Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Community Medicine

Viral Hepatitis and Hepatocellular Carcinoma: A Case-Control Study

Dr. Sarah Ahmed Tamanna[1*], Md. Ziaul Islam[2], Dr. Tasnim Mahmud[3], Dr. Sumaiya Tasnia Khan[4], Dr. Tarim Mahmood[4]

[1]MBBS, MPH, Department of Community Medicine, National Institute of Preventive and Social Medicine (NIPSOM), Q9HX+CPM, Dhaka 1212, Bangladesh
[2]PhD, MBBS, MPH, MSc, Professor and Head of Department of Community Medicine, National Institute of Preventive and Social Medicine (NIPSOM), Q9HX+CPM, Dhaka 1212, Bangladesh
[3]MBBS, MPH, Department of Epidemiology, North South University, Plot # 15, Dhaka 1229, Bangladesh
[4]MBBS, MPH, CCD, Department of Epidemiology, North South University, Plot # 15, Dhaka 1229, Bangladesh
[5]MBBS, MPH, CCD, Department of Maternal and Child Health, National Institute of Preventive and Social Medicine (NIPSOM), Q9HX+CPM, Dhaka 1212, Bangladesh

DOI: 10.36347/sjmcr.2023.v11i08.026 | **Received:** 17.07.2023 | **Accepted:** 14.08.2023 | **Published:** 21.08.2023

***Corresponding author:** Dr. Sarah Ahmed Tamanna
MBBS, MPH, Department of Community Medicine, National Institute of Preventive and Social Medicine (NIPSOM), Q9HX+CPM, Dhaka 1212, Bangladesh

Abstract **Original Research Article**

Background: Hepatocellular carcinoma is the most common primary liver malignancy and cause of cancer-related death worldwide including Bangladesh. The purpose of this study was to determine the relationship between viral hepatitis and hepatocellular carcinoma. ***Methods:*** This age (±2 years) and sex matched case-control study was conducted from January to December 2021 with 60 cases and 60 controls. The participants with hepatocellular carcinoma were considered as cases where those who had no hepatocellular carcinoma were considered as controls. The participants were selected by convenient type of non-probability sampling from four hospitals in Dhaka city. After obtaining informed written consent from participants, data were collected by face-to-face interview and medical record reviewed by using a semi-structured questionnaire and checklist. Data processing and analysis was performed by the latest available version of SPSS software. ***Result:*** The mean±SD age of the cases was 52.83 ± 12.85 years and of controls was 52.58 ± 12.84 years. Significantly higher proportion of cases 78.3% lived in the rural area than controls 51.7% (p=0.002). The cases were more 86.7% from nuclear family than the controls 61.7% (p-=0.002). 80% cases had viral hepatitis than the controls 15% (p=0.000). HBV infection was significantly higher 70.0% in HCC patients than the control groups 8.3%, (OR:25.667, 95%CI: 8.812-74.762, p=0.000) and HCV infection was 10.0% in HCC patients than the controls 6.7%, (OR:1.556, 95%CI: 0.416-5.819, p=0.509) 63.3% cases had experienced other liver diseases than controls 8.3%, (OR:19.000, 95%CI: 6.613-54.589, p=0.000). Family history of hepatocellular carcinoma was significantly higher in 26.7% cases than 5.0% in controls (OR: 6.909, 95%CI: 1.894-25.208,p=0.001) and more than three-fourth of the cases 80% used tobacco than controls 30%, (OR: 9.333, 95%CI: 4.031-21.612, p=0.000). ***Conclusion***: This study provides evidence that HBV infection was strongly associated with the development of HCC.
Keywords: Hepatocellular carcinoma, liver malignancy, HCC patients.

INTRODUCTION

Carcinoma is a global problem. It is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 [1]. Hepatocellular carcinoma (sometimes called hepatic cancer, primary hepatic cancer, or primary hepatic malignancy) is the most frequently encountered type of liver cancer [2]. The Global Burden of Disease Liver Cancer Collaboration found that from 1990 to 2015 the number of new cases of HCC per year increased by 75% [3]. Overall, the annual incidence of HCC is 2–5% in patients with cirrhosis from chronic HBV or HCV infection [4]. Estimates based on the most recent data suggest that each year there are 841,000 new liver cancer diagnoses and 782,000 deaths across the globe. HCC is the most common cancer in Egypt, the Gambia, Guinea, Mongolia, Cambodia, and Vietnam. In terms of gender breakdown, globally HCC is more common in men than in women [5].

In the present situation, HCC is the third most common cancer in Bangladesh [6]. HCC affects roughly half a million people worldwide each year, with nearly the same number dying HCC has a wide range of criteria, with significant differences between geographic regions, racial and ethnic groupings, sexes, and risk factors [7].

Worldwide in 2015, hepatitis A occurred in about 114 million people, chronic hepatitis B affected about 343 million people and chronic hepatitis C about 142 million people [8]. HBV infection is a global public health problem. In 2019, there were 296 million HBV carriers, 1.5 million new infections per year, and an annual mortality of 820,000 individuals (mostly from complications of liver cirrhosis and hepatocellular carcinoma [9-12]. About 5% of the world's population (350–400 million people) is chronically infected with HBV; 75 percent of infected people are Asian with a lower incidence (0.3 percent–1.5 percent) in western countries [13]. It is an infectious disease that is a serious public health concern around the world, impacting hundreds of millions of people. Viral hepatitis is a leading cause of sickness and death in the human population, with acute and chronic complications including chronic active hepatitis, and primary liver cancer (with hepatitis B and C infection).

Bangladesh is a developing country with a population of 180 million. It was estimated that more than 8 million people were chronically infected with HBV [14] and about 1 to 2 million with HCV [15].

Chronic hepatitis is a slowly progressive illness that causes liver fibrosis and cirrhosis due to continuous hepatic inflammation. Cirrhosis develops in around 10–20 percent of individuals after 20 years of persistent hepatic inflammation [16]. There is a 1–5% annual chance of getting hepatocellular cancer once high-grade fibrosis or cirrhosis has occurred. Hepatitis B and C viruses (HBV/HCV) can cause hepatocellular carcinoma in two ways: through induction of chronic inflammation, or directly through viral proteins or, in the case of HBV, by the creation of mutations by integration into the genome of the hepatocyte.

Yet in Bangladesh, which risk factors is the most crucial for the development of HCC is unknown. Numerous research in other countries have found a strong link between HBV infection and HCC, but in Bangladesh, the interaction between HBV and HCV in the development of HCC has not been extensively investigated. The main goal of this study is to use a case-control study to find out the connection between viral hepatitis and HCC in Bangladesh.

Material and Methods

The total study was conducted for one year time frame (1st January 2021 to 31st December 2021. The study was conducted in the following hospitals of Dhaka City Seikh Russel Gastro-liver Institute and Hospital, National Institute of Cancer Research and Hospital (NICRH), Medical College and Hospital, Delta Hospital Limited, Mirpur-1, Dhaka. The study was comprised of two groups, case and control. The study population were the participants attending the inpatient (IPD) and outpatient department (OPD). The cases were hepatocellular carcinoma patients previously diagnosed by the Oncologists/ specialist physician based on the USG guided FNAC for biopsy and histopathology report. The sample size was 138. The controls those who had no hepatocellular carcinoma or who attended in the hospital for other diseases. , data was obtained through a face-to-face interview with a semi-structured questionnaire and review of medical records. Every participant's privacy and confidentiality were respected. During the consenting process, a witness was present.

Case:

Inclusion Criteria for cases:

- Both male and female patients of hepatocellular carcinoma.
- Patients who were diagnosed as hepatocellular carcinoma by specialist physician.
- Patients who gave informed consent.

Exclusion Criteria for cases:

- Severely ill patients

A. Control:

Inclusion Criteria for controls:

- Those who had no hepatocellular carcinoma, as diagnosed by the physician.
- Those who gave informed consent for participating this study.
- Each control was taken by matching sex and age (±2 years) with the corresponding case.

Exclusion Criteria for controls:

- Severely ill patients

Data Analysis:

Collected data were edited and analyzed according to objectives and variables by ‘Statistical Package for Social Sciences’ (SPSS) software latest version. There were two types of analysis:

- Descriptive statistics included mean, frequency, standard deviation.
- Inferential statistics included chi-square test, independent t-test, and logistic regression. Association between viral hepatitis and hepatocellular carcinoma was expressed in ODDs ratio.

Results

Table 1 below shows, the lion's share of the participants in this study were men 49 (81.7%) in both cases and controls, with female participants accounting for 11 (18.3%) in each group. The relationship between participant type and gender was not statistically significant ($p>0.05$).

The majority of 32 (53.3%) controls were between the ages of 40 and 59 compared to 29 (48.3%) cases. 22 (36.7%) of the cases were between the ages of 60 and 85, compared to 19 (31.7%) controls, and 9 (15.0%) of the both cases and controls were between the ages of 23 and 39. The cases had a mean±SD age of 52.83±12.850 years, while the control group had a mean±SD age of 52.58±12.848 years.

In relation to marital status, the majority of cases were married, with 52 (86.7%) compared to 56 (93.3%) controls, followed by widow/widowers, having 7 (11.7%) cases and 4 (6.7%) controls. In the cases, only one (1.7%) was unmarried.

In terms of education level, the greater number of cases 25 (41.7%) were illiterate, compared to 30 (50.0%) controls. About 12 (20.0%) of the cases had a primary education, compared to 13 (21.7%) of the controls. This variation in participant distribution by the level of education was statistically insignificant (p>0.05).

Compared to 35 (58.3%) controls, 34 (56.7%) cases included family members ranging from 5 to 8. Only 4 (6.7%) cases included family members ranging from 9-11, compared to 9 (15.0%) controls and 22 (36.7%) cases compared to 16 (26.7%) controls included family members ranging from 3-4. The average number of family members in cases was 5.08±1.720, whereas in controls it was 6.05±2.213.

Table 1: Comparison of socio-demographic characteristics between cases and controls

Comparison of sex between cases and controls			
Sex	**Type of participants**		**Significance (χ^2 test)**
	Cases f (%)	**Controls f (%)**	
Male	49 (81.7)	49 (81.7)	χ^2 = 0.000 df = 1 p = 1.000
Female	11 (18.3)	11 (18.3)	
Total	60 (100.0)	60 (100.0)	
Comparison of age between cases and controls			
Age group (In years)	**Type of participants**		**Significance (χ^2 test)**
	Cases f (%)	**Controls f (%)**	
23-39	9 (15.0)	9 (15.0)	χ^2 = 0.367 df = 2 p = 0.832
40-59	29 (48.3)	32 (53.3)	
60-85	22 (36.7)	19 (31.7)	
Total	60 (100.0)	60 (100.0)	
Mean ± SD	52.83 ± 12.850	52.58 ± 12.848	t = 0.107 p-value =0.915
Comparison of marital status between cases and controls			
Marital status	**Type of participants**		**Significance (χ^2 test)**
	Cases f (%)	**Controls f (%)**	
Married	52 (86.7)	56 (93.3)	χ^2 = 1.966 df = 2 p = 0.374
Unmarried	1 (1.7)	0 (0.0)	
Widow/Widower	7 (11.7)	4 (6.7)	
Total	60 (100.0)	60 (100.0)	
Comparison of the level of education between cases and controls			
Level of education	**Type of participants**		**Significance (χ^2 test)**
	Cases f (%)	**Controls f (%)**	
Illiterate	25 (41.7)	30 (50.0)	χ^2 = 5.571 df = 5 p = 0.350
Primary	12 (20.0)	13 (21.7)	
Secondary	8 (13.3)	8 (13.3)	
Higher Secondary	6 (10.0)	7 (11.7)	
Graduate	6 (10.0)	2 (3.3)	
Post-graduate	3 (5.0)	0 (0.0)	
Total	60 (100.0)	60 (100.0)	
Comparison of total numbers of family members between cases and controls			
Family member	**Type of participants**		**Significance (χ^2 test)**
	Cases f (%)	**Controls f (%)**	
3-4	22 (36.7)	16 (26.7)	χ^2= 2.885 df = 2 p = 0.236
5-8	34 (56.7)	35 (58.3)	
9-11	4 (6.7)	9 (15.0)	
Total	60 (100.0)	60 (100.0)	
Mean ± SD	5.08 ± 1.720	6.05 ± 2.213	t = -2.672 p-value =0.009

Table 2 below resembles, the majority of the types of viral hepatitis cases 42 (70.0%) had hepatitis B virus (HBV), compared to 5 (8.3%) controls while 18 (30.0%) of the cases did not have HBV compared to 55

(91.7%) of the controls. There was a statistically significant difference in the distribution (OR: 25.667,95 %CI 8.812-74.76, p<0.05).

Among the participants, HBV was found in the majority of cases 22 (52.4%) compared to 3 (60.0%) controls in the 40-59 years age group, followed by 8 (19.0%) cases in the 23-39 years age group with no control group, and 12 (28.6%) cases compared to 2 (40.0%) controls in the 60-85 years age group. This discrepancy in distribution was statistically insignificant (p>0.05).

Among the participants, HCV was found 3 (50.0%) cases compared to two (50.0%) control group in the 40-59 years age group, two (50.0%) controls in the 23-39 years age group with no comparison case group and three (50.0%) case in the 60-85 years age group where there was no control group. This disparity in distribution was determined to be statistically insignificant (p>0.05).

Table 2: Comparison of viral hepatitis between cases and controls

Comparison of types of viral hepatitis between cases and controls					
Variables	**Characteristics**	**Type of participants**		**OR (95% CI)**	**Significance (χ2 test)**
		Cases f (%)	**Controls f (%)**		
HBV	Yes	42 (70.0)	5 (8.3)	25.667 (8.812-74.76)	χ2=47.881 df = 1 p = 0.000
	No	18 (30.0)	55 (91.7)		
	Total	60 (100.0)	60 (100.0)		
HCV	Yes	6 (10.0)	4 (6.7)	1.556 (0.416-5.819)	χ2=0.436 df = 1 p = 0.509
	No	54 (90.0)	56 (93.3)		
	Total	60 (100.0)	60 (100.0)		

Comparison of HBV with age group between cases and controls				
HBV	**Age groups (In years)**	**Type of participants**		**Significance (χ2 test)**
		Cases f (%)	**Controls f (%)**	
Yes	23-39	8 (19.0)	0 (0.0)	χ2 = 1.197 df = 2 p = 0.550
	40-59	22 (52.4)	3 (60.0)	
	60-85	12 (28.6)	2 (40.0)	
	Total	42 (100.0)	5 (100.0)	
No	23-39	1 (5.6)	9 (16.4)	χ2 = 3.910 df = 2 p = 0.142
	40-59	7 (38.9)	29 (52.7)	
	60-85	10 (55.6)	17 (30.9)	
	Total	18 (100.0)	55 (100.0)	

Comparison of HCV with age group between cases and controls				
HCV	**Age groups (In years)**	**Type of participants**		**Significance (χ2 test)**
		Cases f (%)	**Controls f (%)**	
Yes	23-39	0 (0.0)	2 (50.0)	χ2 = 5.000 df = 2 p = 0.082
	40-59	3 (50.0)	2 (50.0)	
	60-85	3(50.0)	0 (0.0)	
	Total	6 (100.0)	4 (100.0)	
No	23-39	9 (16.7)	7 (12.5)	χ2 = 0.500 df = 2 p = 0.779
	40-59	26 (48.1)	30 (53.6)	
	60-85	19 (35.2)	19 (33.9)	
	Total	54 (100.0)	56 (100.0)	

In terms of alcohol intake, 59 (98.3%) of the cases did not consume alcohol, compared to 58 (96.7%) of the controls. Only one case (1.7%) and two controls (3.3%) had a history of alcohol intake. This distributional difference was not statistically significant (p>0.05)

Table 3: Comparison of alcohol consumption between cases and controls

History of alcohol consumption	**Type of participants**		**Significance**
	Cases f (%)	**Controls f (%)**	
Yes	1 (1.7)	2 (3.3)	Fisher's Exact Test p = 1.000
No	59 (98.3)	58 (96.7)	
Total	60 (100.0)	60 (100.0)	

In relation of comorbidities, just one (1.7%) control had obesity compared to eight (13.3%) cases, while 59 (98.3%) controls had no obesity compared to 52 (86.7%) controls. The distribution had a statistically significant difference (p<0.05) (Table 4).

Similarly, 7 (11.7%) cases had type 2 diabetes, compared to 6 (10.0%) controls, whereas only 3 (5.0%) cases and controls had a history of CKD. There were no statistically significant differences in the analyses (p>0.05).

Table 4: Comparison of comorbidity between cases and controls

Comorbidity	Characteristics	Type of participants		Significance
		Cases f (%)	**Controls f (%)**	
Type 2 diabetes mellitus	Yes	7 (11.7)	6 (10.0)	$\chi 2$=0.086 df = 1 p = 0.769
	No	53 (88.3)	54 (90.0)	
	Total	60 (100.0)	60 (100.0)	
Obesity	Yes	8 (13.3)	1 (1.7)	Fisher's Exact Test p = 0.032
	No	52 (86.7)	59 (98.3)	
	Total	60 (100.0)	60 (100.0)	
CKD	Yes	3 (5.0)	3 (5.0)	Fisher's Exact Test p = 1.000
	No	57 (95.0)	57 (95.0)	
	Total	60 (100.0)	60 (100.0)	

The factors associated to hepatocellular carcinoma were determined by binary logistic regression. The logistic regression model had five independent variables (residence type of family, total number of family, viral hepatitis and type of viral hepatitis).

Out of the five independent variables, four made a statistically significant contribution to the model (residence, type of family, viral hepatitis and type of viral hepatitis). The level of presence of viral hepatitis and presence of HBV were the strongest predictors of HCC (p<0.05). According to the odds ratio for viral hepatitis, participants with viral hepatitis were 22 times more likely to develop hepatocellular carcinoma (OR: 22.667, 95%CI 8.767-58.603) and the participants with the presence of HBV were 25 times more likely to develop HCC (OR: 25.667, 95% CI 8.812-74.762). Participants who resided in rural areas (OR: 3.382, 95%CI 1.526-7.497), had a nuclear family (OR: 4.041, 95 % CI 1.629-10.020) and had HCV (OR: 1.556,95 %CI 0.416-5.819) were also shown to be at higher risk factors in developing HCC.

Table 5: Logistic regression model for socio-demographic characteristics and viral hepatitis

Attribute		Co-efficient (B)	S.E	OR	95% CI for CI		p-value
					Upper	**Lower**	
Residence							
Rural		1.219	0.406	3.382	1.526	7.497	0.003
Urban**							
Type of family							
Nuclear		1.396	0.463	4.041	1.629	10.020	0.003
Joint**							
Total number of family							
3-4		1.129	0.685	3.094	0.808	11.843	0.099
5-8		0.782	0.647	2.186	0.615	7.774	0.227
9-11**							
Viral hepatitis							
Yes		3.121	0.485	22.667	8.767	58.603	0.000
No**							
Type of viral hepatitis							
HBV	Yes	3.245	0.545	25.667	8.812	74.762	0.000
	No**						
HCV	Yes	0.442	0.673	1.556	0.416	5.819	0.512
	No**						

DISCUSSION

Among the 60 cases, the male predominance was found, which is not surprising as it is evident that males are more susceptible to HCC than females [17]. In this study, the mean (±SD) age of the cases was 52.83 ± 12.85 years and the controls were 52.58 ± 12.84 years. The peak incidence of hepatocellular carcinoma in this study was 40-59 years and 60- 85 years. (48.3%) and (36.7%) cases which indicates 40-59 and 60-85 years as the most common age group to develop HCC. Another study was conducted in China demonstrated the mean (±SD) age was 51.9± 12.5 in cases and 52.5 ± 12.7 in control group where the proximity of age was were also found above the age of 70 [18].

In relation to marital status, the majority of cases were married, with (86.7%) compared to (93.3%) controls, followed by widow/widowers, having (11.7%) cases and (6.7%) controls. In the cases, (1.7%) was unmarried and the difference in marital status distribution among participants was statistically insignificant (p=0.362). The study conducted by another clinical study, comprised that among the 80 HCC patients (96.2%) were married compared to (90.1%) controls [6].

In this study, educational background represent that the greater number of cases (41.7%) were illiterate, compared to (50.0%) controls. About (20.0%) of the cases had a primary/elementary education, compared to (21.7%) of the controls. (10.0%) of the cases had a higher secondary level of schooling than the (11.7%) controls. In comparison to (3.3%) controls, (10.0%) patients finished graduation and only (5.0%) cases completed post-graduation (p=0.407) and represents the lack of awareness and knowledge as a large portion of patients had no education. Another study conducted in China demonstrated that most of the HCC patients (51.3%) had elementary school compared to (47%) control, where only (9.2%) had no education compared to (14.8%) controls. (28.3%) had completed middle school in cases compared to (27.8%) controls whereas (11.8%) cases had completed high school compared to (10.4%) controls [19].

In this study, medical records of the cases and controls of diabetes mellitus were reviewed. Among cases diabetes mellitus was found present in (11.7%) cases compared to controls (10.0%) (p=0.769). A study conducted in Bangladesh found that (28.7%) cases had diabetes mellitus compared to (25.7%) controls. The difference was not statistically significant (p=0.651) [6]. Another study conducted in Japan found that (8.0%) cases had diabetes mellitus compared to control (15.1%) (OR:1.88 ,95% CI, 1.01-3.50, p=0.047) [20].

Among cases, (13.3%) cases were obese compared to (1.7%) controls whereas (86.7%) cases were not obese compared to controls (98.3%). This was statistically significant (p=0.032; OR 9.077,95% CI 1.098-75.020). Another study conducted in Japan, found that (25.7%) cases were obese compared to (17.2%) and this was statistically significant (OR: 1.88 95% CI 1.13-3.13, p=0.087) [20].

Conclusion

We should screen for hepatitis B and C virus-infected people in the community in attempt to grant early and effective therapies which will not only enhance the survival rate of those diagnosed with the disease but also avoid the emergence of hepatocellular carcinoma. Government and other relevant agencies must take swift and systematic action to control of HBV infection remains of key importance for eliminating HCC ultimately.

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