratio was 0.97:1). The mean ±SD weight, height and body mass index (BMI) of patients were 76.36±13.88 kg, 163.8±8.14 cm and 24.49±3.84 Kg/m^2, respectively (Table 1).

Regarding liver functions tests, it was noticed that ALT, AST, and creatinine were markedly reduced after treatment by SVR for 24 weeks compared to before treatment, while albumin and platelet was significantly elevated after treatment by SVR for 24 weeks compared to before treatment. However, total bilirubin, PC, INR, alpha-fetoprotein (AFP), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), hemoglobin (Hb) and white blood cells (WBCs) before and after treatment showed no significant change (Table 2).

Liver stiffness by fibro scan was significantly lower after treatment by SVR for 24 weeks compared to before treatment. Fib 4 score showed significant decrease after treatment by SVR for 24 weeks compared to before treatment. Also, APRI-score showed significant decrease after treatment by SVR for 24 weeks compared to before treatment therapy (Table 2).

Liver stiffness between fibro scan grades showed significant difference before and after 24 weeks

Table 1. Laboratory data at pre-treatment (baseline) and 24-week post-treatment sustained virological response (SVR24) among 120 patients

Variable	Baseline (N=120)			SVR: 24 weeks post treatment (N=120)			p
	Mean ±SD	Median	Min.-Max.	Mean ±SD	Median	Min.-Max.	
ALT (IU/L)	44.99±22.46	42	15-172	32.62±7.89	32	12-47	0.000
AST (IU/L)	44.19±21.81	38.5	14-118	30.81±7.65	30	14-45	0.000
Albumin (g/dL)	3.67±0.35	3.7	2.5-5.09	4.09±0.38	4.1	3.2-5.2	0.000
Total bilirubin (mg/dL)	0.75±0.29	0.73	0.3-2.7	0.76±0.41	0.7	0.2-2	0.872
AFP(IU/L)	4.35±4.01	3.1	0.1-22.6	3.47±1.94	3.1	0.1-8.5	0.236
Serum creatinine (mg/dL)	0.85±0.19	0.89	0.4-1.4	0.75±0.24	0.7	0.3-1.4	0.001
BUN (mg/dL)	9.94± 0.87	9.80	5.0-17.0	10.07± 0.79	10.0	7.0-20.0	0.262
eGFR (mL/minute/1.73m2)	111.82±7.58	110.0	90.0-120.0	115.40±11.19	111.0	90.0-120.0	0.114
HB (g/L)	13.44±1.54	13.3	10.5-16.8	13.54±1.98	13.8	4.8-17.5	0.279
WBCs (10.8 x 109/L)	7.38±2.21	7	4-15.1	7.29±2.37	6.7	2.7-15.1	0.55
Platelets (109/L)	222.7±64.1	220	84-442	239.7±74.85	234	52-452	0.04
Prothrombin concentration (%)	92.48±11.68	97.25	40-132	92.1±12.11	96	40-132	0.756
INR	1.065±0.12	1	1-1.8	1.069±0.13	0.99	0.99-1.8	0.627

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HB, haemoglobin; WBCs, white blood cells; INR, international normalized ratio;

Table 2. FibroScan score at pre-treatment (baseline) and 24-week post-treatment (SVR) among 120 patients

Variable	Baseline (N=120)			SVR 24 weeks post treatment (N=120)			p
FibroScan	**No (%) of patients**						
F0-1	64 (53.3)			69 (57.5)			0.000
F2	22 (18.3)			23 (19.2)			
F3	6 (5)			8 (6.7)			
F4	28 (23.3)			20 (16.7)			
	Mean ±SD	**Median**	**Min.-Max.**	**Mean ±SD**	**Median**	**Min.-Max.**	
Liver stiffness by FibroScan	9.49±8.5	6.75	3-75	8.019±5.82	6.1	2.7-41	0.000
Fib 4 score	1.65±1.19	1.31	0.35-7.77	1.27±0.69	1.1	0.35-5.33	0.011
APRI-score (IU/L)	0.6±0.47	0.48	0.08-2.89	0.38±0.18	0.34	0.08-1.23	0.000

APRI, aspartate aminotransferase platelet ratio

Table 3. Fibrosis stages at baseline and after 24-week post-treatment among 120 patients

Variable	Fibro scan stages at baseline				p
	No of patients	Mean ± SD	Median	Min.-Max.	
Liver fibro scan (Stiffness)					
F0-1	64	5.16±1.08	5.3	3-7	<0.0001
F2	22	7.89±0.67	7.85	7.1-9.3	
F3	6	10.55±0.68	10.3	10-11.9	
F4	28	20.39±12.1	17.35	12.8-75	
APRI-score (IU/L)					
F0-1	64	0.497±0.37	0.54	0.08-2.89	0.028
F2	22	0.56±0.43	0.54	0.19-2.21	
F3	6	0.71±0.26	0.54	0.48-1.04	
F4	28	0.84±0.64	0.54	0.23-2.38	
Fib 4 score					
F0-1	64	1.54±0.91	1.42	0.58-4.77	0.979
F2	22	1.61±1.13	1.25	0.35-7.64	
F3	6	1.72±1.13	1.46	0.39-4.25	
F4	28	2.41±2.7	1.3	0.61-7.76	
After 24 weeks post treatment					
Liver fibroscan (Stiffness)					
F0-1	69	4.97±1.09	5	2.7-6.8	<0.0001
F2	23	8.13±0.63	8	7.3-9.1	
F3	8	11.14±0.76	11.45	10-12.1	
F4	20	18.23±7.73	14.1	12.8-41	
APRI-score (IU/L)					
F0-1	69	0.352±0.15	0.33	0.08-0.83	0.407
F2	23	0.386±0.23	0.34	0.17-1.23	
F3	8	0.378±0.13	0.34	0.21-0.59	
F4	20	0.45±0.23	0.38	0.16-1.02	
Fib 4 score					
F0-1	69	1.07±0.51	1.02	0.35-2.62	0.001
F2	23	1.48±1.01	1.09	0.63-5.33	
F3	8	1.41±0.62	1.29	0.64-2.33	
F4	20	1.63±0.63	1.51	0.87-3.21	

APRI, aspartate aminotransferase platelet ratio

post treatment, as F4 showed the highest stiffness. APRI- score between fibro scan grades showed significant difference before treatment and did not show significant difference after 24 weeks post treatment, versus Fib 4 score showed significantly difference in all fibro scan grades after 24 weeks post treatment only (Table 3).

To distinguish F0-2 from F3-4, ROC curve was used to assess stiffness, APRI-score, and fib4 calculation. Stiffness may differentiate F0-2 minimal fibrosis from F3-4 massive fibrosis using ROC-curve analysis, with 77.5% sensitivity, 90% specificity, 88.57% positive predictive value (PPV), and 80% negative predictive value (NPV). With sensitivity, specificity, PPV, and NPV of 71.4%, 44.5%, 43.48%, and 71.43%, respectively, the APRI-score can discriminate F0-2 from F3-4 at cutoff 0.314. At a cutoff of 1.18, Fib4 calculation can discriminate F0-2 from F3-4, with sensitivity, specificity, PPV, and NPV of 78.6%, 64.1%, 63.04%, and 78.57%, respectively (Table 4, Figure 1).

DISCUSSION

For more than two decades, the only available drug for HCV infection was interferon, at the first with conventional interferon and then with pegylated interferon in conjunction with ribavirin (14). Recent therapies for HCV, such as direct-acting drugs (DAAs) or interferon-free therapy, have been discovered in recent years. The advantages of this drug over previous therapies are excellent success rates (>90%), decrease duration of treatment (12 or 24 weeks), and minimal complications (15). Regardless, one of the most pressing problems is what occurs with hepatic fibrosis after an SVR. Many researches have demonstrated that SVR in HCV chronic infection can decrease fibrosis (16).

Table 4. Area under curve (AUC) and performance characteristics of stiffness, aspartate aminotransferase (AST) to platelet ratio index (APRI)-score and Fib4 calculation for discrimination between F0-2 non-advanced fibrosis versus F3-4 advanced fibrosis

Variable	AUC	Best cut off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Liver stiffness	0.865	8.00	77.50	90.00	88.57	80.00	87.00
APRI-score	0.601	0.31	71.40	44.50	43.48	71.43	50.00
Fib4 calculation	0.708	1.18	78.60	64.10	63.04	78.57	66.67

PPV, positive predictive value; NPV, negative predictive value

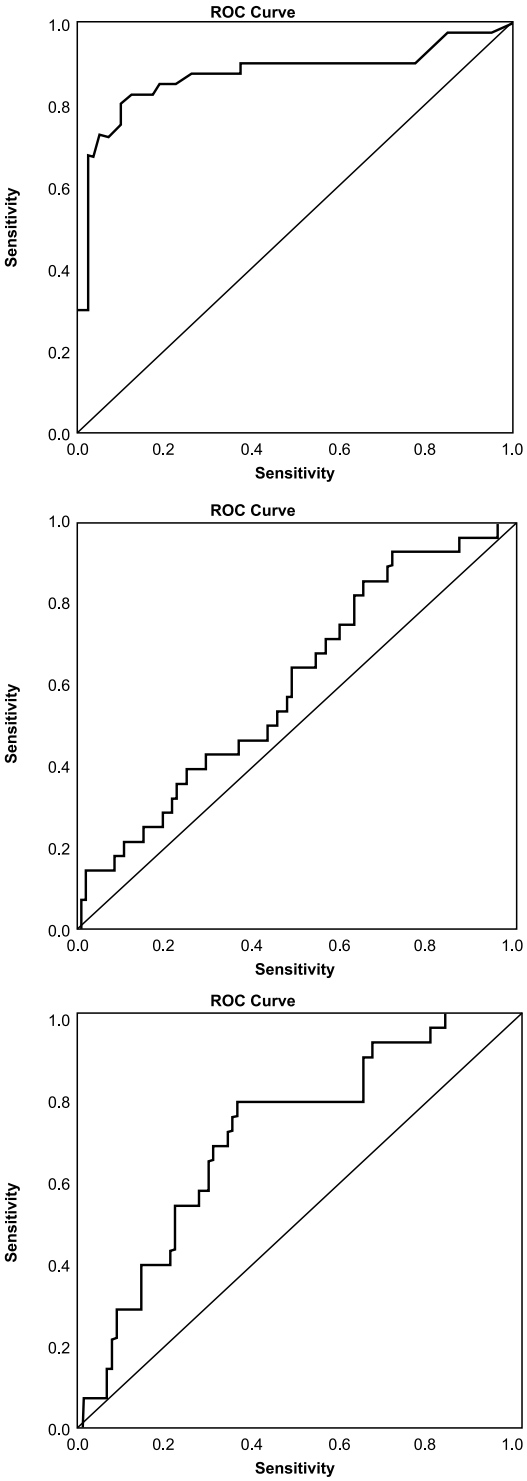

Figure 1. ROC curve for A) stiffness, B) aspartate aminotransferase (AST) to platelet ratio index (APRI) score, C) fib4 calculation

The aim of this study was to see how fibro scan measurements of liver stiffness changed in cases with HCV infection after applying DAAs medication. The study included 120 patients with compensated chronic HCV infection identified by having positive HCV Ab.

In terms of demographic characteristics among the patients before and after treatment the average age was lower than in the Saif-Al-Islam et al. (17) study (49.712.03 vs 56.6 10.2 years, respectively), but similar in Mansour study (50.9±5.7) (18). Males were more prevalent than females in the most studies.

The diagnosis in late age years is consistent with the findings of the Demographic Health Survey - Egypt 2015 (19), which found most of Egyptian cases presented at an older age with severe degree of hepatic fibrosis, owing to the fact that most patients are uninsured and unaware of the disease's danger.

Our study found that ALT and AST concentrations were decreased after 24 weeks of SVR when compared to concentrations before start treatment, whereas albumin levels were significantly increased after 24 weeks of SVR treatment. The findings of Elfiki et al. study (20) were similar to our study, revealing that achieving SVR12 was linked to the reduction of ALT concentrations. Twelve weeks following the termination of the therapy, there was a further drop in ALT levels. Also, Elsharkawy et al. (21) showed that at week four, individuals who got DAA therapy had significantly lower AST and ALT values. They hypothesized that early reductions in AST and ALT levels were primarily due to a decrease in necroinflammation rather than the reduction of fibrosis.

Total bilirubin, PC, INR, AFP, HB, and WBCs, on the other hand, did not differ significantly before and after the treatment. However, when compared to before treatment, serum creatinine was significantly lower after 24 weeks of SVR medication. A study of Mohammed et al. (22) found liver enzymes, liver synthetic functions (albumin, bilirubin, INR), platelets, and AFP all improved significantly after the treatment, however haemoglobin, creatinine and WBCs remained unchanged. In terms of complete blood count (CBC), platelet levels were significantly higher after 24 weeks of SVR treatment compared to the period before the treatment. In agreement with our results, Hsu et al. (23), Deterding et al. (24) and Pons et al. (25) showed that platelet count grew dramatically at the time of the treatment and persisted for 12 weeks after the DAA medication.

The FIB-4 index has previously been shown to be useful for classifying hepatic disease and monitoring HCV-infected patients (26). Assessment of liver stiffness (LS) by transient elastography (TE) and fibro scan is now the most extensively used method for assessing hepatic fibrosis (27).

Knop et al. (28) showed that patients identified as F4 had a greater reduction in liver stiffness (LS) than those classified as F2-F3.

Our study revealed that Fibro scan before and after the treatment by SVR for 24 weeks differed significantly. Stiffness was significantly lower after the treatment by SVR for 24 weeks compared to before the treatment. Fibrosis-4 showed a significant decrease after the treatment by SVR for 24 weeks compared to before the treatment therapy. Also, APRI-score showed significant decrease after the treatment by SVR for 24 weeks compared to before the treatment therapy. In accordance with our results, a study of Tag-Adeen et al. (29) showed that SVR 24 achievement was related to significant changes of liver stiffness measurement (LSM). Also, Mansour et al. (18) showed that the fibrosis was improved after 12 weeks of EOT. This is quite similar to Bachofner et al. (16) who reported a significant decline of LS values and other fibrosis scores as FIB4 and APRI after the termination of the treatment by 12 weeks. Furthermore, Ogasawara et al. (30) demonstrated that LS was significantly reduced in the patients with SVR at EOT, after 24, 48 weeks comparing to measurements before the treatment. Also, Knop et al. (28) stated that cases with SVR showed a reduction of LS between baseline and EOT when compared to SVR after 24 weeks.

Our results were supported by a study of Mohammed et al. (22) as they reported that there was a highly significant strong positive link between LS scores and FIB4, APRI score, ALT, AST, bilirubin, INR and AFP levels; Hb, Plts, TLC, and albumin were significantly negatively correlated to LS scores. Knop et al. (28) found that LS had a strong relationship with ALT, AST, platelets, GGT, bilirubin, APRI score, and FIB-4 score. After DAA-based therapy, our cohort's hepatic elastography improved dramatically. Because LS has a strong correlation with transaminase levels and serum fibrosis markers, it could indicate both necroinflammation and fibrosis reduction (28). According to Tag-Adeen et al. (29) patients, who improved their liver stiffness measurement (LSM), had a significantly higher LSM, bilirubin and transaminase levels before the treatment than those who did not; however, the studied patients were similar in age, albumin, INR, or platelets before and after therapy.

Makhlouf et al. (32) showed that the improvement of LSM was considerably better in naive cases and those who improved their Fib-4 index after the SMV/SOF treatment. Also, Mansour et al. (18) showed that there was a positive link between stiffness and elasticity index, APRI score and FIB4 before the treatment and after the end of the treatment.

In a study by Yosry et al. (31) stiffness and FIB4 had higher sensitivity and specificity in the diagnosis of massive fibrosis.

In conclusion, liver fibrosis measures as fibro scan, FIB-4 and APRI showed a significant improvement when treated with direct-acting antivirals. Also, it improves hepatic function tests, serum creatinine level, and platelet count. In this context, we believe that prospective research is needed to evaluate the true risk of HCC incidence and recurrence, as well as the hepatic- and non-hepatic-related death, following a viral treatment.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

REFERENCES

1. Wasitthankasem R, Vichaiwattana P, Siripon N, Posuwan N, Auphimai C, Klinfueng S, Thanetkongtong N, Vuthitanachot V, Saiyatha S, Thongmai C, Sochoo S. Liver disease burden and required treatment expenditures for hepatitis C virus (HCV) infection in Thailand: implications for HCV elimination in the new therapeutic era, a population-based study. PLoS One 2018; 4:0196301.
2. Naga M, Esmat E, Ahmed H, Abdel Samie R, Hamdy A, Naga Y. Clinical characteristics of HCV in Egyptian patients. EC Gastroenterolog DigSys 2019; 6:168-79.
3. Kim JE, Ryoo BY, Ryu MH, Chang HM, Suh DJ, Lee HC, Lim YS, Kim KM, Kang YK. Sorafenib for hepatocellular carcinoma according to Child-Pugh class of liver function. Cancer Chemother Pharmacol 2011; 5:1285-90.

4. Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol 2014; 20:475.
5. Chin JL, Pavlides M, Moolla A, Ryan JD. Non-invasive markers of liver fibrosis: adjuncts or alternatives to liver biopsy. Frontiers Pharmacol 2016; 7:159.
6. Ebrahim AE, Shehata MA, Abou-saif S, Abd-Elsalam S, Yousef M. Role of Fibroscan for early detection of hepatocellular carcinoma (HCC) in hepatitis C cirrhotic patients. Egyptian J Radio Nucl Med 2020; 51:1-6.
7. Miller MM. Sofosbuvir–velpatasvir: A single-tablet treatment for hepatitis C infection of all genotypes. Americ J Health-Sys Pharm 2017; 74:1045.
8. Ioannou GN, Feld JJ. What are the benefits of a sustained virologic response to direct-acting antiviral therapy for hepatitis C virus infection. Gastroenterol 2019; 156:446-60.
9. Sebastiani G, Gkouvatsos K, Pantopoulos K. Chronic hepatitis C and liver fibrosis. World J Gastroenterol 2014; 20:11033–53.
10. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Lédinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005; 128:343.
11. De Ledinghen V, Vergniol J. Transient elastography (fibroscan). Gastroenterol Clinic Biol 2008; 32:58-67.
12. Liu CH, Lin JW, Tsai FC, Yang PM, Lai MY, Chen JH, Kao JH, Chen DS. Noninvasive tests for the prediction of significant hepatic fibrosis in hepatitis C virus carriers with persistently normal alanine aminotransferases. Liver Intern 2006; 26:1087-94.
13. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, Fontaine H, Pol S. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology 2007; 46:32-6.
14. Niro GA, Ciancio A, Gaeta GB, Smedile A, Marrone A, Olivero A, Stanzione M, David E, Brancaccio G, Fontana R, Perri F. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. Hepatology 2006; 43:713-20.
15. Elbaz T, El-Kassas M, Esmat G. New era for management of chronic hepatitis C virus using direct antiviral agents: A review. J Advanc Res 201; 6:301.
16. Bachofner JA, Valli PV, Kröger A, Bergamin I, Künzler P, Baserga A, Braun D, Seifert B, Moncsek A, Fehr J, Semela D. 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 Internat 2017; 37:369-76.
17. Saif-Al-Islam M, Abdelaal UM, Younis MA, Alghany Algahlan HA, Khalaf S. Effect of Direct-Acting Antiviral Therapy on Thrombocytopenic Patients with Hepatitis C Virus-Related Chronic Liver Disease. Gastroenterol Res Practic 2021;2021.
18. Mansour RH, Zaky S, El Kassas M, Mamdouh H, Esmat G. Evaluating the effect of direct-acting agents on liver fibrosis, by real-time elastography, Fibroscan and FIB4 score in chronic HCV patients. Sci J Al-Azhar Med Fac Girls 2019; 3:237-45.
19. Gomaa A, Allam N, Elsharkway A, El Kassas M, Waked I. Hepatitis C infection in Egypt: prevalence, impact, and management strategies. Hepat Med 2017; 9:17.
20. Elfiki MA, Farid M, Soliman A, Ibrahim BA. The effect of direct acting antiviral therapy for hepatitis C-virus infected Egyptian patients on changes in the parameters of liver fibrosis progression. Bulletin Egy Soci Physiol Sci 2021; 41:203-19.
21. Elsharkawy A, Eletreby R, Fouad R, Soliman Z, Abdallah M, Negm M, Mohey M, Esmat G. Impact of different sofosbuvir based treatment regimens on the biochemical profile of chronic hepatitis C genotype 4 patients. Expert Rev Gastroenterol hepatol 2017; 11:773-8.
22. Mohammed AA, Attia D, Ebeid BA, Ibrahim MB. Study of the effect of direct acting antivirals (DAAs) on fibrosis in chronic hepatitis C patients using transient elastography. World J Adv Res Rev 2021; 10:135-45.
23. Hsu WF, Lai HC, Su WP, Lin CH, Chuang PH, Chen SH, Chen HY, Wang HW, Huang GT, Peng CY. Rapid decline of noninvasive fibrosis index values in patients with hepatitis C receiving treatment with direct-acting antiviral agents. BMC Gastroenterol 2019; 19:1-9.
24. Deterding K, Höner Zu Siederdissen C, Port K, Solbach P, Sollik L, Kirschner J, Mix C, Cornberg J, Worzala D, Mix H, Manns MP. Improvement of liver function parameters in advanced HCV-associated liver cirrhosis by IFN-free antiviral therapies. Aliment Pharmacol Ther 2015; 42:889-901.
25. Pons M, Santos B, Simón-Talero M, Ventura-Cots M, Riveiro-Barciela M, Esteban R, Augustin S, Genescà J. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals. Therap Adv Gastroenterol 2017; 10:619-29.
26. Holmberg SD, Lu M, Rupp LB, Lamerato LE, Moorman AC, Vijayadeva V, Boscarino JA, Henkle EM, Gordon SC, Chronic Hepatitis Cohort Study (CHeCS) Investigators, Holmberg SD. Noninvasive serum fibrosis markers for screening and staging chronic hepatitis C virus patients in a large US cohort. Clinic Infect Dis 2013; 57:240-6.
27. Sezaki H, Suzuki F, Hosaka T, Akuta N, Fujiyama S, Kawamura Y, Kobayashi M, Suzuki Y, Saitoh S, Arase Y, Ikeda K. The efficacy and safety of dual oral therapy with daclatasvir and asunaprevir for genotype 1b in Japanese real-life settings. Liver Internat 2017; 37:1325-33.
28. Knop V, Mauss S, Goeser T, Geier A, Zimmermann T, Herzer K, Postel N, Friedrich-Rust M, Hofmann WP, German Hepatitis C-Registry, Ende K. Dynamics of liver stiffness by transient elastography in patients with chronic hepatitis C virus infection receiving direct-acting antiviral therapy Results from the German Hepatitis C-Registry. J Viral Hepatitis 2020; 27:690-8.
29. Tag-Adeen M, Sabra AM, Akazawa Y, Ohnita K, Nakao K. Impact of hepatitis C virus genotype-4 eradication following direct acting antivirals on liver stiffness measurement. Hepatic Medicine: Evidence Res 2017; 9:45.

30. Ogasawara N, Kobayashi M, Akuta N, Kominami Y, Fujiyama S, Kawamura Y, Sezaki H, Hosaka T, Suzuki F, Saitoh S, Suzuki Y. Serial changes in liver stiffness and controlled attenuation parameter following direct-acting antiviral therapy against hepatitis C virus genotype 1b. J Med Virol 2018; 90:313-9.
31. Yosry A, Fouad R, Alem SA, Elsharkawy A, El-Sayed M, Asem N, Hassan E, Ismail A, Esmat G. FibroScan, APRI, FIB4, and GUCI: Role in prediction of fibrosis and response to therapy in Egyptian patients with HCV infection. Arab J Gastroenterol 2016; 17:78-83.
32. Makhlouf NA, Farouk M, Nafeh HM, Hasanain AF, El-Mokhtar MA, Hetta HF, Mekky MA, Alboraie M, ELamin H, Nasr AM. NS34A resistance-associated substitutions in chronic hepatitis C in Upper Egypt and regression of liver fibrosis after direct-acting antiviral therapy. Egy Liver J 2021; 11:1-7.