Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v2024i1.711
*Biol. Clin. Sci. Res. J., Volume, **2024**: 711*
Original Research Article

INCIDENCE OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS C GENOTYPE III AND ADVANCED HEPATIC FIBROSIS AFTER TREATMENT WITH DIRECT-ACTING ANTIVIRALS

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(Received, 09th November 2023, Revised 29th December 2023, Published 19th February 2024)

Abstract: *A prospective study was conducted at the Gastroenterology Department of Nishtar Hospital from August 2020 to August 2022 to evaluate the incidence of hepatocellular carcinoma (HCC) in chronic hepatitis C (CHC) patients with hepatic fibrosis or cirrhosis, genotype III, who achieved sustained viral response (SVR) after treatment with direct-acting antivirals (DAAs). The study included a total of 500 genotype III patients diagnosed with F3 and F4, who received a 3-month or 6-month course of DAA regimens. HCC was diagnosed by performing triphasic MSCT, and staging was done. During the follow-up, 50 out of 500 patients were diagnosed with HCC. The patients diagnosed with HCC were primarily elderly males and had higher levels of AST, AFP, and bilirubin, as well as reduced platelets and albumin levels compared to non-HCC patients. In cirrhotic patients, the incidence of HCC 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. The study findings suggest that CHC patients with fibrosis and cirrhosis who achieve SVR after treatment with DAAs have a reduced incidence of HCC.*

Keywords: Hepatocellular carcinoma, Hepatitis C, Fibrosis, Cirrhosis

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 (McGlynn et al., 2021). Cirrhotic patients are at high risk of developing HCC, especially those with chronic hepatitis infection, accounting for 3-8% incidence in such patients (Yen et al., 2021). Patients with cirrhosis are at 30% risk of developing HCC in the commencing five years, depending upon demographics, etiology, and stage of cirrhosis (Orci et al., 2022).

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 (Kinoshita et al., 2019). A 5-year follow-up in a Japanese study reported an 18.9% incidence of HCC in patients achieving SVR compared to a 39.4% incidence in non-SVR patients (Dang et al., 2020). The findings were confirmed by Janjua et al. and Dash et al.(Dash et al., 2020; Janjua et al., 2020). The results indicate that sustained viral response after interferon therapy does not eliminate the risk of HCC and reduces it significantly.

Direct-acting antivirals with high efficacy and safety are effective in the treatment of cirrhotic and fibrosis patients with CHC. However, it is still unclear whether the SVR in such patients impacts the risk of developing HCC. Multiple retrospective studies conducted in heterogeneous subjects have reported the increased risk of HCC in such cases, while others contradict these conclusions (Hsu et al., 2022; Yeh et al., 2021). 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 Gastroenterology Department of Nishtar Hospital from August 2020 to August 2022. 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, had undergone interferon therapy, renal dysfunction, liver transplant, liver cell failure, and other cancers were excluded. Informed consent was taken from all patients. The ethical committee of the hospital approved the study design. Patients were evaluated, and history was recorded before the treatment. Physical and clinical examination was performed through necessary tests and radiological tests, including abdominal ultrasound, CT scan, and Fibroscan. Transient elastography was performed to diagnose F3 liver fibrosis, and Child-Pugh classification scoring was used to detect F4 cirrhosis. After initiation of treatments, follow-up visits were done every four weeks until treatment was completed. After treatment completion, follow-up visits were done for 12 weeks to evaluate the achievement of SVR. A 6-month follow-up was done in every patient for a year after the treatment, during which hematological and biochemical tests were performed along with abdominal ultrasound.

[Citation: Kanju, S., Sherwani, U.K., Raza, A., Sarwar, S., Wadhak, M.A. (2024). Incidence of hepatocellular carcinoma in patients with chronic hepatitis c genotype III and advanced hepatic fibrosis after treatment with direct acting antivirals. *Biol. Clin. Sci. Res. J.*, **2024***: 711*. doi: https://doi.org/10.54112/bcsrj.v2024i1.711]

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, ritonavir ± ribavirin, and 30 patients were given sofosbuvir, ledipasvir ± ribavirin. HCC was diagnosed by performing triphasic MSCT, and staging was done (Golfieri et al., 2019).

All the data was analyzed using SPSS version 24. Medians were used to present continuous variables, and percentages were used to represent categorical variables. Quantitative variables were compared using the Wilcoxon Rank, and Fisher's tests compared qualitative variables. 95% confidence interval and HCC incidence were determined by Poisson distribution. A multi-variate Cox analysis was done to estimate the hazard ratio. A probability value of less than 0.001 was significant.

Results

Out of 500 patients, 50 were diagnosed with HCC in the follow-up. HCC patients were elderly, primarily male, and had AST, AFP, and bilirubin and reduced platelets and albumin levels compared to non-HCC patients. The two groups did not differ in ALT and creatinine levels. Most HCC patients had cirrhosis (90%) than liver fibrosis (10%) (Table 1).

In F4 patients before treatment, only 15 (33.3%) reversed to 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 more down, and 20% progressed to F4 (Table 2). 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 developing HCC in F4 patients. No significant risk factor was noted for HCC in F3 patients (Table 3). Only 10% of tumors had PV invasion, and 52% were more significant than 3 cm. Multiple tumors were found in 54% of patients (Table 4).

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
Hemoglobin	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			

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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% Confience 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 tumor	
≤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 assess the incidence of HCC in hepatitis C patients treated with 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 (Watanabe et al., 2019). Our results align with a recent prospective study on HCV genotype III patients treated with DAAs that reported a reduced incidence of 2.7/100 PY compared to 3.7/100 PY in untreated patients (Carrat et al., 2019). Another retrospective study following our methodology reported a 2.12/100 PY incidence in cirrhotic patients treated with DAAs, significantly lower than in untreated patients (4.53/100 py) (Wei and Huang, 2019). Ide et al. also agree with our findings, which were conducted in Japanese patients and were followed for a long time, but this study included a majority of HCV genotype I patients (Ide et al., 2019).

This incidence was higher than in a recent prospective study conducted on 3197 CHC patients treated with DAAs, which reported that the treatment lowers the risk of HCC in the first year during an average follow-up of 536 days. The incidence of HCC was 1.18 per 100 patients out of a 2710 cohort population (Romano et al., 2018). Li et al. reported the incidence of HCC as 2.28 per 100 patients out of 1160 HCV patients treated with DAAs, while this incidence was doubled in untreated patients (Li et al., 2018).

Improvement in the fibrosis stage was associated with lower HCC incidence, evident in cirrhotic patients who improved to F2 or lower stage (2.04/100 PY) than in patients 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 the association between improved fibrosis and the prediction of HCC (Huang et al., 2018).

Improvement in fibrosis was also associated with reduced HCC in F3 patients (0.671/100 PY), significantly lower than in F4 patients. Romano et al. also reported 0.46/100 PY incidence of HCC in F3 CHC patients.15 Sanchez-Azorfra et al. said a comparable incidence of 0.35/100 PY in a two-year follow-up (Sanchez-Azofra et al., 2019).

We identified advanced age, male sex, low AFP, and albumin as predictors of HCC. Other studies confirm our findings (Degasperi et al., 2019; Lleo et al., 2019). 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 (Nakano et al., 2019).

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. We did not perform a biopsy to assess fibrosis stages 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.
Consent for publication
Approved
Funding
Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

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Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, and final approval.
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[Citation: Kanju, S., Sherwani, U.K., Raza, A., Sarwar, S., Wadhak, M.A. (2024). Incidence of hepatocellular carcinoma in patients with chronic hepatitis c genotype III and advanced hepatic fibrosis after treatment with direct acting antivirals. *Biol. Clin. Sci. Res. J.*, **2024***: 711*. doi: https://doi.org/10.54112/bcsrj.v2024i1.711]

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