

Development of hepatocellular carcinoma in patients with chronic hepatitis C who had sustained viral response following direct-acting antiviral therapy

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Abstract

Background and Aim: Several studies have suggested that treatment with direct-acting antivirals (DAAs) in patients with chronic hepatitis C virus (HCV) may be associated with an increased risk of developing hepatocellular carcinoma (HCC). We investigated the incidence and risk factors of HCC in HCV patients who achieved a sustained virologic response (SVR) following DAA therapies.

Materials and Methods: The medical data of patients who were diagnosed with HCV and received DAA therapy in two tertiary centers in Turkey were retrospectively collected.

Results: Among them, 75 patients (52.4%) were noncirrhotic and 68 patients (47.6%) were cirrhotic. The overall SVR rate was 97.2% (139/143). It was 100% in noncirrhotic and 94.1% in cirrhotic patients. HCC was developed in 5 (7.4%) patients, all of whom had baseline cirrhosis. The annual rate of HCC occurrence was 2.94%, and the 5-year cumulative incidence of HCC was 7.3%. The mean Child-Pugh score (CPS) and Model for End-Stage Liver Disease (MELD) score significantly decreased after DAA treatment (CPS 7.0 vs 5.9, $p=0.001$; MELD 10.8 vs 9.5, $p=0.003$).

Conclusion: There was no significant increase in the rate of HCC in cirrhotic HCV patients treated with DAAs. This treatment led to a remarkably high SVR rate and lowered CPS and MELD scores in cirrhotic HCV patients.

Keywords: Chronic Hepatitis C infection; direct-acting antiviral agents; hepatocellular carcinoma.

Introduction

Hepatitis C is a common health problem worldwide, and there are approximately 100 million patients with hepatitis C globally.^[1] The main goal in the treatment of chronic hepatitis C is to obtain sustained virologic response week 12 (SVR12) after the completion of the treatment. One of the clear and biggest benefits of SVR is to decrease the risk of death by >50% in patients with fibrosis scores higher than 4. In cirrhotic patients, SVR slows down the progression of cirrhosis and delays complications and decompensation.^[2,3] In addition, it may also decrease the Model for End-Stage Liver Disease (MELD) score of patients on the transplant waiting list and may allow these patients to be delisted from the transplant list. On the other hand, achieving SVR can decrease the incidence of hepatocellular carcinoma (HCC), particularly in cirrhotic patients.^[4-6]

In recent years, higher rates of SVR have been reported using direct-acting antivirals (DAAs). Unlike the conventional interferon (IFN)-based treatment, DAAs have a lower rate of side effects and can be used to treat patients with decompensated cirrhosis. Although the first publications stated that these drugs reduced the risk of HCC development in cirrhotic patients, later studies reported a high rate of HCC development after achieving SVR in these patients.^[7,8] Meaningfully, this contradiction has caused confusion regarding the use of DAAs, mainly because the underlying mechanism and predisposing factors causing HCC are unclear.

In this study, we aimed to investigate the frequency of HCC in cirrhotic patients treated with DAAs following SVR and to explore whether HCC is an expected complication of cirrhosis or a consequence of DAAs.

Materials and Methods

Study Population

Our study was designed as a retrospective study and included patients who were treated during the period from June 2015 and September 2020. We included patients with chronic hepatitis C virus (HCV) who were treated with DAAs and followed for at least 1 year after therapy. Informed consent was obtained from each patient. The study protocol was conducted in accordance with the ethical rules of the 1975 Declaration of Helsinki, and the study was approved by the local ethics committee.

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Patients were divided into two groups: cirrhotic (n=68) and noncirrhotic patients (n=75). Prior to DAA treatment, routine laboratory tests, HCV RNA test, HCV genotypes, and liver imaging were performed in treatment-experienced patients (n=61, 42.7%) and treatment-naive patients (n=82, 57.3%). Patients were treated with a DAA-based regimen during 8, 12, or 24 weeks of anti-HCV treatment.

All patients were followed up monthly at the beginning of the treatment. After the completion of the treatment, cirrhotic patients were followed up every 3 months and noncirrhotic patients were followed up annually. In all patients, quantitative HCV RNA measurement was performed with a real-time polymerase chain reaction (PCR) test during the follow-up visits to monitor SVR.

Diagnosis of Cirrhosis

The diagnosis of cirrhosis was initially made histopathologically.^[9] If the diagnosis could not be established histopathologically, it was made based on clinical, radiological, and biochemical techniques, including complete blood count, biochemistry, ultrasonography, dynamic liver imaging, and endoscopic examination. The diagnosis was confirmed in the presence of compatible radiographic and endoscopic findings, thrombocytopenia ($<150 \times 10^3$), low albumin levels, albumin/globulin ratio reversal, alanine aminotransferase/aspartate transaminase (AST) ratio reversal, and prolonged international normalized ratio (INR).^[10]

Radiological Examination

Following antiviral therapy, cirrhotic patients were followed up periodically in terms of Child-Pugh score (CPS), MELD score, other complications of chronic liver disease, and the risk of HCC development. Dynamic magnetic resonance imaging (MRI) (Philips Achieva 3 Tesla MR) was performed using liver-specific contrast agent gadoxetate disodium (Primovist®-Bayer) in cirrhotic patients. Alpha-fetoprotein (Elisa-biotech) levels were assessed annually.

Patients who were diagnosed with HCC at the beginning of the treatment and those who were previously diagnosed with HCC and had a history of HCC treatment were excluded from the study. In addition, patients with concomitant chronic hepatitis B infection were also excluded from the study.

HCV RNA Measurement

The HCV RNA level was assessed using the quantitative PCR technique (COBAS AmpliPrep/COBAS TaqMan HCV Test, Roche Diagnostics GmbH, D-68298 Mannheim, Germany). HCV genotyping was studied in our molecular biology laboratory using the reverse hybridization and sequencing method for HCV genotyping (HCV II, Innogenetics, Belgium). Serological markers of HCV and hepatitis B virus were analyzed using the qualitative microparticle enzyme immunoassay (MakroEIA, ELECSYS 2010, Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim, Germany). Biochemical analysis was performed using an autoanalyzer (Beckman AU5800 autoanalyzer, Beckman Coulter, Inc., Brea, CA, USA). Hemogram tests were studied using an analyzer (Abbott Cell-Dyn 4000 analyzer, Abbott Laboratories, Abbott Park, IL, USA).

Ethical Approval and Consent to Participate

Ethics committee approval was received for this study from the Ethics Committee of Dicle University School of Medicine, who approved this study protocol (Ethics committee approval; Date: June 20, 2019; issue: 236).

Statistical Analysis

The data were analyzed using SPSS 25.0 for Windows (IBM Corp., Armonk, NY, USA). The normal distribution of data was assessed using the Shapiro-Wilk test, coefficient of variation, skewness, and kurtosis. Continuous variables with normal distribution were expressed as mean±standard deviation (SD), and those with nonnormal distribution were expressed as median and minimum and maximum values. Categorical variables were expressed as frequencies (n) and percentages (%). Continuous variables were compared using Student's t-test, and categorical variables were compared using the Mann-Whitney U test. In the comparison of patients with cirrhosis and HCC, a two-way ANOVA test followed by the Bonferroni correction was performed in groups with homogeneous variances, whereas Welch's ANOVA test and the Kruskal-Wallis test were performed in groups with nonhomogeneous variances. All tests were bilateral and a value of $p < 0.05$ was considered significant.

Results

A total of 143 patients with HCV infection comprised 75 (52.4%) noncirrhotic patients and 68 (47.6%) cirrhotic patients. The mean age of 143 patients was 55.3 years. Of the 143 patients, 83 (58%) of them were males and 60 (42%) were females. The median follow-up duration was 29 months (6–66 months). In cirrhotic patients, the mean follow-up period was 44.1 months, and these patients had significantly higher AST, gamma-glutamyl transferase, and INR levels and significantly lower platelet and albumin levels compared with noncirrhotic patients ($p < 0.05$ for all). The 61 treatment-experienced patients included 54 patients treated with pegylated IFN and ribavirin and 7 patients treated with telaprevir and boceprevir. The SVR rate was 100% (75/75) in noncirrhotic patients as opposed to 94.1% (64/68) in cirrhotic patients. The HCV RNA levels were significantly higher in cirrhotic patients than in noncirrhotic patients ($p < 0.001$). The most common genotype of HCV was genotype 1b (79.7%), followed by genotype 1a (8.4%), genotype 2 (4.9%), genotype 3 (3.5%), and genotype 4 (1.4%). However, the genotype of 3 (2.1%) patients could not be determined. Both platelet and albumin levels were significantly lower in cirrhotic patients compared with noncirrhotic levels. Of the 4 patients in whom SVR could not be achieved, 2 cirrhotic patients discontinued their medication and the other 2 patients were detected with viral replication after HCC development. HCC was developed in 7.4% (5/68) of cirrhotic patients (Table 1).

The mean CPS was 7.32 in cirrhotic patients and 11.1 in noncirrhotic patients. Of the 68 patients with cirrhosis, 47% (n=32) of them had Child A compensated liver cirrhosis, 32.4% (n=22) had Child B decompensated liver cirrhosis, and 20.6% (n=14) had Child C decompensated liver cirrhosis. In cirrhotic patients, the most common comorbidity was diabetes mellitus (13.2%), followed by coronary artery disease, dyslipidemia, and hypertension.

The most common complication seen in the follow-up period in cirrhotic patients was ascites (n=34, 50%), followed by varicosis (n=27, 39.7%), hepatic encephalopathy (n=9, 13.2%), hepatopulmonary syndrome (n=7, 10.3%), hepatorenal syndrome (n=5, 7.4%), and hepatocellular cancer (n=5, 7.4%).

A significant decrease was observed in CPS and MELD scores in cirrhotic patients treated with DAAs after the achievement of SVR. While the mean CPS decreased from 7.0 to 5.9 ($p = 0.001$), the mean MELD scores decreased from 10.8 to 9.5 ($p = 0.003$). Although there was a decrease in CPS and MELD scores at the beginning of the

Table 1. Demographic data of the cirrhotic and noncirrhotic patients treated with DAAs

	Study population (n=143)	Noncirrhotic (n=75)	Cirrhotic (n=68)	p*
Age (average, median)	55.2±19.4	48.1±15.4 (43)	63.2±18.7 (65)	0.004
Sex (M/F)	83/60 (58%–42%)	44/31 (58.6%–41.4%)	39/29 (57.3%–42.7%)	0.745
Mean follow-ups (months)	33.3 (6–66)	15.5 (6–18)	53.1 (9–66)	
ALT (U/L)	39.4±24.0	38.1±17.2	40.9±25.8	0.122
AST (U/L)	42.1±28.5	33.9±15.4	51.0±26.2	0.002
GGT (U/L)	50.6±45.3	43.8±35.1	58.2±40.7	0.023
Albumin (g/dL)	3.6±1.1	4.0±0.5	3.2±0.9	0.001
Total bilirubin (mg/dL)	0.9±0.7	0.7±0.3	1.1±0.6	0.003
Platelets (×10 ³ mL)	190±94	261±124	113±58	<0.001
INR	1.0±0.9	0.9±0.2	1.2±0.7	0.001
AFP (ng/mL)	6.2±5.5	5.8±4.1	6.6±5.2	0.078
HCV RNA (log 10 mL ⁻¹)	2.6×10 ⁶	4.7×10 ⁴	5.5×10 ⁶	<0.001
HCV genotype, n (%)				
Genotype 1a	12 (8.4%)	9 (6.3%)	3 (2.1%)	
Genotype 1b	114 (79.7%)	54 (37.7%)	60 (42.0%)	
Genotype 2	7 (4.9%)	5 (3.5%)	2 (1.4%)	
Genotype 3	5 (3.5%)	4 (2.8%)	1 (0.7%)	
Genotype 4	2 (1.4%)	1 (0.7%)	1 (0.7%)	
Uncertain	3 (2.1%)	2 (1.4%)	1 (0.7%)	
LED+SOF	60 (41.9%)	3 (2.1%)	57 (39.8%)	
SOF	5 (3.5%)	4 (2.8%)	1 (0.7%)	
OBV+PTV/r±DSV±RBV	69 (48.2%)	59 (41.2%)	10 (7.0%)	
GLE + PIB	9 (6.3%)	9 (6.3%)	0 (0.0%)	
Treatment-naive/treatment experienced, n (%)	82/61 (57.3%/42.7%)	53/22 (70.6%/29.4%)	29/39 (42.6%/57.3%)	
SVR, n (%)	139/143 (97.2%)	75/75 (100%)	64/68 (94.1%)	
HCC development	5/143 (3.5%)	0/75 (0%)	5/68 (7.3%)	

*: Statistical analysis was performed between cirrhotic and noncirrhotic patients; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gama-glutamyl transpeptidase; AFP: Alpha-fetoprotein; INR: International normalized ratio; LED+SOF: Ledipasvir+sofosbuvir; OBV+PTV/r±DSV: Ombitasvir+paritaprevir/ritonavir+dasabuvir; RBV: Ribavirin; GLE+PIB: Glecaprevir + pibrentasvir; SVR: Sustained virologic response; HCC: Hepatocellular cancer.

Table 2. Changes in Child-Pugh and MELD scores in cirrhotic patients treated with DAAs and cirrhotic patients who developed HCC

	Cirrhotic patients (n=63)				Patients who developed HCC (n=5)			
	Initiation of treatment	12 months	24 months	p	Initiation of treatment	12 months	24 months	p
Child-Pugh score	7.0±0.7	6.3±0.7	5.9±0.6	0.001	10.6±1.0	10.0±1.0	10.8±1.2	0.218
MELD score	10.8±1.2	9.8±1.0	9.5±0.9	0.003	14.8±1.5	13.9±1.4	15.5±1.7	0.097

HCC: Hepatocellular cancer; MELD: Model for end-stage liver disease.

treatment, these scores increased again due to decompensation following the development of HCC (Table 2).

In the 4-year follow-up of patients with liver cirrhosis, decompensation occurred in 6 (8.8%) patients, and HCC developed in 5 patients (7.4%). Liver transplantation was performed in 1 patient due to HCC and 2 patients due to decompensated cirrhosis. A total of 6 patients died during this period. Two patients died due to advanced HCC, 3 patients died due to complications of liver cirrhosis, and 1 patient died due to cardiovascular diseases (Fig. 1). The 4-year cumulative mortality rate of patients with cirrhosis was 8.8% (Fig. 2).

Only 5 (7.4%) out of 68 cirrhotic patients developed HCC, all of whom had decompensated cirrhosis. One of these patients was in Child B (4.5%) ([RR]: 4.30, p=0.364) stage and 4 (28.6%) of them were in Child C stage ([RR]: 6.28, p=0.084). However, HCC did not develop in noncirrhotic patients and patients with compensated cirrhosis during the follow-up period. HCC mostly developed within the first 2 years, within an average period of 17.2 months. HCC development rate was 2.94% per year for the first 2 years, and the 5-year cumulative incidence was 7.35%. Viral relapse occurred in 2 (40%) out of 5 cases who developed HCC. Of these 5 patients, 3 were within Milan criteria for

Table 3. Features of patients developing HCC

Age	66.4 (50–81)
Sex (F/M)	2/3
Child A	0/32 (0%)
Child B	1/22 (4.5%) (RR: 4.30, p=0.364 compared with Child A)
Child C	4/14 28.6% (RR: 6.28, p=0.084 compared with Child B)
Following therapy time of HCC	
1 year	2
2 years	2 (median: 17.2 months)
3 years	1
HCV recurrence	2/5 (40%)
AFP level >200	1/5 (19–1572)
Milan compatible	3/5
Milan incompatible	2/5
Transplantation	1
RFA	1
TACE	1
Exitus	2

HCC: Hepatocellular cancer; AFP: Alpha-fetoprotein; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization; RR: Relative risk.

liver transplantation while the remaining 2 were beyond Milan criteria. In these 5 patients, liver transplantation was performed in 1, radiofrequency radiation was performed in 1, and transcatheter arterial chemoembolization was performed in 1 patient. The remaining 2 patients died of HCC after a period (Table 3).

Discussion

At the end of the study, 5 out of 143 patients with HCV developed HCC (68 cirrhotic and 75 noncirrhotic). All HCC patients had a history of decompensated cirrhosis. In addition, virologic recurrence was detected in some patients after developing HCC. We do not know whether this is clinically related to HCC. There are no data on this subject in the literature. However, we can say that the risk of HCC in chronic HCV patients with cirrhosis continues in proportion to the stage of cirrhosis even after successful DAA treatment.

The annual risk of HCC development in cirrhotic patients with HCV is 2%–4%.^[10] In contrast, the annual risk of HCC development in cirrhotic patients treated with INF independent of DAA treatment is 3% (range, 2%–9.1%).^[11–15] In the present study, the annual rate of cirrhosis development was 2.94%, which was consistent with the literature.

Recent studies have reported unexpectedly high rates of de novo HCC and HCC recurrence in patients treated with DAAs, which has caused confusion about the efficacy of DAAs.^[16] There are several hypotheses to explain this situation, including pathological mechanisms such as changes in the immune system and cytokine network, T cell dysfunction, rapid suppression of HCV following DAA treatment which causes temporary immunosuppression through the depression of cytotoxic T lymphocytes and natural killer (NK) cells, and decreased tumor necrosis alpha (TNF- α) caused by DAA treatment.^[17]

Despite these pathophysiological mechanisms, there are conflicting results regarding the development of HCC. The rate of HCC occurrence was found statistically insignificant in five studies that com-

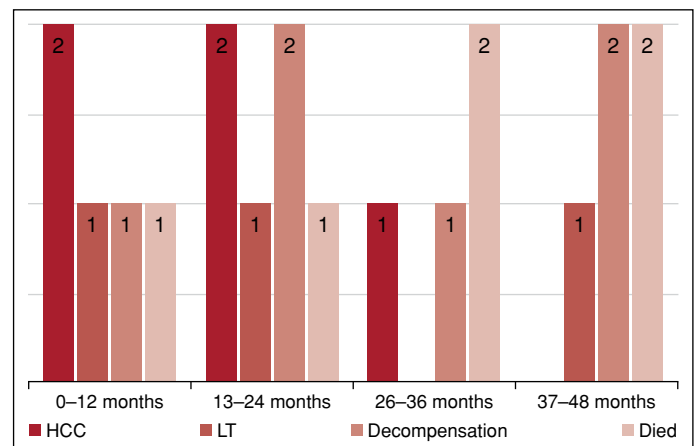


Figure 1. In the follow-up periods of patients with liver cirrhosis, the number of decompensation and HCC development, the number of deaths and the number of liver transplants.

HCC: Hepatocellular cancer.

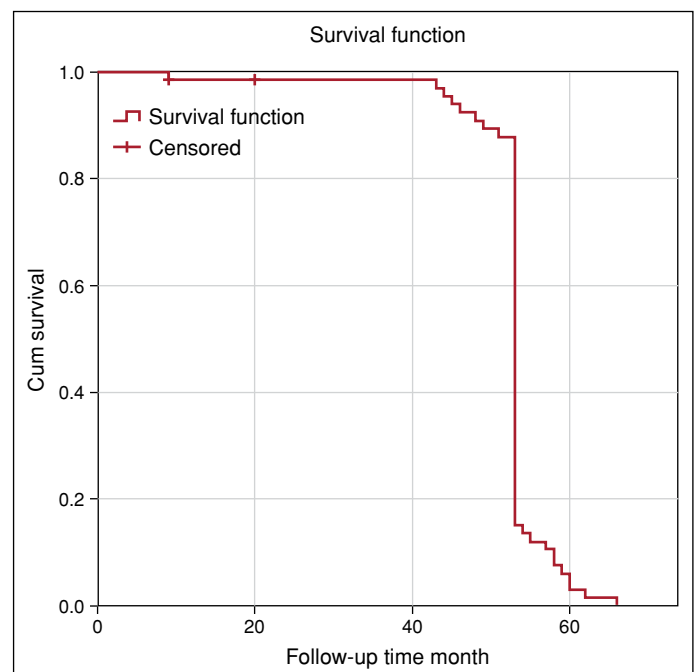


Figure 2. Survival rates of patients with liver cirrhosis.

pared patients treated with and without DAAs, while two other studies found that the rate of HCC occurrence was significantly lower in patients treated with DAAs.^[18] On the other hand, three other studies evaluated patients treated with DAAs or IFN with regard to HCC development and found no significant difference between the two groups.^[19] Similarly, a large multicenter cohort study from the United States and Canada found no significant difference between 304 patients treated with DAAs and 489 patients treated without DAAs with regard to early or general HCC occurrence.^[20]

A large study evaluated 22 500 cirrhotic and noncirrhotic patients with HCV and found no significant difference between patients treated with and without DAAs with regard to the risk of HCC development. In addition, the authors concluded that the incidence of HCC was lower in patients who achieved SVR.^[21]

In a 2019 study, Degasperi et al.^[22] conducted a large cohort study of 505 cirrhotic patients with HCV who were followed up for an average of 25 months and reported that 28 (6%) of these patients developed de novo HCC. The study also noted that achieving SVR with DAAs is likely to prevent liver-related complications in patients with HCV-associated cirrhosis. In a retrospective cohort study conducted with 1760 patients who were followed up for an average period of 3.5 years, cirrhotic HCV patients who were treated with DAAs were found to have a decrease in the rates of HCC development, hepatic decompensation, and cirrhosis-related complications and also had a relatively lower death rate. Accordingly, the authors recommended treating all cirrhotic HCV patients with DAAs regardless of the stage of cirrhosis.^[23]

In our study, significant improvements were observed in CPS and MELD scores in cirrhotic patients after achieving SVR within an average follow-up period of 44 months. It was also observed that achieving SVR following DAA treatment did not change the risk of HCC development in noncirrhotic HCV patients when compared with that in the general population. Therefore, these patients can be excluded from follow-up after successful DAA treatment.

In a recently published meta-analysis that included 44 studies, after HCV treatment, it has been determined that the risk of developing HCC is reduced. The incidence of HCC development in cirrhotic patients was found to be 2.1 per 100 person-years. This rate was found to be 0.5 in patients with early stage fibrosis ($\leq F3$). In this meta-analysis, it is stated that age and decompensated liver disease are associated with the risk of developing HCC.^[24]

A strong point of our study was the long-term and regular follow-up of patients and its prospective design at the time of the initiation of DAA treatment and the administration of real-time HCC screening for other comorbidities in all patients during both treatment and follow-up periods. However, our study was limited due to its relatively small number of patients and the absence of a control group with etiological causes related to cirrhosis other than HCV. In addition, considering the heterogeneous distribution of the genotypes of our patients and therefore the higher risk of HCC development in some genotypes, the results of this study cannot be generalized to all HCV patients or to all regions of the world. This limitation of the study is accepted by the authors.

Conclusions

The results indicated that there was no increase in the risk of HCC development in cirrhotic HCV patients treated with DAAs. Based on our findings, it can be concluded that DAAs are highly effective agents against HCV and that CPS and MELD scores and cirrhosis-related complications can be significantly reduced and that the risk of HCC persists even after achieving SVR. Accordingly, it is important to continue follow-ups in such patients in order not to miss out on possible complications.

Ethics Committee Approval: The Dicle University Clinical Research Ethics Committee granted approval for this study (date: 20.06.2019, number: 236).

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Conflict of Interest: The authors have no conflict of interest to declare.

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