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Original Research Article

Incidence of Hepatocellular Carcinoma in Patients With Chronic Hepatitis C Genotype III and Advanced Hepatic Fibrosis After Treatment With DAA

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Abstract: *Direct-acting antivirals with high efficacy and safety are effective in the treatment of cirrhotic and fibrosis patients with chronic hepatitis C patients.* ***Objective:*** *We conducted this study to assess the incidence of hepatocellular carcinoma in chronic hepatitis C patients genotype III with hepatic fibrosis or cirrhosis after the achievement of sustained viral response after treatment with direct-acting antivirals.* ***Methods:*** *A prospective study was conducted at the Department of Medicine, Arif Memorial Hospital, Lahore, from October 2023 to October 2024. A total of 500 CHC genotype III patients diagnosed with F3 and F4, who were undergoing treatment with direct-acting antivirals, were included in the study. Patients received a 3-month or 6-month course of DAA regimens. HCC was diagnosed by performing triphasic MSCT, and staging was done.* ***Results:*** *Out of 500 patients, 50 patients were diagnosed with HCC in the follow-up. HCC patients were predominantly elderly and male and had elevated AST, AFP, and bilirubin levels, as well as reduced platelet and albumin levels, compared to non-HCC patients. In cirrhotic patients, the HCC incidence per year was 2.920 per 100 people. Advanced age, male gender, increased AFP, and decreased albumin were among the predictors of HCC incidence in F4 patients.* ***Conclusion:*** *A reduced incidence of HCC was observed in patients with CHC fibrosis and cirrhosis who achieved SVR after treatment with DAAs.*

Keywords: Hepatocellular carcinoma, Hepatitis C, Fibrosis, Cirrhosis

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Introduction

Hepatocellular carcinoma is a commonly occurring cancer and a leading cause of global cancer-related mortality, with a 7% mortality rate among all cancers (1). Cirrhotic patients are at high risk of developing HCC, especially those with chronic hepatitis infection, accounting for 3-8% incidence in such patients (2). Patients with cirrhosis are at 30% risk of developing HCC in the commencing 5 years depending upon demographics, etiology, and stage of cirrhosis (3).

Literature has reported that SVR after interferon therapy decreases the risk of developing HCC, liver-related complications, and rate of mortality as compared to those patients who do not achieve SVR (4). A 5-year follow-up study in Japan reported an 18.9% incidence of HCC in patients achieving sustained virological response (SVR), compared to a 39.4% incidence in patients who did not achieve SVR (5). The findings were confirmed by Janjua et al. and Dash et al. (6,7). The results indicate that a sustained viral response after interferon therapy does not eliminate the risk of HCC but rather significantly reduces it.

Direct-acting antivirals with high efficacy and safety are effective in the treatment of cirrhotic and fibrosis patients with CHC. However, it remains unclear whether the SVR in such patients affects the risk of developing HCC. Multiple retrospective studies conducted in heterogeneous populations have reported an increased risk of HCC in such cases, while others contradict these findings (8, 9). This study was conducted to assess the incidence of hepatocellular carcinoma in chronic hepatitis C patients' genotype III with hepatic fibrosis or cirrhosis after achievement of sustained viral response after treatment with direct-acting antivirals.

Methodology

A prospective study was conducted in the Department of Medicine at Arif Memorial Hospital, Lahore, from October 2023 to October 2024. A total of 500 CHC genotype III patients diagnosed with advanced F3 and F4 fibrosis and undergoing treatment with direct-acting antivirals were included in the study. Patients with a history of HCC, hepatitis B, or HIV who had undergone interferon therapy, renal dysfunction, liver transplant, liver cell failure, and other cancers were excluded. Informed consent was taken from all patients. The hospital's ethics committee approved the study design.

Patients were evaluated, and their medical histories were documented before treatment. A physical and clinical examination was performed, including necessary tests and radiological examinations, such as abdominal ultrasound, CT scan, and Fibroscan. Transient elastography was performed for diagnosis of F3 liver fibrosis, and Child-Pugh classification scoring was used to detect F4 cirrhosis. After the initiation of treatments, follow-up visits were conducted every 4 weeks until the treatment was completed. After treatment completion, follow-up visits were conducted over 12 weeks to evaluate the achievement of SVR. A 6-month follow-up was conducted annually in every patient after treatment, during which hematological and biochemical tests were performed, along with an abdominal ultrasound.

Patients received a 3-month or 6-month course of DAA regimens. Two hundred fifty patients were administered sofosbuvir and ribavirin, 120 patients received sofosbuvir and daclatasvir, 75 patients received sofosbuvir, daclatasvir, and ribavirin, 25 patients received ombitasvir, paritaprevir, and ritonavir ± ribavirin, and 30 patients were given sofosbuvir and ledipasvir ± ribavirin. HCC was diagnosed by performing triphasic MSCT, and staging was done.[10]

All the data were analyzed using SPSS version 24. Medians were used to present continuous variables, and percentages were used for categorical variables. Quantitative variables were compared using the Wilcoxon Rank test, and Fisher's test was used to compare qualitative variables. The 95% confidence interval and HCC incidence were determined using the

Poisson distribution. Multivariate Cox analysis was performed to estimate the hazard ratio. A probability value of less than 0.001 was significant.

Results

Out of 500 patients, 50 patients were diagnosed with HCC in the follow-up. HCC patients were predominantly elderly and male and had elevated AST, AFP, and bilirubin levels, as well as reduced platelet and albumin levels, compared to non-HCC patients. The two groups did not differ in terms of ALT and creatinine levels. Most HCC patients had cirrhosis (90%) than liver fibrosis (10%) (Table I).

In F4 patients before treatment, only 15 patients (33.3%) reversed to the F3 or lower stage, and 30 (66.6%) showed no change in the fibrosis stage. In F3 patients before treatment, 40% showed improvement to F2 or lower, and 20% progressed to F4 (Table II). After treatment, the incidence of HCC was 2.342 per 100 person-years. In cirrhotic patients, the incidence per year was 2.920 per 100 people.

Advanced age, male gender, increased AFP, and decreased albumin were among the risk factors for the development of HCC in F4 patients. No significant risk factor was noted for HCC in F3 patients (Table III). Only 10% of tumors had PV invasion, and 52% of tumors were more significant than 3 cm. Multiple tumors were found in 54% of patients (Table IV).

Table 1: Features of HCC Patients

Variable	Patients with HCC (n=50)	Patients without HCC (n=450)	P value
Age	58 (54.4-64)	55 (51-61)	<0.001
Gender			
Male	38 (76%)	230 (51.1%)	<0.001
Female	12 (24%)	220 (48.9%)	
HCV RNA	5.40 (4.61-6.0)	5.58 (4.89-6.13)	0.140
ALT	49 (37.2-81.3)	48 (34-75)	0.530
AST	61 (41-100)	51 (36-77)	0.230
Total bilirubin	1.10 (0.90-1.55)	0.90 (0.65-1.20)	<0.001
Albumin	3.55 (3.20-5)	4 (3.70-4.40)	<0.001
Creatinine	0.85 (0.71-1)	0.83 (0.70-0.95)	0.138
Platelets	95 (63.6-142.7)	140 (95-190)	<0.001
Haemoglobin	14.1 (12.4-15)	14 (13.5-15)	0.220
White blood cells	6.22 (3.77-7.84)	6.50 (4.42-8.25)	0.067
AFP	32 (13.16-732.30)	7.2 (4.20-14.65)	<0.001
Fibrosis			
F3	5 (10%)	130 (28.9%)	<0.001
F4	45 (90%)	320 (71.1%)	
Cirrhosis classification			
A	33 (66%)	340 (75.5%)	0.020
B	17 (44%)	110 (24.6%)	
Diabetes mellitus	12 (24%)	93 (20.7%)	0.515
Hypertension	8 (16%)	70 (15.5%)	0.450
Obesity	28 (56%)	280 (62.2%)	0.156

Table 2: Incidence of HCC post-treatment

	HCC patients	IR/ 100py	95% CI
Number of patients	50	2.342	1.950-2.821
Baseline fibrosis stage			
F3	5	0.671	0.341-1.330
F4	45	2.920	2.412-3.540
F4 Patients at baseline			
Regressed to ≤F2	7	2.045	1.188-3.313
Regressed to F3	8	1.773	1.050-2.815
Stationary at F4	30	3.825	3.093-4.942
F3 Patients at baseline			
Regressed to ≤F2	2	0.438	0.120-1.195
Stationary at F3	2	0.810	0.211-2.195
Progressed to F4	1	1.380	0.240-4.540

Table 3: Predictors of HCC in cirrhotic patients

	Hazards ratio	95% Confidence Interval HR	P
Age	1.068	1.336-1.110	<0.001
Male gender	4.610	1.990-7.522	0.009
Diabetes mellitus	1.180	0.663-2.085	0.590
Hypertension	0.482	0.206-1.141	0.090
Obesity	0.818	0.492-1.383	0.460
Increased AFP	2.842	1.554-5.190	0.001

Decreased albumin	1.861	1.155-2.995	0.010
Decreased platelets	0.885	0.560-1.441	0.650

Table 4: Tumor characteristics

Characteristics	N (%)
Tumor location	
Left lobe	25 (50%)
Right lobe	10 (20%)
Both lobes	15 (30%)
Number of tumors	
Single	23 (46%)
Multiple	27 (54%)
Size of tumour	
≤3 cms	24 (48%)
Greater than three cm	26 (52%)
PV invasion	
Yes	5 (10%)
No	45 (90%)
BCLC	
0	4 (8%)
A	16 (32%)
B	15 (30%)
C	13 (26%)
D	2 (4%)

Discussion

We conducted this study to investigate the incidence of hepatocellular carcinoma (HCC) in patients with hepatitis C who were treated with direct-acting antivirals (DAAs). We noted a 2.34 incidence per 100 person-years in F4 cirrhotic patients. This incidence is significantly lower than the annual incidence of 5.3/100 PY reported by Watanabe et al., who included untreated F4 fibrosis patients (11). Our results are in line with a recent prospective study on HCV genotype III patients treated with DAAs, which reported a reduced incidence of 2.7/100 PY compared to 3.7/100 PY in untreated patients (12). Another retrospective study following the same methodology as ours reported a 2.12/100 PY incidence in cirrhotic patients treated with DAAs, which was significantly lower than in untreated patients (4.53/100 py) (13). Ide et al. also agree with our findings, which were conducted in Japanese patients and followed for a long time. However, this study included a majority of patients with HCV genotype 1 (14).

This incidence was higher than in a recent prospective study conducted on 3,197 CHC patients treated with DAAs, which reported that the treatment lowers the risk of HCC in the first year, with an average follow-up of 536 days. The incidence of HCC was 1.18 per 100 patients in a cohort of 2,710 (15). Li et al. reported an incidence of HCC of 2.28 per 100 patients among 1160 HCV patients treated with DAAs, whereas this incidence was doubled in untreated patients (16).

Improvement in the fibrosis stage was associated with lower HCC incidence, as evident in cirrhotic patients who progressed to F2 or lower stages (2.04/100 PY) compared to those whose fibrosis did not improve (3.825/100 PY). This indicates the positive impact of SVR on reducing hepatic morbidity by resolving fibrosis and reducing HCC incidence. Huang et al. evaluated the effect of the fibrotic stage on the development of HCC in CHC patients treated with Interferon therapy. They reported an association between improved fibrosis and the prediction of HCC (17). Improvement in fibrosis was also associated with reduced HCC in F3 patients (0.671/100 PY), which was significantly lower than in F4 patients. Romano et al. also reported an incidence of 0.46/100 PY of HCC in F3 CHC patients (15). Sanchez-Azorfra et al. reported a comparable incidence of 0.35/100 PY in a two-year follow-up (18).

We identified advanced age, male sex, and low levels of AFP and albumin as predictors of HCC. Other studies confirm our findings (19, 20). Diabetes mellitus was not reported among the predictors in any of the studies similar to ours, but it is a risk factor in CHC patients treated with Interferon.[21]

Our study has some limitations. We did not include any untreated patients due to ethical considerations. Since patients were treated with multiple courses of treatment, patients who did not achieve SVR were not present. Additionally, we did not perform a biopsy to assess the stages of fibrosis and used non-invasive procedures only.

Conclusion

A reduced incidence of HCC was observed in CHC fibrosis and cirrhosis patients achieving SVR after treatment with DAAs.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-MMNCS-88d-23)

Consent for publication
Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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