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Hepatocellular Carcinoma in Cirrhotic Patients with Hepatitis-C Virus Positive Patients

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Author`s Contribution

[1,2]Substantial contributions to the conception or design of the work; or the acquisition, [4,6]Active participation in active methodology, [2,6]analysis, or interpretation of data for the work, [3]Drafting the work or revising it critically for important intellectual content

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ABSTRACT

Objective: To assess the frequency of Hepatocellular carcinoma in cirrhotic patients with hepatitis-C virus positive patients.

Methodology: This study descriptive Cross-Sectional Study was conducted at Gastroenterology department, Isra University Hospital, Hyderabad, Pakistan, during Six months after the approval of synopsis from February 22, 2020 to August 21, 2020. Patients aged 25 to 60 years old, diagnosed as the cases of cirrhosis for more than five years, caused by hepatitis C of either gender, were included. Patients were evaluated clinically, biochemically, and serologically at baseline. CT scan of liver was done to assess hepatocellular carcinoma. A specially designed Proforma was utilized to gather the information, which was then input and analyzed employing SPSS version 23.

Results: The participant's mean age is 42.3 years, with a standard deviation of 7.5 years, and an average body mass index (BMI) reached 16.9+3.6kg/m2. Additionally, the mean duration of cirrhosis is reported as 12.5 years. Majority of the patients were males 74.6%. Among all study participants with liver cirrhosis for over 5 years, 8.30% of patients had developed hepatocellular carcinoma. The HCC occurrence rate was statistically significant, with 1.9% of individuals aged 25-40 years and 6.4% of those over 40 years having hepatocellular carcinoma (p=0.008). However, gender, BMI categories, diabetes mellitus and hypertension did not show a significant association (p->0.05).

Conclusion: In conclusion, hepatocellular carcinoma appeared relatively prevalent among patients having cirrhosis with hepatitis-C virus. Advanced age emerged as a significantly predominant factor contributing to hepatocellular carcinoma.

Key words: Hepatocellular Carcinoma, Cirrhotic Patients, Hepatitis-C Virus, Epidemiology, Treatment, Prevention.

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Introduction

Globally, hepatic carcinoma ranks among the most common causes of cancer-linked mortality.[1] Hepatocellular carcinoma estimated for about 90% of primary liver cancers, with intrahepatic cholangiocarcinoma and other primary hepatic malignancies following behind.[2] It is the fourth biggest contributing factor to mortality around the world, accounting for about 800,000 deaths per year.[2,3] Globally, males, Asians, and the elderly remain the demographic groups with the highest incidence of HCC.[4] The primary risk factors for HCC, hepatitis B virus and the hepatitis C virus, continue to be prevalent, although there is a slight decline observed in most of the Asian nations.[4] The majority of HCC instances arise in addressing

the persistent hepatic disease, where hepatic cirrhosis emerges as the main risk components for cancer of the liver, independent of the underlying cause of liver disease.[5]

It's estimated that approximately one-third of individuals with cirrhosis will develop over the course of their lives, they may develop malignancies of the liver. Longitudinal follow-up research investigations have reported annual incidence rates ranging from 1% to 8%, such as 2% in cirrhotic individuals infected with the Hepatitis B virus and 3% to 8% in those with the infection of hepatitis C virus.[5,6] Hepatitis C virus (HCV) is a leading contributor to HCC globally, primarily due to the widespread prevalence of HCV infections. According to data from the WHO's worldwide hepatitis report, 1% of people worldwide have HCV infection.[7] HCV not only damages the liver and causes fibrosis, which in turn causes cirrhosis of the liver, but it also directly increases the risk of cancer by damaging DNA, causing oxidative stress, and deregulating host cell checkpoints in the cell that becomes infected.[7] Studies have shown that nearly half of the cases of hepatocellular carcinoma in Pakistan are positive for anti-HCV antibodies.[8] Three to four million individuals infected by the HCV annually. There are approximately 150 million individuals who have a chronic infection and are at increased risk for cirrhosis of the liver, carcinoma of the liver, or both. Each year, hepatic diseases associated with hepatitis C threaten the lives of about 350,000 people.[9]

HCV infection exhibits a different distribution across nations, with prevalence rates across the entire population spanning from 0.5% to 6.5% worldwide.[10] In the Western nations and the Australia, this prevalence typically ranges from 0.5% to 1.5%. However, in regions such as South-East Asia and the Eastern Mediterranean, rates reach up to 2.3%, in China, the prevalence stands at 3.2%, while in India and Indonesia, it is 0.9% and 2.2%, respectively.[10] Pakistan bears a higher burden with a prevalence of 6.5%.[10] Hepatitis C is cited as the primary cause of 70-95% of post-transfusion hepatitis cases in Western nations. In Ethiopia, over 60% of cases of chronic liver disease and as much as 80% of HCC cases caused by chronic infections of the hepatitis C virus and the hepatitis B virus.[11]

Although World Health Organization (WHO) identifies Ethiopia as one of the nations with a significant hepatitis burden, ranging from intermediate to hyper endemic levels of endemicity.[11] Hepatitis presents a significant public health challenge in the developing countries including Pakistan, with an approximated 11.55% of the adults affected by infection of hepatitis C virus. Globally, Pakistan stands as the second most affected country by hepatitis C virus (HCV), with roughly a single among every twenty peoples of Pakistan already carrying the infection.[12]

Hepatitis-C promotes cirrhosis of the liver and carcinoma of the liver mostly occurs in people who already have signs and symptoms of chronic liver disease accounted as (5.7%).[13] Therefore, considering HBV's enhanced direct oncogenic implementation, most cases of HBV-related HCC manifest at an earlier stage of cirrhosis, often with more aggressive tumors compared to those related to HCV.[14,15] Similarly, it is anticipated that differences exist in the natural progression and prognosis of HCC attributed to viral and non-viral causes. Pakistan, situated in a region with intermediate prevalence for both HCV and HBV, has limited data on HCC, with available research displaying significant variation.[14,16] Therefore, this study was conducted to assess the prevalence of hepatocellular carcinoma among cirrhotic patients who are positive for hepatitis C virus, aiming to investigate the present scenario.

Methodology

A descriptive cross-sectional Study was carried out at the gastroenterology department, Isra University Hospital, Hyderabad, during a period of Six months after the approval of synopsis from February 2020 to August 2020. The overall sample size of 264 patients was estimated using the W.H.O sample size estimator by a level of confidence of 95%, an estimated margin of error of 2.8%, and the predicted prevalence of 5.7% of carcinoma of the liver in patients with cirrhosis with HCV,13 in viral cirrhotic patients. All the patients aged 25 to 60 years old, diagnosed as the cases of cirrhosis for more than five years, caused by hepatitis C of either gender, were included. Cases with documented history of alcoholic liver disease, patients who were known cases of any autoimmune disease, immunodeficiency disorder (granulocytopenia <600/mm3) or already on cancer chemotherapy and patients with liver cirrhosis due to causes other than hepatitis C were excluded. All of the study participants who fulfilled the inclusion criteria and visited to outpatient department of Gastroenterology Isra University Hospital, Hyderabad were further studied.

Participants provided informed consent after receiving detailed explanations of the study's procedure, potential risks, and advantages. Clinical assessments and baseline laboratory evaluations were conducted for all patients. Automated techniques were utilized to perform routine biochemical tests (including hepatic and kidneys function

tests) as well as hematological investigations. Third-generation commercial ELISA was employed to detect HCV antibodies. Additionally, the HCV RNA load was quantified. The HCV RNA load was measured. CT scan of liver was done to assess outcome variable i.e. hepatocellular carcinoma (yes/no) aligns with the operational definition. All the procedure was performed by investigator performed the study worked under supervision of the consultant gastroenterologist and hepatologist. All the information was collected on a prescribed Proforma with Biasness and confounders were regulated by closely adhering to both inclusion and exclusion specifications. The information gathered was entered into SPSS version 23.0 and analyzed accordingly. The quantitative variable presented by calculating mean and standard deviation. Each of the qualitative parameters were expressed as frequencies and percentages. The role of effect modifiers on carcinoma of the liver was investigated using stratification. Chi square / Fisher's Exact test as appropriate was applied and considered $P \leq 0.05$ as significant.

Results

In accordance to the descriptive statistics of demographic and clinical characteristics reveal that the patients' overall average was 42.3±7.5 years. The average weight is 67.1 kg with a standard deviation of 8.4 kg, and the mean height is 163.2 cm with a standard deviation of 13.7 cm. The body mass index (BMI) of the patients has a mean of 16.9±3.6 kg/m^2. Additionally, the mean duration of cirrhosis is reported as 12.5 years. In terms to the gender distribution, the most of the study participants were males, accounting for 74.6%, while females were 25.4%. Regarding comorbidities, 32.6% had diabetes mellitus, while 47.3% cases were hypertensive. (Table I)

Table I: Baseline and clinical characteristics of the patients (n=264)

Variables		Descriptive statistics
Mean age		42.3±7.5 years
Mean weight		67.1±8.4 kg
Mean height		163.2±13.7 cm
Mean BMI		16.9±3.6 kg/m^2
Duration of cirrhosis (Mean+SD)		12.5±4.9 years
Gender	Males	197(74.6%)
	Females	67(25.4%)
Diabetes mellitus	Yes	86(32.6%)
	No	178(67.4%)
Hypertension	Yes	125(47.3%)
	No	139(52.7%)

Among all study participants with liver cirrhosis for over 5 years, 8.30% of patients had developed hepatocellular carcinoma. (Figure 1)

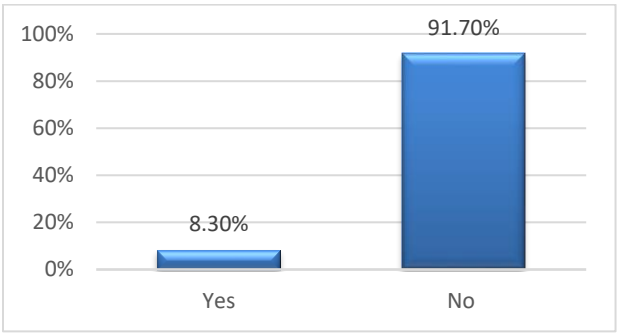

Figure 1. Frequency of heaptocellular carcenoma. (n=264)

For age groups, a statistically significant difference was observed, with 1.9% of individuals aged 25-40 years and 6.4% of those over 40 years having hepatocellular carcinoma (p=0.008). Gender did not show a significant difference, with 6.1% of males and 2.3% of females affected (p-0.831). BMI categories also did not reveal a significant difference, with 4.9% of individuals with a BMI of 18-24 kg/m^2 and 3.4% of those with a BMI over 24 kg/m^2 having hepatocellular carcinoma (0.220). Diabetes mellitus and hypertension status similarly did not show a significant association (p->0.05). (Table II)

Table II: Hepatocellular carcinoma with respect to the age, gender, BMI, diabetes and hypertension. (n=264)

Variables		Hepatocellular Carcinoma		P-value
		YES	NO	
Age groups	25 – 40 years	5(1.9%)	126 (47.7%)	0.008
	> 40 years	17(6.4%)	116 (43.9%)	
Gender	Male	16(6.1%)	181 (68.6%)	0.831
	Female	6(2.3%)	61 (23.1%)	
BMI	18 – 24 kg/m^2	13(4.9%)	110 (41.7%)	0.220
	> 24 kg/m^2	9 (3.4%)	132 (50.0%)	
Diabetes mellitus	Diabetic	7 (2.7%)	79 (29.9%)	0.937
	Non-Diabetic	15 (5.7%)	163 (61.7%)	
Hypertension	Hypertensive	10 (3.8%)	115 (43.6%)	0.853
	Non-Hypertensive	12 (4.5%)	127 (48.1%)	

Discussion

Because of the high frequency of HCV chronic infection, which affects over 170 million individuals worldwide, is a primary cause of HCC. The two main causes of cirrhosis in developed nations are heavy consumption of alcohol and HCV infection, and these conditions are frequently linked to HCC.[17,18] Meanwhile, alcohol consumption is still the primary cause of cirrhosis and HCC in other affluent nations (accounting for over 60% of cases), with HCV coming in second (approximately 25%–30%). In this study, the mean age of participants was 42.3±7.5 years.

Comparable studies have reported varying mean ages. Tariq et al.[13] reported an average age of 41.1±7.1 years, while a study from India noted a mean age of 45.1±13.1 years.[19] Paranaguá-Vezozzo et al[20] reported a mean age of 52.25 years, and Nguyen et al.[21] noted a mean age of 57.8±9.7 years. Additionally, Mohammad et al.[22] reported an average age of 41.03±14.94 years. Regarding body mass index (BMI), our study recorded a mean of 26.9±5.6 kg/m2. Contrastingly, Liang et al.[23] noted a BMI of 24.6±4.8 kg/m2, Zykus et al,[24] reported it as 26.7±4.2 kg/m2, and Takuma et al,[25] observed it as 23.4±3.6 kg/m2.

The mean duration of liver cirrhosis in our study was 16.5±8.9 years, slightly different from Tariq et al,[13] finding of 15.3±8.6 years. In terms of gender distribution, out of 264 patients, 197 (74.6%) were male and 67 (25.4%) were female in our study. Comparable studies reported varying gender distributions: Tariq et al,[13] observed 114 (80.9%) males and 27 (19.1%) females, while Paranaguá-Vezozzo et al,[20] found 60 (64.5%) males and 33 (35.5%) females. The predominance of males in cirrhosis caused by HCV infection can be attributed to several factors like, males have been more likely to engage in behaviors associated with HCV transmission, such as intravenous drug use and high-risk sexual behavior. Certain occupations, such as those involving healthcare, tattooing, or body piercing, may increase the risk of HCV transmission, and these are often more common among males and may due to sex hormones may play a role in the progression of liver disease, with estrogen potentially offering protective effects in females.

In this study, diabetes mellitus was present in 86 (32.6%) patients. This aligns closely with findings from Liang et al,[23] who reported a similar prevalence of 31.7% (181 patients). Hypertension was observed in 125 (47.3%) patients in our study. This differs from the findings of Ilyas et al,[26] who reported a prevalence of diabetes in 42% (42 patients), and Santos et al,[27] who noted hypertension in 41.6% (20 patients). In our current study, HCC was diagnosed in 22 (8.3%) patients. This contrasts with the findings of Tariq et al,[13] who demonstrated that a proportion of HCC among patients of cirrhosis caused by hepatitis C virus around 5.7%. In a prospective investigation involving Italian individuals diagnosed with HCV and compensated cirrhosis, findings revealed a 5-year cumulative incidence of hepatocellular carcinoma (HCC) ranging from about 4% to 6%.89 In present study, when examining confounders/effect modifiers concerning HCC, there were no significant distinctions found across the age groups (P=0.970), gender (P=0.831), body mass index (P=0.220), diabetes mellitus (P=0.937), and hypertension (P=0.853). HCC necessitates a multidisciplinary approach to management, involving various specialties such as Gastroenterology/hepatology, surgical procedures, transplantation surgery, interventional and conventional radiology, radiation therapy, and the nuclear medicine. Furthermore, achieving early diagnosis, appropriate treatment, and referral to specialized services demand heightened vigilance and the seamless integration of all healthcare services.

Conclusion

It is to be concluded that hepatocellular carcinoma was observed in 8.30% of cirrhosis patients with hepatitis C virus. Older people are much more likely to develop carcinoma of the liver. Further studies with large sample sizes and involving multiple research centers across Pakistan are necessary to expand the epidemiological and research data on hepatitis C virus, and to validate the findings of the current study.

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