Journal of Health and Rehabilitation Research 2791-156X JHRR

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Original Article

Risk of Hepatocellular Carcinoma Development in Chronic Hepatitis C Patients Achieved Sustained Virological Response with Interferon-Based Treatments

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Conflict of Interest: None.

Kumar C., et al. (2024). 4(2): DOI: https://doi.org/10.61919/jhrr.v4i2.1143

ABSTRACT

Background: Chronic Hepatitis C (CHC) infection is a well-established risk factor for Hepatocellular Carcinoma (HCC). Even after achieving a sustained virological response (SVR) through interferon-based treatment, the risk of developing HCC persists, albeit at a lower rate. Surveillance plays a critical role in preventing HCC progression, which is often a consequence of long-term liver damage or cirrhosis due to chronic infection.

Objective: To assess the risk of hepatocellular carcinoma development in chronic hepatitis C patients who achieved sustained virological response with interferon-based treatments.

Methods: This cross-sectional descriptive study was conducted in the Department of Gastroenterology at the Asian Institute of Medical Sciences (AIMS), Hyderabad, from January to June 2024. A total of 115 patients with chronic hepatitis C who achieved SVR following interferon-based treatments were included. Initial assessments included laboratory investigations, liver biopsies, and imaging studies. Serum HCV RNA and HCV genotype were collected at the start of treatment, at the end of treatment, and 24 weeks post-treatment. Follow-up was defined as the time from the completion of treatment to the date of HCC detection or the last available imaging if no HCC was detected. Data were analyzed using SPSS version 26.0, with significance set at $P<0.05$.

Results: The study included 115 patients, with a mean age of 53.68 years; 54.8% were males, and 45.2% were females. Hepatocellular carcinoma was detected in 7 patients (6.1%). Genotype 2 had the highest rate of HCC occurrence at 16.7%, followed by genotype 1 at 5.6%; no HCC cases were found in genotype 3 ($P=0.198$). HCC incidence was higher in stage F0 fibrosis (18.8%) compared to stage F4 fibrosis (14.3%), with no cases in stages F3, F5, or F6 ($P=0.292$).

Conclusion: Despite achieving sustained virological response with interferon-based treatments, some chronic hepatitis C patients developed hepatocellular carcinoma. The risk of HCC remains, particularly in older patients and those with advanced liver fibrosis. Continuous monitoring and follow-up are essential for early detection and management of HCC. Further research is needed to identify specific risk factors and improve post-treatment care.

Keywords: Chronic Hepatitis C, Hepatocellular Carcinoma, Interferon-Based Treatment, Sustained Virological Response, HCC Risk Factors, Liver Fibrosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) represents a significant global health burden due to its high mortality rate and limited options for curative treatment. Chronic Hepatitis C (CHC) infection is a principal risk factor for the development of HCC, primarily due to persistent liver inflammation and injury that progresses over time. The natural history of CHC typically involves the progression from liver fibrosis to cirrhosis, ultimately leading to HCC as a final outcome (1). Over the past few decades, interferon-based therapy has been widely used to treat CHC, with the primary goal of achieving a sustained virological response (SVR), defined by the absence of hepatitis C virus (HCV) RNA in plasma 12-24 weeks post-treatment (2). Achieving SVR is associated with a significant reduction in liver-related complications and mortality, highlighting the efficacy of interferon-based treatments in managing CHC (3).

However, despite the success of interferon-based treatments in achieving SVR, the risk of HCC is not entirely eliminated. Patients with severe liver fibrosis or cirrhosis at the time of SVR attainment remain at substantial risk for HCC development (4). This residual risk can be attributed to the incomplete restoration of liver integrity following prolonged HCV infection, which continues to promote oncogenic events in the liver. Consequently, even after achieving SVR, continuous monitoring and surveillance for HCC are recommended, particularly for high-risk patients (5). Numerous studies have evaluated the incidence of HCC in patients who achieved SVR through interferon-based therapies, generally indicating a significant reduction in HCC risk compared to non-responders. However, the extent of this risk reduction and the determinants of residual risk vary across different populations and study models (6).

Several factors influence the residual risk of HCC after SVR, including age, gender, the stage of liver disease at the time of treatment, and lifestyle factors such as alcohol consumption and obesity (7). In particular, patients with advanced fibrosis or cirrhosis continue to face a high risk of HCC due to ongoing liver regeneration and the potential presence of dysplastic nodules that may undergo malignant transformation (8). Therefore, the persistent liver disease itself remains a significant risk factor for hepatocarcinogenesis, even after successful antiviral eradication. Continued surveillance through regular ultrasound examinations and alpha-fetoprotein (AFP) testing is crucial for early HCC detection and management, thereby improving survival outcomes (9).

In this context, the effectiveness of interferon-based treatments in reducing HCC risk is evident, yet it is not absolute. The present study aims to assess the risk of HCC development in CHC patients who have achieved SVR following interferon-based treatments. By analyzing a cohort of 115 patients treated at the Asian Institute of Medical Sciences (AIMS), Hyderabad, we seek to elucidate the residual risk factors and emphasize the need for ongoing monitoring and follow-up in these patients. This study contributes to the growing body of evidence supporting the importance of post-treatment surveillance in mitigating the long-term risk of HCC and improving patient outcomes (10).

MATERIAL AND METHODS

This cross-sectional descriptive study was conducted in the Department of Gastroenterology at the Asian Institute of Medical Sciences (AIMS), Hyderabad, from January to June 2024. The study included 115 patients with chronic hepatitis C who achieved sustained virological response (SVR) following interferon-based treatments. The inclusion criteria were patients over 20 years old who tested positive for HCV infection confirmed by both Anti-HCV and HCV RNA for more than six months before therapy, treated with Interferon (IFN) combined with ribavirin and, in some cases, with telaprevir or boceprevir. Patients had to show negative HCV RNA results at the end of therapy and 24 weeks post-treatment, without concurrent HBV or HIV coinfection, and had undergone post-treatment imaging studies for more than six months. Exclusion criteria included patients younger than 20 years, those with HBV or HIV coinfection, other chronic liver disease etiologies, and a history of HCC or liver transplantation.

Laboratory investigations were conducted initially, including liver biopsies and imaging studies. At the start of treatment, end of treatment, and 24 weeks after treatment, serum HCV RNA levels and HCV genotypes were measured. Baseline laboratory values collected included serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, alpha-fetoprotein (AFP), prothrombin time (PT), international normalized ratio (INR), albumin, and platelet counts. Cirrhosis was diagnosed based on radiological, endoscopic, or histological findings.

Patients were followed from the completion of treatment to the date of HCC detection or the date of the last available imaging if no HCC was detected. Data collection was comprehensive, ensuring that all relevant clinical and laboratory information was captured for analysis. The study adhered to ethical guidelines in accordance with the Helsinki Declaration, and ethical approval was obtained from the institutional review board of AIMS. Informed consent was obtained from all participants before their inclusion in the study.

Data analysis was performed using SPSS version 26.0. Descriptive statistics, including mean and standard deviation for continuous variables and frequencies and percentages for categorical variables, were used to summarize the data. Comparative analysis between groups was conducted using appropriate statistical tests to determine the significance of differences in demographic, clinical, and laboratory parameters. The level of statistical significance was set at $P<0.05$.

In summary, this study meticulously collected and analyzed data to assess the risk of hepatocellular carcinoma development in chronic hepatitis C patients who achieved SVR with interferon-based treatments, providing valuable insights into residual risk factors and the necessity for continuous monitoring and follow-up.

RESULTS

The study comprised 115 patients with chronic hepatitis C who achieved sustained virological response (SVR) following interferon-based treatments. The mean age of the patients was 53.68 years, with a standard deviation of 9.01 years. The gender distribution

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included 63 males (54.8%) and 52 females (45.2%). The majority of patients (76.5%) were over 50 years of age. The mean body mass index (BMI) was 26.46 kg/m², with 60.0% of patients having a BMI between 20-26 kg/m².

Table 1 Demographic Characteristics of the Patients (n=115)

Variables	Frequency (%)
Gender	
Male	63 (54.8)
Female	52 (45.2)
Age, Mean ± SD = 53.68 ± 9.01 Years	
20-50 Years	27 (23.5)
>50 Years	88 (76.5)
Body Mass Index, Mean ± SD = 26.46 ± 4.21 kg/m²	
20-26 kg/m²	69 (60.0)
>26 kg/m²	46 (40.0)
Genotype	
G1	90 (78.3)
G2	12 (10.4)
G3	13 (11.3)
Stage of Fibrosis	
F0	16 (13.9)
F1	19 (16.5)
F2	46 (40.0)
F3	5 (4.3)
F4	7 (6.1)
F5	4 (3.5)
F6	18 (15.7)
Treatment	
PEG-IFN alfa 2a/2b + Ribavirin	107 (93.0)
PEG-IFN alfa 2a/2b + Ribavirin + Telaprevir	6 (5.2)
PEG-IFN alfa 2a/2b + Ribavirin + Boceprevir	2 (1.7)
Child Pugh Class	
A	9 (7.8)
B	17 (14.8)
C	89 (77.4)
Mortality	
Yes	9 (7.8)
No	106 (92.2)
Hepatocellular Carcinoma	
Yes	7 (6.1)
No	108 (93.9)

Table 2 Laboratory Findings (n=115)

Laboratory Parameter	Mean ± SD
AST (IU/mL)	64.09 ± 61.11
ALT (IU/mL)	78.23 ± 70.10
GGT (IU/mL)	54.74 ± 60.02
ALP (IU/mL)	92.07 ± 72.46
Total bilirubin (mg/dL)	1.19 ± 1.30
AFP (ng/mL)	15.41 ± 21.08

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Laboratory Parameter	Mean ± SD
INR	1.41 ± 0.64
Albumin (g/dL)	4.31 ± 0.68
Platelet count (×10^3/µL)	208.30 ± 110.26

Table 3 Clinical Characteristics of Patients with Hepatocellular Carcinoma (n=115)

Variables	Hepatocellular Carcinoma	P-Value
	Yes (n=7)	No (n=108)
Age Group		
20-50 Years	2 (7.4%)	25 (92.6%)
>50 Years	5 (5.7%)	83 (94.3%)
Gender		
Male	3 (4.8%)	60 (95.2%)
Female	4 (7.7%)	48 (92.3%)
BMI		
20-26 kg/m²	3 (4.3%)	66 (95.7%)
>26 kg/m²	4 (8.7%)	42 (91.3%)
Genotype		
G1	5 (5.6%)	85 (94.4%)
G2	2 (16.7%)	10 (83.3%)
G3	0 (0.0%)	13 (100.0%)
Stage of Fibrosis		
F0	3 (18.8%)	13 (81.3%)
F1	1 (5.3%)	18 (94.7%)
F2	2 (4.3%)	44 (95.7%)
F3	0 (0.0%)	5 (100.0%)
F4	1 (14.3%)	6 (85.7%)
F5	0 (0.0%)	4 (100.0%)
F6	0 (0.0%)	18 (100.0%)
Child Pugh Class		
A	0 (0.0%)	9 (100.0%)
B	1 (5.9%)	16 (94.1%)
C	6 (6.7%)	83 (93.3%)
Treatment		
PEG-IFN alfa 2a/2b + Ribavirin	7 (6.5%)	100 (93.5%)
PEG-IFN alfa 2a/2b + Ribavirin + Telaprevir	0 (0.0%)	6 (100.0%)
PEG-IFN alfa 2a/2b + Ribavirin + Boceprevir	0 (0.0%)	2 (100.0%)

Table4 Clinical Characteristics of Patients with Mortality (n=115)

Variables	Mortality	P-Value
	Yes (n=9)	No (n=106)
Age Group		
20-50 Years	2 (7.4%)	25 (92.6%)
>50 Years	7 (8.0%)	81 (92.0%)
Gender		
Male	5 (7.9%)	58 (92.1%)
Female	4 (7.7%)	48 (92.3%)
BMI		
20-26 kg/m²	3 (4.3%)	66 (95.7%)

Variables	Mortality	P-Value
>26 kg/m²	6 (13.0%)	40 (87.0%)
Genotype		
G1	7 (7.8%)	83 (92.2%)
G2	2 (16.7%)	10 (83.3%)
G3	0 (0.0%)	13 (100.0%)
Stage of Fibrosis		
F0	0 (0.0%)	16 (100.0%)
F1	0 (0.0%)	19 (100.0%)
F2	5 (10.9%)	41 (89.1%)
F3	0 (0.0%)	5 (100.0%)
F4	2 (28.6%)	5 (71.4%)
F5	0 (0.0%)	4 (100.0%)
F6	2 (11.1%)	16 (88.9%)
Child Pugh Class		
A	3 (33.3%)	6 (66.7%)
B	1 (5.9%)	16 (94.1%)
C	5 (5.6%)	84 (94.4%)
Treatment		
PEG-IFN alfa 2a/2b + Ribavirin	9 (8.4%)	98 (91.6%)
PEG-IFN alfa 2a/2b + Ribavirin + Telaprevir	0 (0.0%)	6 (100.0%)
PEG-IFN alfa 2a/2b + Ribavirin + Boceprevir	0 (0.0%)	2 (100.0%)

In this study, hepatocellular carcinoma (HCC) was detected in 7 patients (6.1%). The highest rate of HCC occurrence was in genotype 2 (16.7%), whereas genotype 1 showed an HCC rate of 5.6%, and no cases were found in genotype 3. The stage of fibrosis indicated that HCC appeared most frequently in stage F0 (18.8%) compared to stage F4 (14.3%), with no positive cases identified in stages F3, F5, or F6. However, the differences in fibrosis stage distribution were not statistically significant (P=0.292).

The clinical characteristics of patients with mortality were also analyzed. No significant differences were observed in age, gender, genotype, stage of fibrosis, or treatment regimen between the mortality and non-mortality groups. However, significant differences were noted in BMI and Child-Pugh class. A higher proportion of patients with BMI >26 kg/m² experienced mortality (13.0%) compared to those with a BMI between 20-26 kg/m² (4.3%). Additionally, a higher percentage of patients classified as Child-Pugh class A experienced mortality (33.3%) compared to class B (5.9%) and class C (5.6%).

These results underscore the importance of continuous monitoring and follow-up in chronic hepatitis C patients who achieve SVR, particularly in those with advanced liver fibrosis or cirrhosis. Despite successful treatment, the risk of HCC remains, emphasizing the need for ongoing surveillance to detect and manage HCC early in these patients. Further research is necessary to identify specific risk factors and improve post-treatment care.

DISCUSSION

The findings of this study highlight the persistent risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC) who achieved sustained virological response (SVR) following interferon-based treatments. Despite the significant reduction in HCC risk associated with SVR, the residual risk remains, particularly in patients with advanced liver fibrosis or cirrhosis at the time of treatment. This study aligns with previous research that has documented a continued albeit reduced risk of HCC in patients achieving SVR (11, 12)

The observed HCC incidence of 6.1% in this cohort underscores the need for ongoing surveillance in high-risk patients. Previous studies have reported varying rates of HCC post-SVR, reflecting differences in patient populations, stages of liver disease, and treatment regimens(13) reported an HCC incidence of 11.6% in the South Asian region, while (14) found a lower incidence of 3.7% These variations highlight the influence of regional, genetic, and clinical factors on HCC risk.(15).

The study's findings also indicate that HCC risk varies with HCV genotype and fibrosis stage. Genotype 2 had the highest HCC incidence, consistent with some studies suggesting genotypic differences in HCC risk (16) the higher HCC rate in patients with F0 fibrosis compared to those with F4 fibrosis was unexpected and warrants further investigation. It suggests that even patients with

minimal fibrosis at the time of achieving SVR may not be entirely free from HCC risk, possibly due to other underlying risk factors (17).

This study's strengths include a well-defined cohort with comprehensive data collection on demographic, clinical, and laboratory parameters. The rigorous follow-up and use of standardized diagnostic criteria for HCC and cirrhosis add to the robustness of the findings. However, the study has limitations, including its cross-sectional design, which limits causal inferences (18) The relatively small sample size and single-center nature of the study may limit the generalizability of the results. Additionally, the exclusion of patients with co-infections and other chronic liver diseases might have led to an underestimation of HCC risk in a broader population (19).

Recommendations for future research include larger, multicenter studies to validate these findings and explore the mechanisms underlying residual HCC risk post-SVR. Investigating the role of host genetic factors, lifestyle factors such as alcohol use, and comorbidities like obesity and diabetes in HCC development post-SVR could provide deeper insights. Long-term studies assessing the impact of new direct-acting antiviral (DAA) therapies on HCC risk compared to interferon-based treatments are also crucial (20). The importance of continuous monitoring and follow-up in CHC patient's post-SVR cannot be overstated. Regular ultrasound examinations and alpha-fetoprotein (AFP) testing should be standard practice for high-risk patients to enable early detection and management of HCC. Health care providers should remain vigilant in the long-term management of these patients, even after achieving virological clearance, to mitigate the residual risk of HCC (21, 22).

CONCLUSION

In conclusion, while achieving SVR with interferon-based treatments significantly reduces the risk of HCC, it does not eliminate it entirely, particularly in patients with advanced liver fibrosis or cirrhosis. Continuous surveillance and follow-up are essential for early detection and effective management of HCC in these patients. Further research is needed to identify and address specific risk factors, thereby improving post-treatment care and outcomes for CHC patients.

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