

# Prevalence of Hepatocellular Carcinoma in Patients with Chronic Hepatitis C Virus

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## Author's Contribution

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<sup>3,5</sup>analysis, or interpretation of data for the work, <sup>3</sup>Drafting the work or revising it critically for important intellectual content

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## ABSTRACT

**Objective:** To determine the frequency of Hepatocellular carcinoma (HCC) among patients with chronic hepatitis C virus (HCV) infection visiting to a tertiary care hospital.

**Methodology:** This descriptive cross-sectional study was conducted at department of Gastroenterology, Asian Institute of Medical Sciences, Hyderabad, Pakistan, from June 2020 to January 2021. Patients with age between 30 to 70 years with chronic hepatitis-C of either gender were included. Ultrasound, CT of liver and alpha fetoprotein levels were done to assess hepatocellular carcinoma. All the collected data were entered and analyzed using SPSS version 23.

**Results:** Mean of age was  $43.5 \pm 8.5$  years, mean body mass index (BMI) was  $26.7 \pm 5.2$  kg/m<sup>2</sup> and males were in majority. Overall average duration of chronic liver disease was  $12.5 \pm 2.3$  years. Out of 279 patients, 207 (74.1%) were male while 72 (25.9%) were female. Hepatocellular carcinoma was found to be in 18 (6.5%) patients. The prevalence of HCC was higher among patients aged >40 years (4.7% vs 1.8%), in males compared to females (5.4% vs 1.1%) and BMI >24 kg/m<sup>2</sup> (4.3% vs 2.2%), though the findings were statistically insignificant ( $p > 0.05$ ), while disease duration >10 years showed a significant association with HCC ( $p = 0.018$ ).

**Conclusion:** The prevalence of hepatocellular carcinoma was observed to be 6.5% among patients with chronic HCV infection, with the prolonged duration and severity of disease as the significant factor for development of HCC.

**Key Words:** HCC, Cirrhosis, Hepatitis-C Virus

## Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver and ranks as the third leading cause of cancer-linked mortality throughout the world.<sup>1</sup> The rates of the mortality are increasing globally, and cirrhosis remains the predominant risk factor, with HCV constituting one of the most significant and well-established etiological drivers of hepatic carcinogenesis.<sup>2</sup> Consistent with the Global Burden of Disease Study 2021, age-standardized incidence rates of HCV-attributable HCC showed a concerning resurgence between 2019 and 2021, despite earlier declines following the introduction of direct-acting antiviral (DAA) therapy, underscoring the persistent and evolving nature of this health challenge of the population.<sup>3</sup> Though the population-attributable fraction of HCC varies substantially by geographic region, HCV accounts for 3%

to 56% of HCC cases across different countries, reflecting its dominant etiological role across multiple regions.<sup>4</sup>

The chronic HCV infection comprises one of the most potent hepatic carcinogens known, prolonged inflammation, mitochondrial dysfunction, oxidative stress, dysregulation of immune, genomic instability, epithelial-mesenchymal transition, and oncogenic signaling pathways as key HCV-to-HCC mechanisms pathophysiologically.<sup>5,6</sup> Worldwide, an estimated 58 million individuals are chronically infected with HCV, with approximately 1.5 million new infections occurring annually, and chronic infection is implicated in more than 290,000 deaths each year predominantly through cirrhosis, decompensated liver disease, and the hepatocellular malignancy.<sup>5</sup>

The chronic HCV infection transition to HCC follows a well-characterized pathological trajectory: for those with the chronic hepatitis C, the annual risk of developing HCC ranges from 1.2% to 1.7%, rising to between 1.4% and 2.5% in those with established cirrhosis, with annual HCC incidence rates among high-risk cirrhotic patients reaching approximately 2% per year in contemporary prospective cohorts.<sup>2,7</sup> Prospective cohort data confirm that approximately 90% of HCV-associated HCC occurs in patients with cirrhosis, and the cumulative five-year incidence of HCC among DAA-treated HCV patients with advanced fibrosis reaches 5.9%.<sup>8</sup> Even after achieving sustained virological response (SVR) with DAAs a therapeutic milestone associated with SVR rates exceeding 95% viral eradication does not fully abrogate the risk of de novo HCC development, particularly in patients with pre-existing advanced fibrosis or cirrhosis.<sup>9</sup>

Multivariate analyses confirm that age  $\geq 60$  years, male sex, elevated BMI, alpha-fetoprotein  $\geq 6$  ng/mL, high FIB-4 score, and advanced chronic liver disease status remain independent predictors of HCC risk following SVR, irrespective of the antiviral regimen.<sup>10</sup> Pakistan presents a uniquely alarming epidemiological context for HCV-related HCC. Pakistan carries the second highest burden of HCV globally, with a nationwide anti-HCV prevalence of 4.8% and an estimated 9.7 million individuals living with viremic HCV infection, representing a viraemic prevalence of 4.3%.<sup>11</sup>

Mathematical modeling confirms that achieving WHO HCV elimination targets between 2022 and 2030 would be required to prevent an estimated 104,000 incident cases of HCC over that period alone.<sup>11</sup> The country is currently not on track to meet the WHO target of complete HCV elimination by 2030, and a rising number of liver cancer cases driven by a unique pattern of healthcare-associated HCV transmission further compound the urgency of the situation.<sup>12</sup> Evidence from Pakistani tertiary care centers reinforces the direct causal link as the HCV was the predominant underlying etiology in HCC cases among co-infected patients and identified advanced age, male sex, and cirrhosis as independent risk factors for malignant transformation.<sup>13</sup>

Despite this undeniable and growing burden, locally generated prevalence data on HCC among patients with chronic HCV infection remain scarce, and insufficient to guide evidence-based national surveillance policy and clinical management protocols. The present study therefore aimed to determine the prevalence of HCC among patients with chronic HCV infection, with the goal of generating context-specific evidence to inform hepatic surveillance guidelines, early detection strategies, and liver cancer prevention programmes in Pakistan.

## Methodology

This descriptive cross-sectional study was conducted at the Department of Gastroenterology, Asian Institute of Medical Sciences, Hyderabad, Pakistan, a tertiary care referral center providing specialized hepatology services to patients across the Sindh region. This study was conducted over a period of seven months following approval of the synopsis by the CPSP, from June 2020 to January 2021. Sample size of 279 patients was calculated using the WHO sample size calculator for proportion estimation, based on a reported prevalence of hepatocellular carcinoma of 4% among patients with chronic HCV infection,<sup>14</sup> a margin of error (d) of 2.3%, and a confidence level of 95%. The estimated minimum required sample size was calculated to be  $n = 279$  participants. The non-probability consecutive sampling technique was employed. All the patients aged between 30 and 70 years of either gender, diagnosed with chronic hepatitis C virus infection in accordance with the operational definition stated above, and with a documented duration of HCV infection of one year or more were included. However the patients with history of alcoholic liver disease, patients with known autoimmune diseases, or those already receiving cancer chemotherapy and those who had cirrhosis of liver by causes other than hepatitis C, as well as those with end-stage liver disease, were excluded. Chronic HCV was defined as persistently elevated serum aminotransferases (ALT and AST  $>250$  U/L) for a minimum duration of 12 months, accompanied by a positive qualitative PCR for (HCV) RNA, in accordance with standard diagnostic criteria of the Institute. The informed consent was obtained from all participants following a thorough explanation of the study objectives, procedures, potential risks, and expected benefits. HCV antibody status was determined using a third-generation commercial enzyme-linked immunosorbent assay (ELISA), and quantitative HCV RNA viral load was measured by PCR. All the patients were assessed for HCC,, which was defined as the presence of an arterial enhancing lesion within the hepatic parenchyma demonstrating washout appearance on the venous phase of a Triphasic Computed Tomography (CT) scan of the liver, consistent with internationally recognized non-invasive diagnostic criteria for HCC as per diagnostic protocol of institute. All the clinical procedures and investigations were performed by the principal investigator under the direct supervision of a consultant gastroenterologist with a minimum of five years of specialist experience. A structured, pre-designed proforma was used for standardized data collection. The collected data were entered and analyzed using IBM SPSS Statistics version 23.0.

Continuous variables were computed using mean and standard deviation, while categorical variables were expressed as frequencies and percentages. Stratified analyses were performed and associations examined using the Chi-square test taking a p-value of  $\leq 0.05$  as statistically significant.

## Results

Overall 279 patients with chronic HCV infection were studied, with male predominance 207 (74.1%) while 72 (25.9%) were female, with an overall mean of  $43.5 \pm 8.5$  years, mean BMI was  $26.7 \pm 5.2$  kg/m<sup>2</sup> suggesting that the average patients was in the overweight category. Additionally, the average duration of HCV infection was  $12.5 \pm 2.3$  years reflecting a predominantly prolonged chronic infection burden

**Table I: Descriptive statistics of demographic and clinical variables. (n=270)**

| Variable     | Mean (Units)           | SD   | 95% CI          | Min | Max |
|--------------|------------------------|------|-----------------|-----|-----|
| Age          | 43.5 years             | 8.5  | 42.49 – 44.50   | 30  | 70  |
| Weight       | 66.8 kg                | 11.1 | 65.49 – 68.10   | 45  | 105 |
| Height       | 162.1 cm               | 12.2 | 160.66 – 163.53 | 138 | 186 |
| BMI          | 26.7 kg/m <sup>2</sup> | 5.2  | 26.08 – 27.31   | 18  | 34  |
| HCV duration | 12.5 years             | 2.3  | 12.22 – 12.77   | 1   | 20  |

among the study participants, as shown in table I.

In this study the overall frequency of hepatocellular carcinoma was 6.50%, out of all 279 patients of chronic HCV infection. Figure 1.

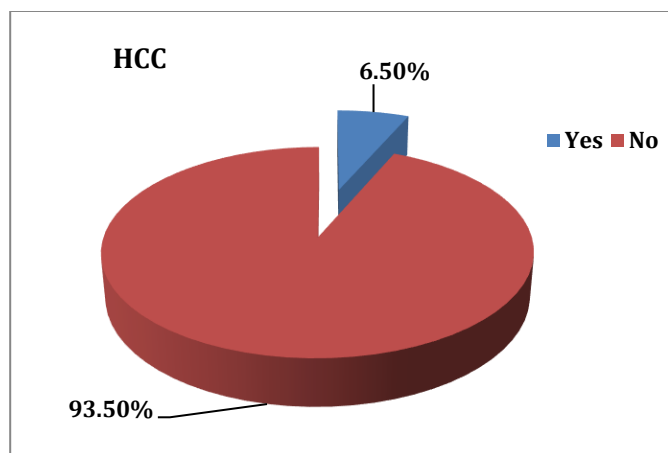


**Figure 1. Prevalence of hepatocellular carcinoma in chronic HCV patients. (n=279)**

The stratification analysis demonstrated that the HCC was more prevalent in cases aged above 40 years (4.7% versus 1.8%),  $p=0.050$ , among males compared to females (5.4% versus 1.1%) respectively,  $p=0.271$ , and

those with BMI more than 24 kg/m<sup>2</sup> (4.3% versus 2.2%),  $p=0.244$ , however the differences were statistically insignificant, while the duration of HCV infection greater than 10 years showed a significant association with the development of HCC (3.9% versus 2.5%),  $p=0.018$ , indicating prolonged HCV infection as a significant risk factor for hepatic malignancy. Table II.

**Table II: Stratification by age, gender, BMIU and duration of disease. (n=279)**

| Variables                   |               | HEPATOCELLULAR CARCINOMA |              | P-Value |
|-----------------------------|---------------|--------------------------|--------------|---------|
|                             |               | YES                      | NO           |         |
| Age groups                  | 30 – 40 years | 5(1.8%)                  | 132(44.7.3%) | 0.050   |
|                             | > 40 years    | 13(4.7%)                 | 129(46.2%)   |         |
| Gender                      | Male          | 15(5.4%)                 | 192(68.8%)   | 0.271   |
|                             | Female        | 3(1.1%)                  | 69(24.7%)    |         |
| BMI [In kg/m <sup>2</sup> ] | 18 – 24       | 6(2.2%)                  | 124(44.4%)   | 0.244   |
|                             | > 24          | 12(4.3%)                 | 137(49.1%)   |         |
| HCV duration n              | 1 – 10 years  | 7(2.5%)                  | 174(62.1%)   | 0.018   |
|                             | >10 years     | 11(3.9%)                 | 88(31.4%)    |         |

## Discussion

The HCC represents is a most common form of primary malignancy of liver and constitutes a leading contributor to cancer-related mortality throughout the world. The incidence of it continues to rise, most especially in the areas where chronic viral hepatitis infection remains endemic highly. In this study the prevalence of HCC prevalence was found 6.5%. In concordance with the present observations Leal et al<sup>8</sup> conducted a prospective cohort study of 1,075 chronic HCV patients and reported the incidence of HCC around 5.9%, with an overall rate of incidence around 1.46 per 100 patient, emphasizing that a meaningful proportion of develop HCC in chronic HCV patients even in the era of antiviral treatment.<sup>8</sup> Moreover Iqbal et al<sup>13</sup>, in their cross-sectional retrospective study, revealed a prevalence of HCC around 20.98% in the co-infected patients of HBV-HCV, and this higher figure may due to the synergistic carcinogenic effect of co-infection of the HBV and HCV. Unlike the findings of the present study, Resham et al,<sup>15</sup> in their recent retrospective study reported the higher frequency of HCC around 18.5% among patients with chronic viral hepatitis and they also included both HBV and HCV infected patients. Like our findings, there was stated that the in the cases of chronic HCV infection, around one in five will progress to liver cirrhosis over a period of two to three decades, and once cirrhosis is established, the annual risk of developing HCC ranges from 1% to 4%.<sup>16,17</sup>

Confirming the observations of the current study, Shiha G et al<sup>18</sup> reported that the HCC incidence in chronic HCV cases with advanced fibrosis of liver who achieved SVR following DAAs was around 4.82% in 109 cases out of 2,263 individuals. Our findings were comparable to the studies conducted on chronic HCV mono-infected populations, and expectedly lower than figures documented in studies conducted on HBV-HCV co-infection, where the synergistic oncogenic effect of dual viral infection substantially amplifies the risk of malignancy of liver. The differences across studies may also vary due to the differences in sample selection criteria, severity of the disease, fibrosis staging and antiviral treatments.

In the present study, HCC was more prevalent in patients aged above 40 years, male patients and BMI above 24 kg/m<sup>2</sup>. Such findings were supported by different studies.<sup>13,19,20</sup> The raised HCC risk among older male cases with elevated BMI in the present study may due to age-related cumulative hepatocellular DNA damage, shortening of the telomere length, and progressive fibrogenesis. In our country, males face greater HCV exposure through barbershops and unsafe medical procedures, and carry additional biological risk through androgen-mediated HCV replication and absence of oestrogen-mediated hepatoprotection. Raised BMI further potentiates carcinogenesis through hepatic steatosis, insulin resistance, and a chronic pro-inflammatory metabolic microenvironment synergistically interacting with HCV-driven oxidative stress.

Moreover in this study a significant association found between HCV infection duration exceeding 10 years and HCC development, indicating a prolonged viral persistence as the only independent significant predictor of HCC. These findings are related to the study by Iqbal et al<sup>13</sup> who reported that the infection duration ≥5 years was observed in 72.60% of HCC cases compared to 60.36% of non-HCC cases. Moreover, a recent systematic review on HCV epidemiology confirmed that

approximately one in five patients with chronic HCV develops cirrhosis within two decades, and in this group, HCC risk over three decades is 1–5%, accelerating significantly in older adults and those with metabolic comorbidities, reinforcing that disease duration is a cardinal determinant risk of HCC.<sup>21</sup> The findings collectively indicated that the carcinogenic potential of HCV is time-dependent, driven by cumulative hepatocellular oxidative stress, progressive fibrogenesis, and epigenetic dysregulation that increase with prolonged viral determination. However, the present study possess several limitations, like cross-sectional design, relatively limited sample size may have reduced the statistical power to detect significant relations for certain variables. Additionally, important clinical parameters including disease severity, HCV treatment status, dietary factors, fibrosis stage, alpha-fetoprotein levels, HCV genotype distribution, and comorbid conditions such as diabetes were not assessed into the stratification analysis, which may have influenced the magnitude and interpretation of the observed associations.

## Conclusion

The prevalence of hepatocellular carcinoma was observed to be 6.5% among patients with chronic HCV infection, with the prolonged duration of chronic HCV exceeding 10 years as a significant factor of HCC development. Overall findings emphasize the critical importance of early HCV diagnosis, antiviral therapy timely, and long-term hepatic surveillance, specifically in our country where HCV burden remains highest and most of the patients present with advanced stages without prior proper screening and follow-up. However, the targeted strategies for high-risk group surveillance are required to enable early detection and treatment of disease to reduce HCV-related liver malignancy and mortality.

## References

1. Chaudhuri U, Thornton CT, Crawford TN, Triplett D. Trends in incidence of hepatocellular carcinoma between 2000 and 2020: a SEER-based analysis. *Cureus*. 2025;17(5):e84487. doi: [10.7759/cureus.84487](https://doi.org/10.7759/cureus.84487).
2. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. *Nat Rev Clin Oncol*. 2023;20(12):864-884. doi: [10.1038/s41571-023-00825-3](https://doi.org/10.1038/s41571-023-00825-3).
3. Sequeira L, Ying X, Ozturk NB, Reidy D, Jesudian AB, Gurakar A. Revealing new trends in the global burden of hepatocellular cancer related to hepatitis C virus by region, sociodemographic index, and sex. *J Clin Med*. 2025;14(17):6006. doi: [10.3390/jcm14176006](https://doi.org/10.3390/jcm14176006).
4. Llovet JM, Vogel A, Mahfouz A, Pikarsky E, Dopazo C, Reig M, et al. Public health strategies for hepatocellular carcinoma: from risk factors to prevention and control. *J Liver Cancer*. 2025. doi: [10.17998/jlc.2025.07.08](https://doi.org/10.17998/jlc.2025.07.08).
5. Aydin Y, Kurt R, Tahan V, Daglilar E. Chronic hepatitis C in the direct-acting antivirals era: carcinogenesis and clinical implications. *Diseases*. 2025;13(12):393. doi: [10.3390/diseases13120393](https://doi.org/10.3390/diseases13120393).

6. Heredia-Torres TG, Rincón-Sánchez AR, Lozano-Sepúlveda SA, Galan-Huerta K, Arellanos-Soto D, García-Hernández M, et al. Unraveling the molecular mechanisms involved in HCV-induced carcinogenesis. *Viruses*. 2022;14(12):2762. doi: [10.3390/v14122762](https://doi.org/10.3390/v14122762).
7. Kanwal F, Khaderi S, Singal AG, Marrero JA, Loo N, Asrani SK, et al. Incidence and risk factors for hepatocellular carcinoma in cirrhosis: the multicenter Hepatocellular Carcinoma Early Detection Strategy (HEDS) study. *Gastroenterology*. 2023;165(4):1053-1063. doi: [10.1053/j.gastro.2023.06.027](https://doi.org/10.1053/j.gastro.2023.06.027).
8. Leal C, Strogoff-de-Matos J, Theodoro C, Teixeira R, Perez R, Guaraná T, et al. Incidence and risk factors of hepatocellular carcinoma in patients with chronic hepatitis C treated with direct-acting antivirals. *Viruses*. 2023;15(1):221. doi: [10.3390/v15010221](https://doi.org/10.3390/v15010221).
9. Briceno Noriega D, Simons-Linares CR, Bhatt H, Calderon G, Rao BB, Stevens T, et al. Hepatocellular carcinoma in patients with chronic hepatitis C and liver cirrhosis treated with DAA: a focused review. *J Clin Med*. 2025;14(5):1580. doi: [10.3390/jcm14051580](https://doi.org/10.3390/jcm14051580).
10. Kao YT, Liu YC, Cheng YT, Wen YW, Hsieh YC, Hsu CE, et al. Hepatocellular carcinoma incidences and risk factors in hepatitis C patients: interferon versus direct-acting agents. *Viruses*. 2024;16(9):1485. doi: [10.3390/v16091485](https://doi.org/10.3390/v16091485).
11. Mooneyhan E, Qureshi H, Mahmood H, Tariq M, Maqbool NA, Anwar M, et al. Hepatitis C prevalence and elimination planning in Pakistan, a bottom-up approach accounting for provincial variation. *J Viral Hepat*. 2023;30(4):345-354. doi: [10.1111/jvh.13802](https://doi.org/10.1111/jvh.13802).
12. Stockdale AJ, Shawa I, Hullegie SJ, Bhagani S, Bhatti AB, Jawa A, et al. A health systems strengthening approach to address the high burden of hepatitis C in Pakistan. *J Viral Hepat*. 2025;32(1):e14050. doi: [10.1111/jvh.14050](https://doi.org/10.1111/jvh.14050).
13. Iqbal S, Qureshi Z, Mudasar HM, Khan A, Sohail A, Ahmad J, et al. Prevalence and risk factors of hepatocellular carcinoma in patients co-infected with HBV and HCV: a cross-sectional retrospective study. *Cureus*. 2025;17(6):e85985. doi: [10.7759/cureus.85985](https://doi.org/10.7759/cureus.85985).
14. Zampino R, Pisaturo MA, Cirillio G, Marrone A, Macera M, Rinaldi L, et al. Hepatocellular carcinoma in chronic HBV-HCV co-infection is correlated to fibrosis and disease duration. *Ann Hepatol*. 2015;14(1):75-82. doi: [10.1016/S1665-2681\(19\)30803-8](https://doi.org/10.1016/S1665-2681(19)30803-8).
15. Resham S, Khan M, Rahman E, Adnan F, Manzoor S. Determine the frequency distribution of hepatocellular carcinoma (HCC) and evaluation of viral persistence in the development of HCC among Pakistani patients. *J Pak Med Assoc*. 2025;75(9):1409-1416. doi: [10.47391/JPMA.22562](https://doi.org/10.47391/JPMA.22562).
16. Axley P, Ahmed Z, Ravi S, Singal AK. Hepatitis C virus and hepatocellular carcinoma: a narrative review. *J Clin Transl Hepatol*. 2018;6(1):79-84. doi: [10.14218/JCTH.2017.00067](https://doi.org/10.14218/JCTH.2017.00067).
17. Omeland LH, Krarup H, Jepsen P, Georgsen J, Harritshøj LH, Riisom K, et al. Mortality in patients with chronic and cleared hepatitis C viral infection: a nationwide cohort study. *J Hepatol*. 2010;53:36-42. doi: [10.1016/j.jhep.2010.01.033](https://doi.org/10.1016/j.jhep.2010.01.033).
18. Shiha G, Mousa N, Soliman R, Mikhail NNH, Adel Elbasiony M, Khattab M. Incidence of HCC in chronic hepatitis C patients with advanced hepatic fibrosis who achieved SVR following DAAs: a prospective study. *J Viral Hepat*. 2020;27(7):671-679. doi: [10.1111/jvh.13276](https://doi.org/10.1111/jvh.13276).
19. Petruzzello A. Epidemiology of hepatitis B virus (HBV) and hepatitis C virus (HCV) related hepatocellular carcinoma. *Open Virol J*. 2018;12:26-32. doi: [10.2174/1874357901812010026](https://doi.org/10.2174/1874357901812010026).
20. Liao CY, Lee CY, Wei CY, Chao Y, Huang YH, Hou MC, et al. Differential prognoses among male and female patients with hepatocellular carcinoma. *J Chin Med Assoc*. 2022;85(5):554-565. doi: [10.1097/JCMA.0000000000000722](https://doi.org/10.1097/JCMA.0000000000000722).
21. Toma D, Anghel L, Patraş D, Ciubară A. Hepatitis C virus: epidemiological challenges and global strategies for elimination. *Viruses*. 2025;17(8):1069. doi: [10.3390/v17081069](https://doi.org/10.3390/v17081069).