Journal of Hepatocellular Carcinoma Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Long-Term Outcomes of Patients with Liver Cirrhosis After Eradication of Chronic Hepatitis C with Direct-Acting Antiviral Drugs (DAAs)

Mohsen Salama*, Nehad Darwesh*, Maha Mohammad Elsabaawy*, Eman Abdelsameea*, Asmaa Gomaa*, Aliaa Sabry*

Department of Hepatology and Gastroenterology, National Liver Institute, Menofia University, Shebeen El-Kom, Menofia, Egypt

*These authors contributed equally to this work

Correspondence: Asmaa Gomaa, National Liver Institute, Menofia University, Shebeen El-Kom, Menofia, Egypt, Tel +20-1006157160, Email aibrahim@liver-eg.org

Purpose: This research was designed to determine the long-term outcomes in patients with liver cirrhosis who achieved sustained virological response (SVR) after direct-acting anti-viral drugs (DAAs) based regimens.

Patients and Methods: This study involved 193 patients with HCV-related cirrhosis who had previously completed DAAs regimens and accomplished SVR. Clinical, laboratory, and radiological features at the first and 3rd-year follow-up after the end of treatment were analyzed. Overall survival (OS) and incidence of liver decompensation or hepatocellular carcinoma (HCC) were determined at the 5-year follow-up.

Results: About 68.4% of our patients with HCV-related cirrhosis were males and their mean age was 54.8 ± 7.7 years. Follow-up at the first and the 3rd-year showed significant improvements in albumin ($P = 0.001$), liver enzymes ($P = 0.001$), alpha-fetoprotein (AFP) ($P < 0.001$), platelet count ($P = 0.001$), the model for end-stage liver disease (MELD) score ($P = 0.001$ and 0.01), FIB4 and Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) scores ($p < 0.001$). The liver stiffness (LS) also significantly improved ($p = 0.001$). At the 5th year, the mean OS was 58.3 months, with 14.5% and 17.6% of patients developing de-novo HCC and decompensation, respectively. The mean OS at the 5th-year follow-up was shorter in patients who developed HCC and those with liver decompensation ($p = 0.001$). Alfa-fetoprotein and LS are predictive factors for HCC development.

Conclusion: Despite achieving SVR, continuous surveillance for HCC and new-onset decompensation is mandatory in patients with liver cirrhosis.

Keywords: long-term outcomes, cirrhotic patients, sustained virological response, DAAs

Introduction

Chronic infection with hepatitis C virus (HCV) persists as a significant universal public health issue, which affects almost seventy-one million individuals who are persistently infected with HCV.[1] Chronic inflammation of the liver causes fibrosis, which can eventually develop into cirrhosis. This increases the vulnerability of individuals to hepatic decompensation, HCC, and mortality related to hepatic disease.[2,3]

During the interferon (IFN) era, achieving SVR was linked to better long-term results and a reduced risk of liver-related diseases, such as HCC.[2] However, even the most efficient IFN therapy plans were hindered by extended periods of treatment, significant adverse effects, and limited effectiveness in combating the virus. Furthermore, the primary determinant is the likelihood of achieving positive therapeutic outcomes in individuals with advanced liver disease for whom IFN-based treatment may not be suitable.[4]

The implementation of IFN-free DAAs has significantly increased SVR rates in all patient groups, including those with severe liver disease or prior treatment experience, consequently altering the progression of chronic HCV infections. The SVR

Received: 2 June 2024
Accepted: 15 October 2024
Published: 30 October 2024

rates achieved with DAA regimens surpass 95%, demonstrating an outstanding safety and tolerability profile. This has expanded the range of individuals eligible for HCV treatment, along with those who have successfully been cured.[5–9]

Noteworthy, Egypt has shifted from having the highest rates of HCV infection globally to one of the lowest by lowering the prevalence from 10% to 0.38% in just over a decade. It has diagnosed 87% of inhabitants having chronic hepatitis C and offered treatment to 93% of those diagnosed and was awarded the "gold tier" status on the path to elimination of hepatitis C, as per WHO criteria. The treatment was offered to a large number of patients including those with advanced liver disease and cirrhosis, which raised attention about the long term consequences on those patients, especially decompensation events and risk of HCC.[10]

Research on the immediate effects of DAA therapy in advanced liver disease patients has shown enhancements in the MELD score and other biochemical markers of liver function.[11–14] Nevertheless, it remains unclear how the elimination of a virus and potential improvements in liver function may be connected to the development of long-term clinical outcomes in real-world settings.

Subjects and Methods

Study Population and Design

This study is a retrospectively prospective cohort study, which included 193 patients aged ≥18 years who attained SVR after DAA-based regimens for HCV-related cirrhosis at a tertiary referral center, the National Liver Institute, Menofia University, Egypt (Figure 1). The patients were followed up from January 2018 to December 2021. Non-cirrhotic patients, those with co-infection (HBV or HIV) or HCC at the time of recruitment or elevated alfa-fetoprotein (AFP) >100ng/mL and Individuals who have already underwent liver transplantation were excluded. An ethical approval from the Institutional Review Board of the National Liver Institute (IRB00280) was received, and a written informed consent was obtained from all patients included in the study.

Assessment of Cirrhosis

At the time of enrollment, the establishment of cirrhosis relied on an integration of clinical criteria, imaging, and laboratory tests. Before initiating DAA therapy, the presence of cirrhosis was ascertained by liver stiffness (LS) measurement using fibroscan 504® machine, echosens, France, with liver stiffness >12.5 kPa.[15] Non-invasive serum panels compatible with Fibrosis index score (FIB-4) [age (years) × AST (U/L)/platelet count ($\times 10^9$/L) × ALT (U/L)] >3.25, Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) score [(AST of the sample/reference AST) × 100/platelets] >2.[16–19] Imaging studies of the liver revealed a nodular architecture, signs of portal hypertension or ascites. The Baseline Child–Pugh score was calculated using a reliable algorithm.[20] The MELD score was computed at the beginning and during the monitoring period.[21]

Screening for HCC was performed by a combination of abdominal ultrasound and AFP monitoring every 4 months after the end of HCV therapy, according to the Egyptian Society of Liver Cancer Recommendation Guidelines. If any suspected hepatic focal lesion was detected, the diagnostic work-up was completed with triphasic CT scan and/or dynamic MRI to exclude the presence of HCC.[22]

Esophagogastroduodenoscopy (EGD) in patients with compensated cirrhosis with FibroScan >20 kPa and/or platelet count <100 was performed for the diagnosis of esophageal varices at baseline, and the follow-up interval was determined according to the findings of the baseline endoscopy.

Hepatic decompensation was determined by 1) the presence of new-onset ascites, hepatic encephalopathy, or variceal bleeding. 2) Worsening pre-existing hepatic decompensation. 3) Patients with settled any new decompensation events apart from those formerly present at the initiation of antiviral therapy.

Sustained Virological Response

Patients with no detectable HCV viraemia at least 12 weeks after receiving antiviral medication were classified as having sustained virologic response (SVR). The Abbott Real-Time HCV RNA test measured HCV RNA with a lower detection limit of 12 IU/mL.

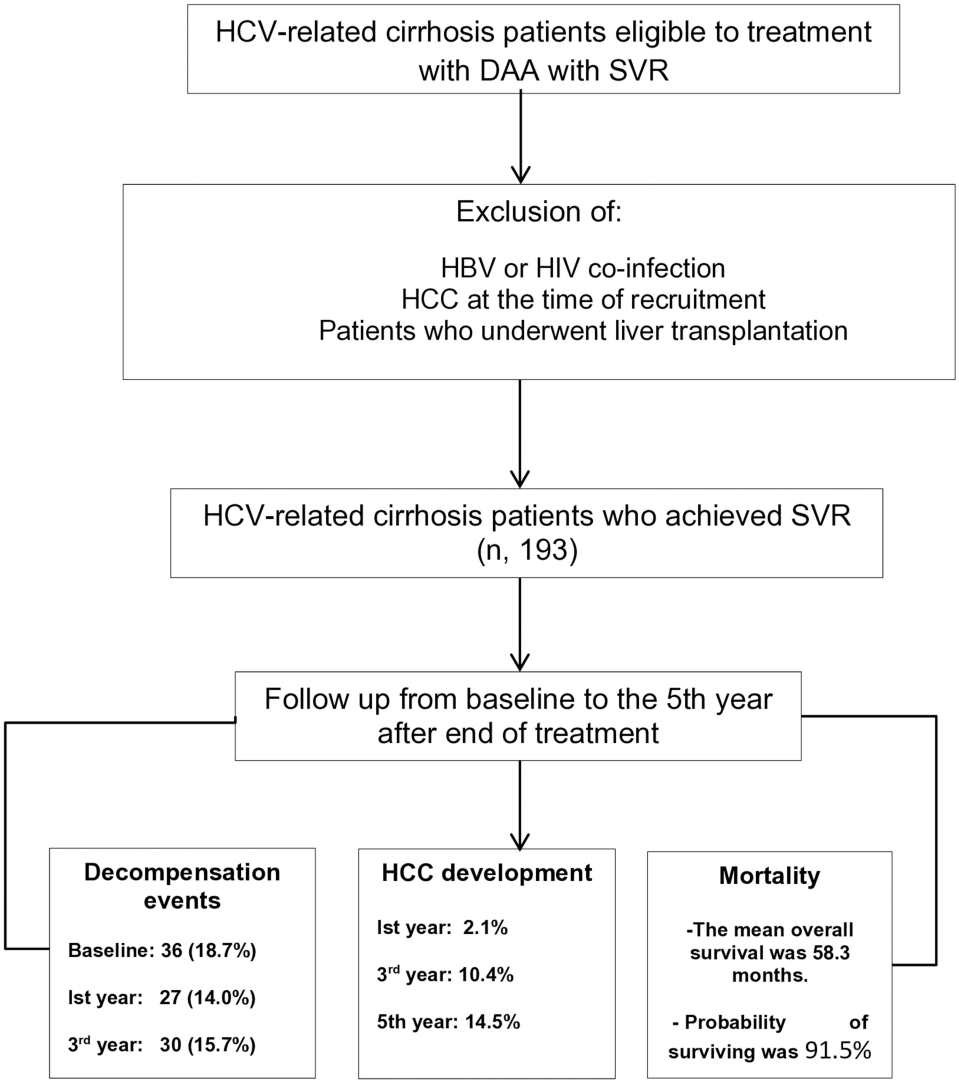

Figure 1 Patients flowchart.
Abbreviations: HCV, hepatitis C virus; DAA, direct acting antiviral; HBV, hepatitis B virus; HIV, human immunodeficiency virus; SVR, sustained virological response; HCC, hepatocellular carcinoma.

Received Treatment Regimens

Treatment regimens and durations were given as per the National Committee for Control of Viral Hepatitis (NCCVH Guidelines) in Egypt, which started in 2015 and were frequently updated according to international guidelines and drug availability. The most frequently used regimen was Sofosbuvir (pan-genotypic HCV NS5B polymerase inhibitor) plus daclatasvir (HCV NS5A inhibitor) in 67.3% of our patients, 49.7% without and 17.6% with Ribavirin. Other patients received either Sofosbuvir plus Ledipasvir (HCV NS5A inhibitor) or Sofosbuvir plus Simeprevir (HCV NS3/4A Protease Inhibitor) with or without Ribavirin (Table 1). The dose of ribavirin was weight-based (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively).

The Study Endpoints and Clinical Outcome

The primary endpoint was to determine the impact of achieving SVR in patients with HCV-related liver cirrhosis after treatment with sofosbuvir-based therapy on clinical disease progression or regression, liver stiffness variations assessed using transient elastography, and the incidence and characteristics of HCC after DAAs. Relevant clinical events and biochemical, endoscopic, and radiological data of the patients were collected at baseline, one, three, and 5 years post-

Table 1 Baseline Characteristics of the Studied Patients

		Overall N =193
Age/years	Mean ± SD (Range)	54.8±7.7 (21.0–70.0)
Gender, n (%)	Male	132 (68.4%)
	female	61 (31.6%)
BMI (Kg/m^2)	Mean ± SD (Range)	29.92±4.28 (19.0–44.98)
Diabetes mellitus, n (%)	N (%)	40 (20.7%)
Hypertension, n (%)	N (%)	26 (13.5%)
Ascites	•No	173 (89.6%)
	•Mild	13 (7.3%)
	•Moderate	5 (2.6%)
	•Marked	1 (0.5%)
Previous episode of hepatic encephalopathy	N (%)	4 (2.1%)
Previous episode of variceal bleeding	N (%)	20 (10.4%)
History of prior HCV treatment, n (%)	No	177 (91.7%)
	Yes[a]	16 (8.3%)
DAA regimens	•SOF+DCV	96 (49.7%)
	•SOF+DCV +RBV	34 (17.6%)
	•SOF +RBV	25 (13.0%)
	•SOF+LDV+RBV	15 (7.8%)
	•SOF +RBV +IFN	15 (7.8%)
	•SOF + SIM	4 (2.1%)
	•SOF + SIM +RBV	2 (1.0%)
	•SOF+LDV	2 (1.0%)
Duration of treatment	•12 weeks	130 (67.4%)
	•24 weeks	63 (32.6%)

Notes: [a] Prior HCV treatment (14 patients received interferon-ribavirin 48 weeks, 2 patients received sofosbuvir- ribavirin 24 weeks).

Abbreviations: SD, standard deviation; BMI, body mass index; DAA, direct acting antiviral; SOF, sofosbuvir; DCV, daclatasvir; RBV, ribavirin; LDV, Ledipasvir SIM, simeprevir.

SVR and evaluated. A general evaluation score was performed at baseline to predict HCC risk after DAAs treatment, which relied on age, sex, fibrosis stage, albumin, and α-fetoprotein (AFP). Patients were categorized into low-, intermediate-, and high-risk categories based on their scores.[23]

Statistical Analysis

This statistical analysis was performed with SPSS, version 22.0 for Windows, developed by IBM Corp in Armonk, NY, USA. Quantitative variables are represented by means and standard deviations in descriptive statistics, while qualitative variables are represented by numbers and percentages. If appropriate, the Fisher's exact or chi-square test was employed to compare categorical data. The paired *t*-test or the Wilcoxon signed-rank test was used to analyze the changes in

continuous variables over a period of time. The Mann–Whitney, Kruskal–Wallis, and Friedman tests were employed to analyze nonparametric data. A one-way analysis of variance (ANOVA) test with post-hoc analysis was conducted to evaluate three variables: one categorical variable and two continuous variables that follow a normal distribution. Univariate and multivariate logistic regression models were employed to forecast a binary outcome, while a receiver operating characteristic (ROC) curve was utilized to identify the threshold value of any variable under examination. The results of all tests were deemed statistically significant if the p-value was below 0.05.

Results

Baseline Patients' Characteristics

One hundred ninety-three cirrhotic individuals chronically infected with HCV and successfully achieved SVR after treatment with DAA regimens were recruited in the study. These patients received follow-up for 5 years after achieving the SVR. The mean patient age was 54.8 ± 7.7 years, 68.4% of them were male, and the mean body mass index (BMI) was 29.92 ± 4.28kg/m^2. Diabetes mellitus (DM) and hypertension (HTN) were present in 20.7% and 13.5%, respectively. Most patients had no previous history of ascites (89.6%). Pre-enrollment episodes of hepatic encephalopathy and variceal bleeding occurred in 2.1% and 10.4% of patients, respectively. Combined Sofosbuvir and daclatasvir plus ribavirin was the most used regimen (49.7%), mainly for 12 weeks duration (67.4%). Ribavirin was administered 1000–1200 a total daily dose, depending on body weight (Table 1).

Laboratory, Radiological, Endoscopic and Decompensation Events Data of the Studied Patients at Baseline, 1st, and 3rd-Year Follow-Up After the End of Treatment

As indicated in Table 2, during the first and third-year follow-up, AFP showed an early significant decrease in the first year, but higher levels were detected in the third year, parallel with new HCC case detection ($p < 0.001$). The Child–

Table 2 Comparison of Laboratory, Radiological, Endoscopic and Decompensation Events Data of the Studied Patients at Baseline, 1st and 3rd Year of Follow-Up After the End of Treatment

Variables	Baseline [M ± SD or N %]	Ist yr [M ±SD or N %]	P1 value	3rd yr [M ± SD or N %]	P2 value	P3 value
Bilirubin (mg/dl)	1.1±0.7	0.99 ± 0.57	0.009	1.03 ± 0.72	0.343	0.402
Albumin (g/dl)	3.8±0.62	3.9±0.49	0.001	3.9±0.57	0.001	0.436
INR	1.05 ± 0.22	1.04 ± 0.21	0.655	1.06 ± 0.24	0.527	0.416
ALT (IU/L)	61.60 ± 50.52	28.45±14.25	<0.001	27.05±16.81	<0.001	0.276
AST (IU/L)	63.02 ± 43.74	30.99±13.68	<0.001	29.14±17.9	<0.001	0.148
Hb (g/dl)	13.2 ± 2	12.97±1.98	0.015	12.99±1.95	0.033	0.712
TLC ($^{\times}10^3$ /ul)	5.8±2.07	5.9±1.8	0.201	5.9±1.8	0.550	0.881
Platelets ($^{\times}10^3$ /ul)	127.7±52.1	136.52±55.11	<0.001	144.75±60	<0.001	<0.001
AFP (ng/mL)	10.6±13	7.83 ± 11.76	<0.001	24.1±11.1	<0.001	0.368
Creatinine (mg/dl)	0.8±0.2	0.84±0.18	0.223	0.85±0.23	0.055	0.216
Child–Pugh score, n (%) •A •B •C	 169 (87.6%) 20 (10.4%) 4 (2.1%)	 174 (90.2%) 14 (7.3%) 5 (2.6%)	0.285	 164 (85.0%) 20 (10.4%) 7 (3.6%)	0.096	0.009
MELD score	8.5 ±2.3	8.0 ±2.2	0.001	8.3 ±2.8	0.010	0.193

(*Continued*)

Table 2 (Continued).

Variables	Baseline [M ± SD or N %]	Ist yr [M ±SD or N %]	P1 value	3rd yr [M ± SD or N %]	P2 value	P3 value
APRI score	1.74±1.41	0.81±0.59	<0.001	0.73±0.64	<0.001	<0.001
FIB-4 score	4.16 ± 2.62	2.79±1.63	<0.001	2.6±1.6	<0.001	<0.001
Upper endoscopy, n (%) •Not performed •No OV •Non risky varices •Risky varices	 77 (39.9%) 31 (16.1%) 57 (29.5%) 28 (14.5%)	 87 (45.1%) 26 (13.5%) 55 (28.5%) 25 (13.0%)	0.058	 84 (44.2%) 26 (13.7%) 59 (31.1%) 21 (11.1%)	0.884	0.176
Ascites, n (%) •No •Mild •Moderate •Marked	 173 (89.6%) 13 (7.3%) 5 (2.6%) 1 (0.5%)	 178 (92.2%) 10 (5.2%) 4 (2.1%) 1 (0.5%)	0.157	 170 (88.1%) 10 (5.2%) 8 (4.1%) 3 (1.6%)	0.285	0.011
Episode of hepatic encephalopathy, n (%)	4 (2.1%)	5 (2.6%)	0.655	10 (5.2%)	0.058	<0.001
Episode of variceal bleeding	20 (10.4%)	13 (6.7%)	0.052	11 (5.7%)	0.074	0.754
LSM (kPa) (M ± SD)	27.6±13.1	24.6±13.6	0.001	22.2±14.0	0.001	<0.001

Notes: P1 between baseline and 1st year, p 2 between baseline and 3rd year, p 3 between 1st year and 3rd year.
Abbreviations: SD, standard deviation; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; TLC, total leucocytic count; AFP, alpha fetoprotein; MELD, model of end stage liver disease; APRI, Aspartate Aminotransferase-to-Platelet Ratio Index; FIB-4, Fibrosis 4 (index); Ov, esophageal varices; LSM, liver stiffness measurement; kPa, kilo Pascal.

Pugh score showed non-significant improvement after 1 year. However, in the third year, worsening occurred, which was attributed mainly to the deterioration of patients with HCC, who were mostly Child A at baseline. Liver stiffness measurement showed a significant decrease in the first- and third-year follow-up in comparison to the baseline ($p = 0.001$ for each) and decreased in the third-year follow-up in comparison to the first-year ($p < 0.001$).

Decompensation Events from Baseline to the 5th Year of Follow-Up

Five years after the termination of antiviral therapy, the total number of patients who completed the follow-up was 172, as 16 patients died (all of them due to liver-related complications) and five patients were lost to follow-up. Because of the COVID-19 epidemic, 32.6% (n = 63) of patients were affected, and only five patients died due to deterioration of their liver disease. Only decompensation events and HCC data were available in the 5th year of follow-up: 19.2% of patients had decompensated liver disease with a predominance of ascites, which occurred in nearly 14% of cases (Table 3).

Logistic Regression Analysis for the Factors Predicting Hepatic Decompensation

Analysis of the baseline data revealed that liver stiffness was the only independent risk factor for de novo hepatic decompensation ($p = 0.033$) (Table 4).

Liver Stiffness and Denovo Hepatic Decompensation Development

Liver stiffness >30 kPa had a sensitivity of 51.43% and 72.48%, with an accuracy of 68.48% in predicting de-novo hepatic decompensation development (Figure 2).

Table 3 Decompensation Events from Baseline to 5th Year Follow-Up

	Baseline		1st year		3rd year		5th year		P
	N	%	N	%	N	%	N	%	
Decompensation									
No	157	81.3	166	86.0	161	84.3	138	78.0	< 0.001
Yes	36	18.7	27	14.0	30	15.7	34	19.2	
Events									
No	157	81.3	166	86.0	161	84.3	138	80.2	< 0.001
Ascites	11	5.7	11	5.7	15	7.9	24	14.0	
Hepatic encephalopathy	0	0.0	2	1.0	1	0.5	1	0.6	
Variceal bleeding	11	5.7	8	4.1	6	3.1	8	4.7	
Jaundice	5	2.6	1	0.5	0	0.0	0	0.0	
Ascites and jaundice	0	0.0	1	0.5	1	0.5	0	0.0	
Variceal bleeding and ascites	5	2.6	1	0.5	2	1.0	1	0.6	
Hepatic encephalopathy and Variceal bleeding	0	0.0	1	0.5	1	0.5	0	0.0	
Hepatic encephalopathy and Ascites	0	0.0	0	0.0	2	1.0	0	0.0	
Hepatic encephalopathy, variceal bleeding and Ascites	4	2.1	2	1.0	2	1.0	0	0.0	

Table 4 Univariate and Multivariate Logistic Regression Analysis for the Parameters Predicting Hepatic Decompensation

	OR (95%C.I)	P	OR (95%C.I)	P
Age/years	1.022 (0.973–1.074)	0.389		
Gender (female)	1.354 (0.630–2.910)	0.437		
Treatment status (Naïve)	3.566 (0.455–27.940)	0.226		
HCV RNA measurement	1.0 (1.0–1.0)	0.417		
Diabetes mellitus	1.157 (0.480–2.789)	0.745		
Hypertension	0.792 (0.255–2.462)	0.687		
Body mass index	0.952 (0.867–1.045)	0.297		
Bilirubin total (mg/dl)	0.889 (0.493–1.605)	0.697		
Serum albumin (g/dl)	0.917 (0.507–1.657)	0.773		
INR	–	0.999		
ALT (U/L)	0.998 (0.990–1.006)	0.595		
AST (U/L)	0.999 (0.991–1.008)	0.872		
APRI	1.025 (0.794–1.322)	0.852		
FIB-4	1.072 (0.940–1.224)	0.299		
LSM at baseline (kPa)	1.028 (1.002–1.056)	0.033	1.028 (1.002–1.056)	0.033

Abbreviations: INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, Aspartate Aminotransferase-to-Platelet Ratio Index; FIB-4, Fibrosis 4 (index); LSM, liver stiffness measurement; kPa, kilo Pascal.

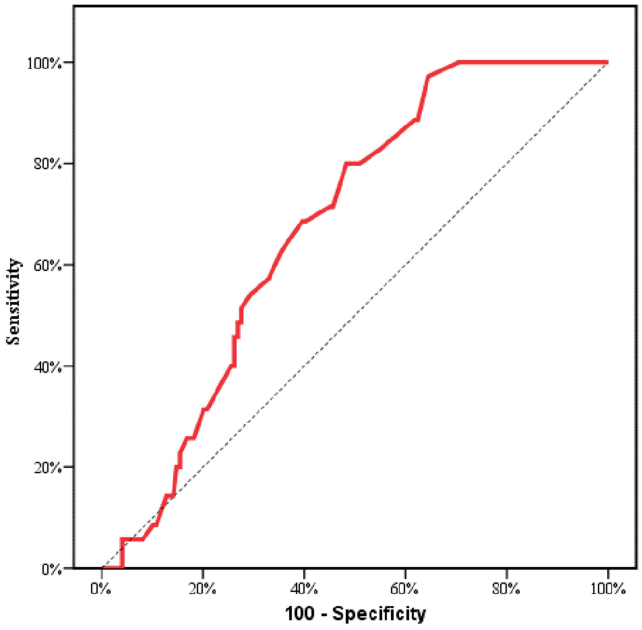

Figure 2 ROC curve of Liver stiffness measurement (Kpa) to predict hepatic decompensation.
Abbreviation: Kpa, kilo Pascal.

Hepatocellular Carcinoma in the Studied Patients

Criteria of HCC at 1st, 3rd and 5th Year of Follow Up

Table 5 shows the development of HCC in the study population and their inclusion criteria throughout the follow-up time.

Table 5 Criteria of Hepatocellular Carcinoma at 1st, 3rd and 5th Year of Follow-Up

	After 1 year		After 3 years		After 5 years	
	N	**%**	**N**	**%**	**N**	**%**
Total number	8	100	22	100	25	100
Died	0	0	2	9.09	4	16
Still alive	8	100	20	90.91	21	84
Site						
Right Lobe	5	62.5	11	50	13	52
Left lobe	2	25	2	9.091	4	16
Bilobar	1	12.2	7	31.82	4	16
Size						
<5 cm	4	50	15	68.18	15	60
>5 cm	4	50	5	22.73	6	24
Number						
Single	2	25	7	31.82	11	44
Multiple	6	75	13	59.09	10	40

(*Continued*)

Table 5 (Continued).

	After 1 year		After 3 years		After 5 years	
	N	%	N	%	N	%
Portal vein thrombosis						
No	6	75	15	68.18	16	64
Yes	2	25	5	22.73	5	20
Extra hepatic metastasis						
No	7	87.5	19	86.36	18	72
Yes	1	12.5	1	4.54	3	12
Treatment						
Conservative	3	37.5	7	31.82	6	24
TACE	3	37.5	4	18.18	3	12
RFA	2	25	8	36.36	11	44
Resection	0	0.0	1	4.55	1	4

Abbreviations: RFA, Radiofrequency ablation; TACE, Trans-arterial chemoembolization.

Cumulative Rates of HCC Development

Cumulative rates of HCC development were 2.1%, 4.1%, 10.4%, and 14.5% during the first, second, third and fifth year of follow-up, respectively (Mean, 25 months) (Figure 3).

Logistic Regression Analysis for the Parameters Predicting HCC Development

Univariate analysis of the baseline data revealed that DM, AFP, sofosbuvir, and daclatasvir regimens, liver stiffness measurements, and intermediate GES scores at baseline were linked to risk factors for the development of HCC (p = 0.04, 0.014, 0.04, 0.001, and 0.002, respectively). In the multivariate analysis, all previous factors were reported to be independent risk factors for HCC development, except for DM (Table 6).

Validity (AUC, Sensitivity, Specificity) of AFP and Liver Stiffness Measurements to Predict HCC

AFP at 6 ng/mL had a sensitivity and specificity of 64.2% and 62.7%, respectively, with an accuracy of 63% in predicting HCC development. Additionally, liver stiffness >30 kPa had a sensitivity and specificity of 62.96% and 73.86%, respectively, with an accuracy of 72% in predicting HCC development (Figures 4 and 5).

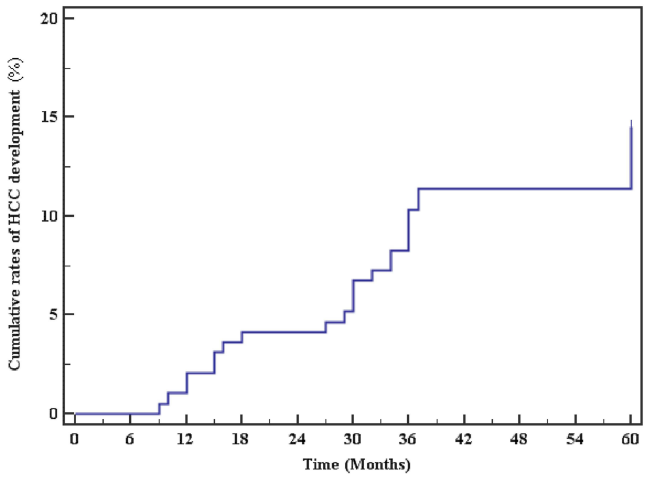

Figure 3 Kaplan–Meier curve for Cumulative rates of HCC development.
Abbreviation: HCC, hepatocellular carcinoma.

Table 6 Univariate and Multivariate Logistic Regression Analysis for the Parameters Predicting HCC Development

	Univariate		Multivariate	
	P	**OR (LL – UL 95%C.I)**	**P**	**OR (LL – UL 95%C.I)**
Age/years	0.145	1.043 (0.986–1.104)		
Gender (male)	0.209	1.850 (0.708–4.834)		
Treatment status (Naïve)	0.333	2.774 (0.352–21.884)		
Diabetes mellitus	0.048	2.407 (1.010–5.741)	0.039	3.120 (1.061–9.171)
Hypertension	0.279	0.436 (0.097–1.958)		
Treatment regimens				
SOF+LED	0.213	5.926 (0.360–97.610)		
SOF+DCV	0.048	2.361 (1.008–5.531)	0.005	4.759 (1.611–14.056)
SOF+DCV+RBV	0.363	0.555 (0.156–1.976)		
SOF+LED+RBV	0.866	0.876 (0.187–4.109)		
SOF+RBV	0.348	0.486 (0.108–2.193)		
SOF+RBV+IFN	0.415	0.422 (0.053–3.358)		
SOF+SIM	0.999	–		
SOF+SIM+RBV	0.999	–		
Ascites (Moderate + Severe)	0.999	–		
Encephalopathy	1.000	–		
Variceal Bleeding	0.464	0.460 (0.057–3.684)		
Child–Pugh score (B+C)	0.386	0.513 (0.113–2.320)		
Body mass index	0.540	1.029 (0.940–1.126)		
Bilirubin total (mg/dl)	0.547	0.809 (0.405–1.615)		
Serum albumin (g/dl)	0.808	1.086 (0.559–2.108)		
ALT (U/L)	0.883	0.999 (0.991–1.008)		
AST (U/L)	0.762	1.001 (0.993–1.010)		
HB (g/dl)	0.395	1.093 (0.890–1.343)		
TLC (10^3/ul)	0.491	0.932 (0.762–1.139)		
Platelets (10^3/ul)	0.781	1.001 (0.994–1.009)		
AFP (ng/mL)	0.014	1.030 (1.006–1.005)	0.003	1.053 (1.018–1.090)
Creatinine (mg/dl)	0.238	3.732 (0.418–33.320)		
LSM (Kpa)	0.001	1.048 (1.018–1.078)	0.002	1.052 (1.019–1.085)
APRI	0.825	0.967 (0.721–1.298)		
FIB4	0.929	1.007 (0.865–1.173)		
MELD	0.736	0.968 (0.803–1.168)		

(*Continued*)

Table 6 (Continued).

	Univariate		Multivariate	
	P	**OR (LL – UL 95%C.I)**	**P**	**OR (LL – UL 95%C.I)**
GES score				
Low	0.062	0.445 (0.190–1.043)		
Intermediate	0.002	3.882 (1.674–9.005)	0.006	3.925 (1.480–10.412)
High	0.103	0.184 (0.024–1.411)		

Abbreviations: SOF, sofosbuvir; LDV, Ledipasvir; DCV, daclatasvir; RBV, ribavirin; IFN, Interferon; SIM, simeprevir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; TLC, total leucocytic count; AFP, alpha fetoprotein; LSM, liver stiffness measurement; kPa, kilo Pascal; APRI, Aspartate Aminotransferase-to-Platelet Ratio Index; FIB-4, Fibrosis 4 (index); MELD, model of end stage liver disease; GES, general evaluation score.

The Overall Survival of the Studied Subjects

The mean survival was 58.3 months, and the probability of survival was 91.5% with CI of 57.5–59.1.

Logistic Regression Analysis for the Parameters Affecting Mortality

Univariate analysis of baseline data revealed that moderate and severe ascites, encephalopathy, variceal bleeding, Child B and C, pretreatment HCV RNA level, total bilirubin, albumin, PC, ALT, HB, TLC, platelet count, urea, and MELD were associated risk factors for patient mortality, while multivariate analysis revealed that only MELD can be considered an independent risk factor for patient mortality (Table 7).

Patients' Survival and the Development of HCC

It was found that the average survival time was substantially higher in patients without HCC (58.9 months) compared to those who developed HCC (54.9 months), (p = 0.001) (Figure 6).

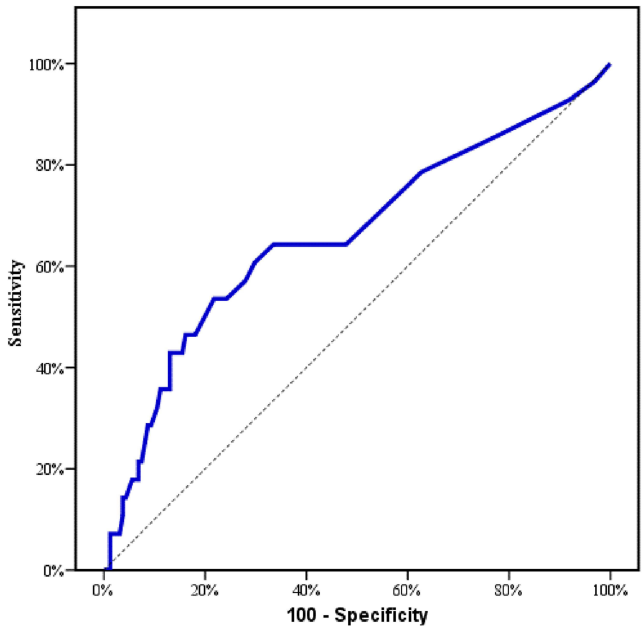

Figure 4 ROC curve of AFP to predict HCC.
Abbreviations: AFP, alpha fetoprotein; HCC, hepatocellular carcinoma.

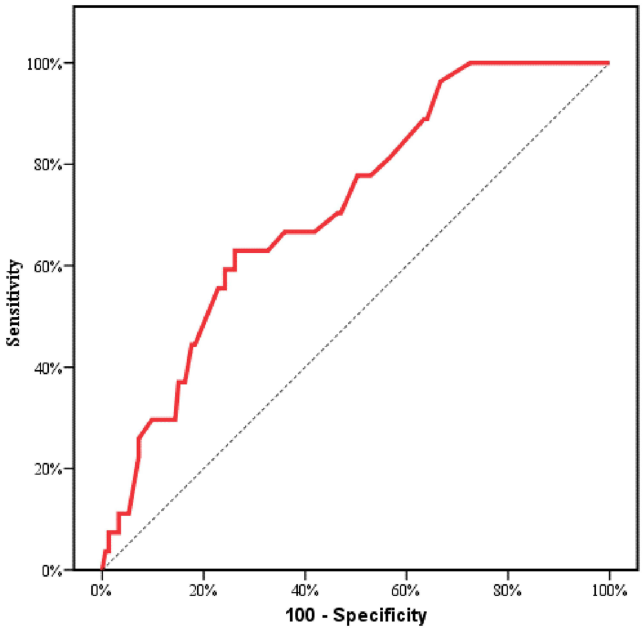

Figure 5 ROC curve for liver stiffness measurement (Kpa) to predict HCC.
Abbreviations: Kpa, kilo Pascal; HCC, hepatocellular carcinoma.

Patients' Survival and Liver Decompensation at the Baseline

The average survival time was substantially more significant in the compensated group (58.9 months) compared to the non-compensated group ($P = 0.001$) (Figure 7).

Table 7 Univariate and Multivariate Logistic Regression Analysis for the Parameters Affecting Mortality

	Univariate		Multivariate	
	P	**OR (95%C.I)**	**P**	**OR (95%C.I)**
Age/years	0.719	0.988 (0.927–1.053)		
Gender	0.617	1.311 (0.453–3.792)		
Treatment status	0.999	–		
Treatment regimen				
SOF+LED	0.091	11.400 (0.678–191.564)		
SOF+DCV	0.126	2.359 (0.786–7.077)		
SOF+DCV+RBV	0.848	0.858 (0.179–4.115)		
SOF+LED+RBV	0.790	0.752 (0.092–6.124)		
SOF+RBV	0.427	0.432 (0.054–3.427)		
SOF+RBV+IFN	0.999	–		
SOF+SIM	0.999	–		
SOF+SIM+RBV	0.999	–		

(*Continued*)

Table 7 (Continued).

	Univariate		Multivariate	
	P	**OR (95%C.I)**	**P**	**OR (95%C.I)**
Diabetes mellitus	0.290	1.832 (0.596–5.624)		
Hypertension	0.371	0.389 (0.049–3.080)		
Ascites (Moderate + Severe)	<0.001	28.333 (4.705–170.637)	0.937	1.324 (0.001–1455.235)
Encephalopathy	0.016	12.143 (1.588–92.857)	0.675	0.169 (0.000–688.943)
Variceal Bleeding	0.003	6.061 (1.809–20.304)	0.887	1.276 (0.044–37.267)
Child–Pugh score (B+C)	<0.001	7.583 (2.490–23.096)	0.916	0.769 (0.006–102.397)
HCV RNA measurement	0.017	1.0 (1.0–1.0)	0.080	1.000 (1.000–1.000)
Body mass index	0.792	0.984 (0.870–1.112)		
Bilirubin (mg/dl)	0.001	2.555 (1.456–4.482)	0.196	0.220 (0.022–2.185)
Serum albumin (g/dl)	<0.001	0.185 (0.078–0.438)	0.150	0.220 (0.028–1.731)
ALT (U/L)	0.008	0.960 (0.932–0.989)	0.311	0.970 (0.914–1.029)
AST (U/L)	0.062	0.980 (0.960–1.001)		
HB (g/dl)	<0.001	0.506 (0.353–0.726)	0.080	0.182 (0.027–1.225)
TLC (10^3/ul)	0.019	0.686 (0.501–0.940)	0.152	0.497 (0.191–1.294)
Platelets (10^3/ul)	0.029	0.985 (0.972–0.998)	0.339	0.982 (0.946–1.019)
AFP (ng/mL)	0.169	1.020 (0.992–1.048)		
Urea (mg/dl)	0.039	1.081 (1.004–1.164)	0.520	1.065 (0.880–1.288)
Creatinine (mg/dl)	0.269	4.807 (0.297–77.877)		
LSM (Kpa)	0.075	1.037 (0.996–1.079)		
APRI	0.349	0.799 (0.500–1.278)		
FIB-4	0.392	1.081 (0.904–1.292)		
MELD	<0.001	1.480 (1.236–1.771)	0.029	3.134 (1.121–8.763)

Abbreviations: SOF, sofosbuvir; LDV, Ledipasvir; DCV, daclatasvir; RBV, ribavirin; IFN, Interferon; SIM, simeprevir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; TLC, total leucocytic count; AFP, alpha fetoprotein; LSM, liver stiffness measurement; kPa, kilo Pascal; APRI, Aspartate Aminotransferase-to-Platelet Ratio Index; FIB-4, Fibrosis 4 (index); MELD, model of end stage liver disease.

Discussion

Chronic hepatitis C infection is a primary contributor to the development of severe liver fibrosis and cirrhosis, leading to a substantially increased risk of cirrhosis-related complications including portal hypertension and hepatocellular carcinoma (HCC0) occurrence.[24,25]

Historically, many prolonged follow-up researches have recorded that patients with early cirrhosis who attain SVR with interferon (IFN)-based therapy experience enhanced long-term results.[25] However, managing patients with severe fibrosis and cirrhosis is complex due to the extended duration, significant side effects, and limited effectiveness of treatment.[4,26] The availability of potent DAAs has dramatically improved the treatment of chronic HCV, especially in patients with severe fibrosis and cirrhosis, who can achieve SVR rates exceeding 95%.[27–30]

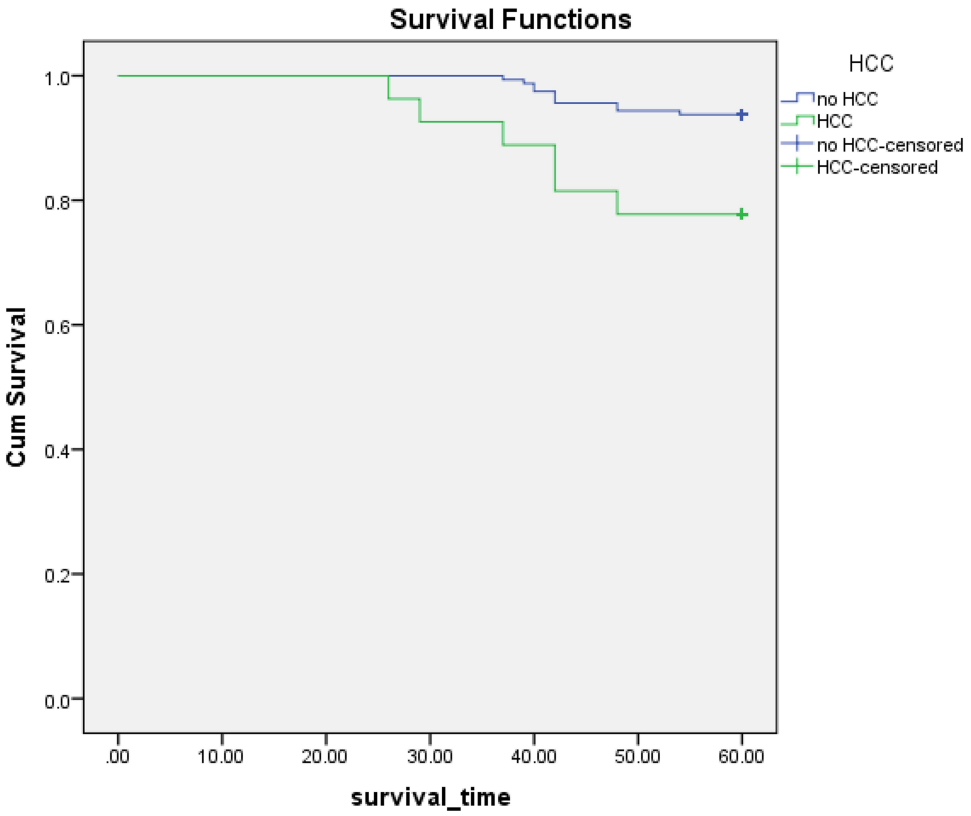

Figure 6 Kaplan–Meier curve of patients' survival and the development of HCC.
Abbreviation: HCC, hepatocellular carcinoma.

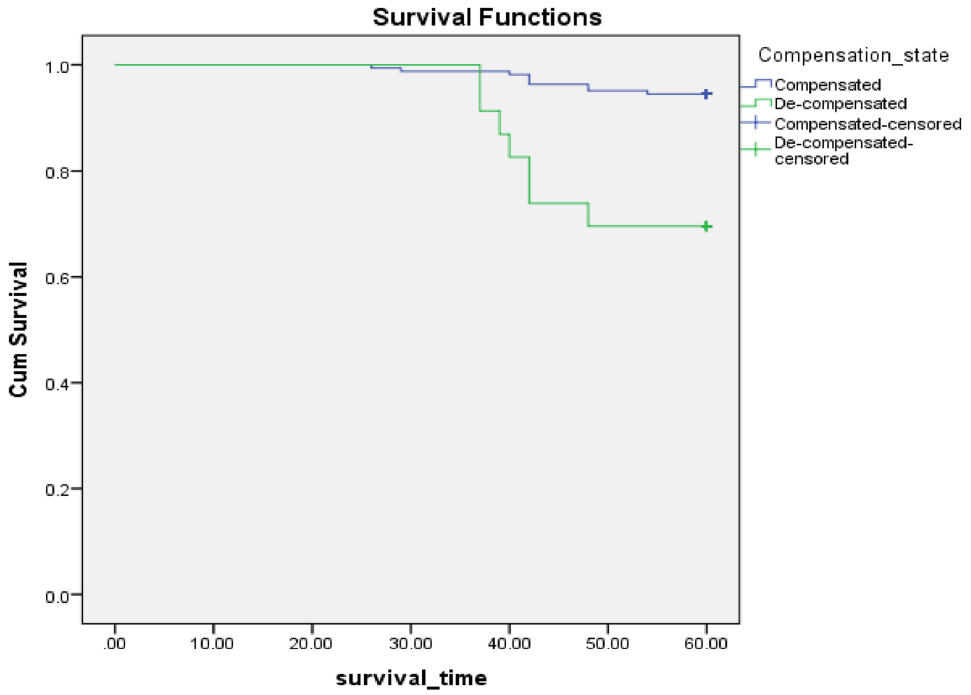

Figure 7 Kaplan–Meier curve of patients' survival and the presence of liver decompensation at the baseline.

Following SVR, patients can experience enhanced hepatic capacity, as assessed by MELD or CTP scores. Nevertheless, achieving long-term transplantation and survival without hepatocellular carcinoma (HCC) are attainable objectives in treatment.[14,31–33]

Therefore, this work was designed to detect the long-term impact of achieving SVR in cirrhotic patients following DAA treatment by determining decompensation, HCC development, and liver stiffness changes. This study included 193 subjects who attended the HCV outpatient unit at the National Liver Institute, Menofia University.

Throughout the follow-up period, a considerable rise in the mean albumin serum level and a decline in the serum bilirubin level was recorded which resulted in alterations in both the Child–Pugh and MELD scores.

The SOLAR-1 and SOLAR-2 studies demonstrated that patients with decompensated cirrhosis who were treated with DAAs along with a low dosage of RBV experienced enhancements in both their MELD and Child–Pugh scores.[34,35] These findings were also consistent with the results presented in another research, where the administration of sofosbuvir plus daclatasvir, along with a low dosage of RBV, demonstrated a positive impact on liver function for all genotypes.[36]

Moreover, in a study by Essa et al 2019, evaluating the impact of DDAs on hepatitis C virus-related decompensated liver cirrhosis, a significant improvement in the mean serum albumin and serum bilirubin levels was observed.[37]

Nevertheless, despite the high rates of SVR, Verna et al observed that the alterations in the MELD score and liver parameters throughout both short- and long-term monitoring were minimal. Among their patients, 56% showed improvement in MELD at SVR12. However, the average short-term change in MELD was less than one point overall. A clinically significant improvement of at least three MELD points was observed in just 24% of patients. After a prolonged period of observation (with a median duration of 213 weeks), there were very slight and insignificant average changes in the MELD score (a drop of 0.30 points). Furthermore, only a quarter of the participants attained a MELD score below 10, which was considered a benchmark for acceptable synthetic function.[36] In addition, Krassenburg et al 2021, found that an improvement in MELD score did not result in a favorable clinical outcome.[38]

The APRI and FIB-4 scores revealed remarkable improvement over the three-year follow-up ($p < 0.001$). Moreover, Liver stiffness (LS) measurements showed a significant decrease in the first- and third-year follow-up in relation to baseline and decreased in the third year when compared to the first year. In an 18-month study that al. reported considerable amelioration of liver stiffness among those who attained SVR.[39]

A notable decrease in the average LS was observed in a group of 554 individuals with compensated liver cirrhosis from Spain. The LS decreased from an initial measurement of 20.2 kPa to 13.9 kPa following 1 year of treatment with DAA medication.[40] In another study by Laursen et al 2020, a decline in LS by 15% in 71 patients with advanced liver disease was reported. This reduction occurred between the completion of therapy and the 1-year follow-up period. The patients were successfully treated with IFN-free therapy.[41]

Decompensation events noticed in 29% of patients, with a predominance of ascites. They were de-novo in 18.1% and progressed in 10.9% of cases. Baseline liver stiffness >30 kPa had a sensitivity of 51.43% and 72.48%, with an accuracy of 68.48% in predicting de-novo hepatic decompensation development.

In addition, Verna et al confirmed that previous decompensation events were more prevalent among patients who were followed up for longer duration, along with an increase in total bilirubin and albumin levels.[38]

Regarding The cumulative rates of HCC development, it was, 2.1%, 4.1%, 10.4%, and 14.5% during the first, second, third and fifth year of follow-up, respectively. During the early stages of the era of IFN-free, concerns were expressed regarding a potential link between DAA medication and a higher-than-predicted occurrence of HCC based on previously published reports.[42,43] However, this association was not supported after controlling for baseline covariates.

In contrast, a report from Metteke et al 2015, pointed that DAA treatment for patients with HCV-related chronic hepatitis did not change the early risk of HCC in those with liver cirrhosis, and a declined occurrence of HCC might be more obvious after a longer duration of follow-up.[44]

However, a lower incidence was confirmed by a previous prospective study on 1630 hCV-G4 patients with advanced fibrosis or cirrhosis who was treated with DAAs, and showed that, the overall crude incidence of HCC was 2.15 per 100 PYs. Moreover, it was diminished in patients without cirrhosis (F3 fibrosis) compared to those with cirrhosis,[45] which was also confirmed by Ioannou et al 2018.[46] Another study in a similar patients population found that, the incidence of

HCC in patient who did not receive treatment for their HCV-related cirrhosis was 5.57 per 100 PYs, while performing a screening program for HCC before the availability of DAAs.[47]

Similarly, in another study involving a broad population, it was found that treatment based on DAA was linked to a lower likelihood of developing liver cancer compared to both no HCV treatment or interferon-based regimen in the era before DAAs.[48] In addition, Muzica et al 2020, carried out an in-depth review of the present debate over the raised possibility of HCC after DAA therapy where they concluded that there was a decreased occurrence of both new and recurring cases of HCC after SVR.[49]

In our study, AFP at 6 ng/mL had a sensitivity and specificity of 64.2% and 62.7%, respectively, with an accuracy of 63% in predicting HCC development. Additionally, liver stiffness >30 kPa had a sensitivity and specificity of 62.96% and 73.86%, respectively, with an accuracy of 72% in predicting HCC development.

Consistent with our results, Wu et al 2016, found that older age, liver cirrhosis, and repeated AFP levels ≥15 ng/mL and APRI ≥0.7, pre- and post-treatment were indicators for HCC development in patients with SVR.[50]

The mean time of survival of our patients was 58.3 months, and the probability of survival was 91.5%. Baseline MELD was the only independent risk factor for mortality in multivariate analysis. The mean survival time was significantly prolonged in patients without HCC than in those with HCC and compensated patients.

Ochi et al 2021, documented a 48-month survival rate of 91.0% in the DAA group compared to 68.7% in the untreated group.[51]

Moreover, patients who successfully obtained sustained virologic response (SVR) experienced a noteworthy decrease in mortality. This improved outcome becomes evident within the initial 18 months of treatment.[52]

Furthermore, in earlier research assessing the impact of DAAS on the survival of patients with HCV-related HCC, the median overall survival was found to be 24.2 months. Patients who successfully achieved sustained virologic response at 12 weeks had a median overall survival of 75.6 months, compared to 26.7 months in those who did not reach SVR12 ($p < 0.0001$). Additionally, poor survival was associated with increased MELD score, greater tumor size, and the presence of tumors in both lobes of the liver ($p < 0.05$).[53]

Conclusion

Long-term elimination of the virus is linked to a gradual yet substantial enhancement in the stiffness of the liver. Nevertheless, liver function measurements exhibited improvement during the initial year and subsequently maintained stability. Moreover, the potential for the development of new cases of HCC is still a concern, particularly in patients who have elevated levels of alpha-fetoprotein (AFP) and increased liver stiffness at the onset of treatment and the possibility of new-onset decompensation persists even after achieving sustained virologic response (SVR). Consequently, it is required to monitor patients with advanced liver disease or cirrhosis even after having sustained virologic response (SVR).

The Limitations of the Current Study

First of all our study was single center study. Only decompensation events and HCC data were available after the 5th year of follow-up because of the COVID-19 epidemic. Finally, the sample size with longer duration of follow-up should be addressed in future research.

Ethics

This research adhered to the Declaration of Helsinki (revised 2013) and received ethical approval from the Institutional Review Board of the National Liver Institute (IRB00280). Written consent was obtained from all patients included in the study.

Disclosure

All author(s) declared no relevant conflicts of interest in the current study.

References

1. Blach S, Zeuzem S, Manns M.; Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol*. 2017;2(3):161–176. doi:10.1016/S2468-1253(16)30181-9
2. Van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. *J Hepatol*. 2016;65(1 Suppl):S95–S108. doi:10.1016/j.jhep.2016.07.039
3. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol*. 2010;8(3):280–288. doi:10.1016/j.cgh.2009.11.018
4. Vezali E, Aghemo A, Colombo M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis. *Clin Ther*. 2010;32(13):2117–2138. doi:10.1016/S0149-2918(11)00022-1
5. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol*. 2020;73:1170–1218.
6. D'Ambrosio R, Degasperi E, Colombo M, Aghemo A. Direct-acting antivirals: the endgame for hepatitis C? *Curr Opin Virol*. 2017;24:31–37. doi:10.1016/j.coviro.2017.03.017
7. Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet*. 2019;393(10179):1453–1464. doi:10.1016/S0140-6736(18)32111-1
8. Foster GR, Irving WL, Cheung MCM, et al. Impact of direct-acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*. 2016;64(6):1224–1231. doi:10.1016/j.jhep.2016.01.029
9. Fernandez Carrillo C, Lens S, Llop E, et al. Treatment of hepatitis C virus infection in patients with cirrhosis and predictive value of model for end-stage liver disease: analysis of data from the heap-C registry. *Hepatology*. 2017;65(6):1810–1822. doi:10.1002/hep.29097
10. World Health Organization, "Access to treatment and care for all: the path to eliminate hepatitis C in Egypt". Accessed on Jan. 17, 2024. Available from: https://www.who.int/news-room/feature-stories/detail/access-to-treatment-and-care-for-all–the-path-to-eliminate-hepatitis-c-in-egypt.
11. Maan R, van Tilborg M, Deterding K, et al. Safety and effectiveness of direct-acting antiviral agents for treatment of patients with chronic hepatitis C virus infection and cirrhosis. *Clin Gastroenterol Hepatol*. 2016;14(12):1821–1830. doi:10.1016/j.cgh.2016.07.001
12. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med*. 2015;373(27):2618–2628. doi:10.1056/NEJMoa1512614
13. Cheung MCM, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*. 2016;65(4):741–747. doi:10.1016/j.jhep.2016.06.019
14. Belli LS, Berenguer M, Cortesi PA, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: a European study. *J Hepatol*. 2016;65(3):524–531. doi:10.1016/j.jhep.2016.05.010
15. Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol*. 2008;48(5):835–847. doi:10.1016/j.jhep.2008.02.008
16. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. *Gastroenterology*. 2008;134(4):960–974. doi:10.1053/j.gastro.2008.01.034
17. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317–1325. doi:10.1002/hep.21178
18. Castera L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology*. 2005;128(2):343–350. doi:10.1053/j.gastro.2004.11.018
19. Poynard T, Vergniol J, Ngo Y, et al. Staging chronic hepatitis C in seven categories using fibrosis biomarker (FibroTest) and transient elastography (FibroScan(R)). *J Hepatol*. 2014;60(4):706–714. doi:10.1016/j.jhep.2013.11.016
20. Kaplan DE, Dai F, Aytaman A, et al. Development and performance of an algorithm to estimate the Child-Turcotte-Pugh score from a national 26 electronic healthcare database. *Clin Gastroenterol H*. 2015;13(13):2333. doi:10.1016/j.cgh.2015.07.010
21. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*. 2000;31(4):864–871. doi:10.1053/he.2000.5852
22. Omar A, Kaseb A, Elbaz T, et al. Egyptian society of liver cancer recommendation guidelines for the management of hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2023;10:1547–1571. doi:10.2147/JHC.S404424
23. Shiha G, Waked I, Soliman R, et al. GES: a validated simple score to predict the risk of HCC in patients with HCV-GT4-associated advanced liver fibrosis after oral antivirals. *Liver Int*. 2020;40(11):2828–2833. doi:10.1111/liv.14666
24. World Health Organization (WHO). *Hepatitis C Fact Sheet*. Geneva, Switzerland: World Health Organization; 2016.
25. Axley P, Ahmed Z, Ravi S, Singal AK. Hepatitis C virus and HCC: a narrative review. *J Clin Transl Hepatol*. 2018;6(1):79. doi:10.14218/JCTH.2017.00067
26. Van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;308(24):2584–2593. doi:10.1001/jama.2012.144878
27. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med*. 2014;370(21):1973–1982. doi:10.1056/NEJMoa1402869
28. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med*. 2015;373(27):2599–2607. doi:10.1056/NEJMoa1512610
29. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med*. 2014;370(16):1483–1493. doi:10.1056/NEJMoa1316366
30. Feld JJ, Ramji A, Shafran SD, et al. Ledipasvir-sofosbuvir plus ribavirin in treatment-naive patients with hepatitis C virus genotype 3 infection: an open-label study. *Clin Infect Dis*. 2017;65(1):13–19. doi:10.1093/cid/cix289
31. El-Sherif O, Jiang ZG, Tapper EB, et al. Baseline factors associated with improvements in decompensated cirrhosis after direct-acting antiviral therapy for hepatitis C virus infection. *Gastroenterology*. 2018;154(8):2111–2121e2118. doi:10.1053/j.gastro.2018.03.022
32. Crespo G, Trota N, Londono MC, et al. The efficacy of direct anti-HCV drugs improves early post-liver transplant survival and induces significant changes in waiting list composition. *J Hepatol*. 2018;69(1):11–17. doi:10.1016/j.jhep.2018.02.012

33. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. *Clin Infectious Dis*. 2015;61(5):730–740. doi:10.1093/cid/civ396
34. Manns M, Forns X, Samuel JD, et al. Ledipasvir/sofosbuvir with ribavirin is safe and efficacious in decompensated and post liver transplantation patients with HCV infection: preliminary results of the prospective solar 2 trial. *J Hepatol*. 2015;62:187–188. doi:10.1016/S0168-8278(15)30003-9
35. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology*. 2015;149(3):649–659. doi:10.1053/j.gastro.2015.05.010
36. Poordad F, Schiff ER, Vierling JM, et al. LO8: daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: Phase 3 ALLY1 study. *Hepatology*. 2015;62:S261–S262. doi:10.1016/S0168-8278(15)30154-9
37. Essa M, Sabry A, Abdelsameea E, Tharwa ES, Salama M. Impact of new direct-acting antiviral drugs on hepatitis C virus related decompensated liver cirrhosis. *Eur J Gastroenterol Hepatol*. 2019;31(1):53–58. doi:10.1097/MEG.0000000000001250
38. Verna EC, Morelli G, Terrault NA, et al. DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: real-world experience from HCV-TARGET cohort. *J Hepatol*. 2020;73(3):540–548. doi:10.1016/j.jhep.2020.03.031
39. Omar H, Said M, Eletreby R, et al. Longitudinal assessment of hepatic fibrosis in responders to direct-acting antivirals for recurrent hepatitis C after liver transplantation References 158 using noninvasive methods. *Clin Transplant*. 2018;32(8):e13334. doi:10.1111/ctr.13334
40. Krassenburg L, Maan R, Ramji A, et al. Clinical outcomes following DAA therapy in patients with HCV related cirrhosis depend on disease severity. *J Hepatol*. 2021;74(5):1053–1063. doi:10.1016/j.jhep.2020.11.021
41. Laursen TL, Siggaard CB, Kazankov K, et al. Time-dependent improvement of liver inflammation, fibrosis and metabolic liver function after successful direct-acting antiviral therapy of chronic hepatitis C. *J Viral Hepat*. 2020;27(1):28–35. doi:10.1111/jvh.13204
42. Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol*. 2016;65(4):719–726. doi:10.1016/j.jhep.2016.04.008
43. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol*. 2016;65(4):727–733. doi:10.1016/j.jhep.2016.06.015
44. Mettke F, Schlevogt B, Deterding K, et al. Interferon-free therapy of chronic hepatitis C with direct-acting antivirals does not change the short-term risk for de novo hepatocellular carcinoma in patients with liver cirrhosis. *Aliment Pharmacol Ther*. 2018;47(4):516–525. doi:10.1111/apt.14427
45. Kilany S, Ata L, Gomaa A, et al. Decreased incidence of hepatocellular carcinoma after directly acting antiviral therapy in patients with hepatitis C–related advanced fibrosis and cirrhosis. *J Hepatocell Carcinoma*. 2021;8:925. doi:10.2147/JHC.S295330
46. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. *J Hepatol*. 2018;68(1):25–32. doi:10.1016/j.jhep.2017.08.030
47. Eltabbakh M, Zaghla H, Abdel-Razek W. Elshinnawy H, Ezzat S, Gomaa A, Waked I. Utility and cost-effectiveness of screening for hepatocellular carcinoma in a resource-limited setting. *Med Oncol*. 2015;32(1):432. doi:10.1007/s12032-014-0432-7
48. Singer AW, Reddy KR, Telep LE, et al. Direct-acting antiviral treatment for hepatitis C virus infection and risk of incident liver cancer: a retrospective cohort study. *Aliment Pharmacol Ther*. 2018;47(9):1278–1287. doi:10.1111/apt.14593
49. Muzica CM, Stanciu C, Huiban L, et al. Hepatocellular carcinoma after direct-acting antiviral hepatitis C virus therapy: a debate near the end. *World J Gastroenterol*. 2020;26(43):6770–6781. doi:10.3748/wjg.v26.i43.6770
50. Wu CK, Chang KC, Hung CH, et al. Dynamic alpha-fetoprotein, platelets and AST-to-platelet ratio index predict hepatocellular carcinoma in chronic hepatitis C patients with sustained virological response after antiviral therapy. *J Antimicrob Chemother*. 2016;71(7):1943–1947. doi:10.1093/jac/dkw097
51. Ochi H, Hiraoka A, Hirooka M, et al. Direct-acting antivirals improve survival and recurrence rates after treatment of hepatocellular carcinoma within the Milan criteria. *J Gastroenterol*. 2021;56(1):90–100. doi:10.1007/s00535-020-01747-y
52. Butt AA, Yan P, Simon TG, Abou-Samra A. Effect of paritaprevir/ritonavir/ombitasvir/dasabuvir and ledipasvir/sofosbuvir regimens on survival compared with untreated hepatitis c virus-infected persons: results from ERCHIVES. *Clin Infect Dis*. 2017;65(6):1006–1011. doi:10.1093/cid/cix364
53. Kamp WM, Sellers CM, Stein S, Lim JK, Kim HS. Impact of direct acting antivirals on survival in patients with chronic hepatitis C and hepatocellular carcinoma. *Sci Rep*. 2019;9(1):1–8. doi:10.1038/s41598-019-53051-2