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Prevalence of hepatocellular carcinoma in hepatitis B or C seropositive patients

Misha Anam[1*], Syeda Rukhsana Noor[2], Memoona Jahangir[3]
[1-3] Medical Ward, Unit 2, Allied Hospital, Faisalabad Medical University, Punjab, Pakistan

Abstract
The objective is to evaluate the contribution of hepatitis B and C in the development of Hepatocellular Carcinoma (HCC) and to estimate the burden of HCC in patients with chronic liver disease. It is a prospective, cross-sectional study and the 109 patients are selected by consecutive sampling technique. The study is conducted at Medical Ward 2, Allied Hospital, Faisalabad, from November 2018 to May 2019. Out of 109 patients of Hepatitis induced Decompensated Chronic Liver Disease (DCLD), 64 are females, 45 are males, with female to male ratio of 1.44. Out of the total, 87 patients have developed liver cirrhosis and 22 have developed HCC in the background of liver cirrhosis. HCC develops most commonly within 6 to 10 years of chronic hepatitis. Among all these patients, 1 and 108 patients are seropositive for hepatitis B and C, respectively. Hepatitis C is more prevalent than hepatitis B in our setup, with the female preponderance. Progression of Hepatitis to DCLD and then to HCC is faster, more common within 6 to 10 years after hepatitis B or C infection.

Keywords: prevalence, hepatitis, chronic liver cirrhosis, decompensated chronic liver disease (DCLD), hepatocellular carcinoma (HCC)

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. In 2015's survey, it is ranked 6th most commonly occurring malignancy and 3rd in cancer related mortality, worldwide [1]. The incidence of HCC is persistently rising [2]. Its annual incidence rate matches with its annual mortality rate, because of the fulminant course and grave prognosis. It is the 5th most common malignancy in males and 8th in females [3], more prevalent in males with the male to female ratio of 3.6:1 [4]. The prevalence of HCC in Asian countries is more than the rest of the world [5], reasons include the general lack of awareness, endemic of hepatitis B and C, inadequate screening of the causative factors, which results in the late presentation of HCC at its non-resectable stage. The pathogenesis of HCC is multifactorial including environmental, nutritional, infectious, metabolic and endocrine factors. The most common etiological factors are chronic viral hepatitis B or C infection, aflatoxin intake, hemochromatosis, non-alcoholic steatohepatitis and chronic alcohol intake. All of these factors lead to hepatic cirrhosis which is characterized by decreased hepatocyte regeneration capacity and increased fibrous tissue scaring ultimately resulting in formation of cancerous nodules. Approximately 70-90% of HCC develops in the background of liver cirrhosis [6].

Hepatitis B is the most important occupational hazard. It is caused by hepadnavirus, which replicates via RNA intermediate. After the HBV infection, HBV genome enters into hepatocyte and incorporates with its DNA makes a covalently closed circular DNA. The genomic corporation of HBV persists even during anti-retroviral therapy by using nucleotide analogues. The therapy results in suppression of HBV replication. Therefore, disease recurrence is possible even after successful therapy and clearance of HBsAg. HBV infection is preventable by vaccination with 95% efficacy. It is detectable by serology, within 30-60 days after infection [5.6].

Pakistan has the 2nd highest prevalence of hepatitis C in the world, ranging from 4.5% to 8% [7] and can be as high as 40% among the high-risk group [8]. The transmission of both, hepatitis B and C, is through blood and body fluids through IV drug abuse, reuse or inadequate sterilization of medical equipment, transfusion of unscreened blood and blood products, vertical transmission, sexual transmission, incarcerated persons, tattoos, piercing and use of shared intranasal sprays [13]. Hepatitis C is an enveloped virus, have exclusively cytoplasmic life cycle by maintaining itself as rough endoplasmic episome. The incubation period is 2 weeks to 6 months. Majority of the hepatitis C patients (80%) remains asymptomatic until they develop signs and symptoms of severe liver damage i.e. fever, fatigue, anorexia, nausea, dark colored urine, clay colored stool, vomiting, abdominal pain and joint pain. In HCV patients, liver cirrhosis plays major role in HCV associated hepatic carcinogenesis with the interplay of host, environmental and viral factors [14].

The spread of infectious diseases and their progression into a cul-de-sac, is preventable with robust surveillance. This can be done by improving community health-care facilities, accurately monitoring the disease trends, ensuring timely responses to disease transmission along with implementation of effective and evidence-based interventions. Our current study is based on an estimation of the burden of hepatitis B and C in the community leading to the development of primary liver cancer hence the conversion of an infection into an inevitable death. Our study portrays the bird's eye view of

the prevalence of untreated cases of hepatitis B and C and their percentage towards contributing into the catastrophic outcome, the hepatocellular carcinoma. The aim of this study is to draw attention of the health policy makers to this currently prevailing health hazard and to make the amendments accordingly [15].

2. Materials and Methods

A total of 109 patients, seropositive for chronic hepatitis are included in this study. The patients present with the significant history, signs and symptoms of Decompensated Chronic Liver Disease (DCLD). The detailed history, clinical examination and baseline investigations of all the patients are done. The history is taken via pre-structured, questionnaire-based interview is scheduled. Those who were not willing to participate, there rights were respected and were not included in the study. Out of 109, most of the patients are anemic due to Upper GI bleed (UGIB). PT, APTT, serum albumin level and Liver Function Tests (LFTs) are markedly deranged. The patients included are seropositive for either hepatitis B or C. Further investigations are done for the screening of HCC. In most of the cases, ultrasound abdomen only showed picture of cirrhotic liver. To rule out HCC in such patients, alpha-fetoprotein and Biphasic CT scan is done. The data of this present research is based on the patients having chronic hepatitis for significant period of time, now developed liver cirrhosis, and having more than one screening test positive for HCC. Data collected by this study is finally analyzed by SPSS 22.0.0.0.

2.1 Inclusion Criteria

- Patients who are HBsAg and anti-HCV seropositive for 6 months or more, with or without persistently high levels of HBeAg.
- Undiagnosed and untreated cases of hepatitis B and C, now presenting with liver cirrhosis.
- New clinical diagnosis of HCC by pathology, significantly raised levels of alpha-fetoprotein along with at least one radiological investigation suggestive of new mass defect in the liver (ultrasound and/or CT abdomen).
- Clinical presentation, Radiological and lab investigations suggestive of liver cirrhosis which requires further screening for HCC (size <2cm).

2.2 Exclusion Criteria

- Patients who are seronegative for HBsAg and anti-HCV or seropositive for less than 6 months.
- Patients who are hepatitis B and C positive but have not yet developed signs and symptoms decompensated chronic liver disease or cirrhosis.
- No lab investigation or radiological finding suggestive of CLD

3. Results

The results of this study show female preponderance. Out of 109 patients, 64 are females and 45 are males with the female to male ratio of 1.44. (Table 1)

Table 1: Frequency table of gender of the patients.

Gender	Frequency	Percent	Valid Percent	Cumulative Percent
Valid Female	64	58.72	58.72	58.72
Male	45	41.28	41.28	100.0
Total	109	100.0	100.0	

The incidence of DCLD gradually increases from the age group of 20 to 30 years, peaks at 50's and 60's, and then tapers off to the 7th decade of life, as shown in (Table 2).

Table 2: Age and gender distribution of Liver Cirrhosis in relation with hepatitis B and C seropositivity.

Age Groups	Gender Female Male	Seropositive for hepatitis B or C for (years) 0-5 6-10 11-15	Frequency of DCLD	Percent	Valid Percent	Cumulative Percent
Valid 11-20years	- -	- - -	0	0	0	0
21-30years	1 -	- 1 -	1	0.91	0.91	0.91
31-40years	8 5	7 5 1	13	11.9	11.9	12.8
41-50 years	21 12	22 9 2	33	30.2	30.2	43.0
51-60 years	28 11	24 11 4	39	35.7	35.7	78.7
61-70 years	8 8	7 2 7	16	14.6	14.6	95.4
71-80 years	3 2	2 2 1	5	4.58	4.58	100.0
81-90years	- -	- - -	0	0	0	
Total	64 45	62 30 15	109	100.0	100.0	

According to the data collected, 109 patients were admitted in emergency with the sign and symptoms of DCLD due to chronic hepatitis. Out of 109 patients, 108 were having hepatitis C and only 1 patient was seropositive for hepatitis B (P=0.009). After the appropriate investigations, 87 patients were diagnosed with liver cirrhosis of various grades and 22 patients were diagnosed with HCC (after definitive investigations) in the background of liver cirrhosis (P=0.20). The prevalence of liver cirrhosis and HCC varies greatly in different age groups. In all age groups, female preponderance is noted. The maximum number of patients with liver cirrhosis and HCC are found in the age of 5Th, 6Th and 7th decade within 6 to 10 years of hepatitis B and C seropositivity (Table 2-3). Because of lack of regular screening tests facility, the exact duration of chronic hepatitis in these patients is unknown. The duration of hepatitis B and C is calculated starting from the year when the patient was diagnosed positive for chronic hepatitis via screening for HBsAg or Anti-HCV, either incidentally or after developing sign and symptoms of hepatitis. (table 2-3).

Table 3: Age and gender distribution of HCC in relation with duration of hepatitis B and C seropositivity.

Age Groups	Gender Female Male	Seropositive for hepatitis B or C for (years) 0-5 6-10 11-15	Frequency of HCC	Percent	Valid Percent	Cumulative Percent
Valid 11-20 years	- -	- - -	-	0	0	0
21-30 years	- -	- - -	-	0	0	0
31-40 years	- -	- - -	-	0	0	0
41-50 years	2 3	- 3 2	5	22.7	22.7	22.7
51-60 years	7 3	2 7 1	10	45.45	45.45	68.15
61-70 years	3 3	- - 6	6	27.27	27.27	95.4
71-80 years	- 1	- 1 -	1	4.5	4.5	100.0
81-90 years	- -	- - -	-	0	0	
Total	12 10	2 11 9	22	100.0	100.0	

4. Discussion

Contrary to the western world, in Pakistan, DCLD and HCC are more common with HCV than HBV, Xie Y *et al*. [12], probably because of their relevant difference on the impact of cirrhosis. Liver cirrhosis is more strictly associated with HCC in chronic HCV infection. The HCV viral proteins get incorporated with hepatic stellate cells resulting in release of profibrogenic mediators along with inflammatory cytokines and chemokines that magnifies the cycles of tissue damage and repair, resulting in fibrosis and hence, liver cirrhosis. The results of our study correlates with Alla *et al*. [9]

The major characteristic of HCC is hyper vascularization. The extension of tumor into hepatic or portal vein/s or formation of arteriovenous shunting results in portal hypertension followed by formation of varices with the possibility of rupture, R Dharnasekaran *et al*. [19] HCC is an aggressive tumor and every patient is suspected to have HCC if previously he was having CLD (deranged LFTs, clinically jaundiced, having associated symptoms) and now presenting with DCLD (i.e. gross ascites, hepatic encephalopathy, worsening jaundice, upper GI bleed) along with weight loss, early satiety, pain and/or mass in right hypochondria or epigastrium etc. Asymptomatic phase of chronic hepatitis and hence absence of pathognomic signs and symptoms results in late diagnosis of the tumor and grave prognosis of the patient. The factors resulting in poor prognosis are large tumor size (non-resectable tumor), vascular invasion, poor functional status and nodal metastasis, G. Falkson *et al*. [19]

HCC has a median subclinical period of 3.2 years. In this period if screening is performed, early detection of tumor has a potential for cure. Ultrasound can detect the tumor as small as 1.6cm. One of the major reason of high Hepatitis incidence is that here is no vaccination available for hepatitis C. Among the general population of Pakistan, Lack of awareness about chronic hepatitis and poor knowledge of its complications is the reason that proper screening and treatment protocol is not followed. If someone undergoes screening then the common trend in Pakistan is 6 monthly USG with serum AFP level. The serum AFP level is neither specific nor sensitive and alone is never enough to rule out HCC. Ultrasound can detect the tumor as small as 1.6cm. Although the USG sensitivity and specificity for detecting HCC is more than 90%, the view gets compromised in the background of liver cirrhosis, additionally, the ultrasound is highly operator dependent so, there is always a high risk of personal error, M.F. Yuen *et al*. [10]. Delayed diagnosis is associated with poor prognosis.

As patients remain asymptomatic for much longer duration of time after getting HBV and HCV infection, they do not undergo any surveillance test or any diagnostic procedure till they develop liver cirrhosis with all the signs and symptoms of it. The mean time for chronic hepatitis to develop liver cirrhosis is 25 years. Majority of patients in Pakistan only receive supportive care as they present in the late course of disease when the tumor become unresectable or metastasize, C Ayuso *et al*. [20]

Globally, the research in HCC lags behind certain other common malignancies and so in Pakistan. Majority of cases of HCC in Pakistan are hepatitis C related. Even today due to lack of research and data, we are unaware of exact prevalence of hepatitis C in Pakistan. It is assumed that currently, there are more than 10 million people who are infected with hepatitis C virus, Bhattii AH *et al*. [11]

Evident with the results, Hepatitis C is epidemic in Pakistan, AG Lim *et al*. [17] Both Hepatitis B and C are infectious diseases and are completely preventable but there is lack of knowledge and awareness among people about the risk factors and spread of disease, carelessness of healthcare providers in handling the bodily fluids and its contamination with the healthy person via blood transfusion and inappropriate sterilization of the instruments etc. which is accelerating the impact of this disease, day by day, DK Henderson *et al*.[18] The masses need to be educated regarding modes of spread, necessary precautions and risk factors. Additionally, the patients infected with the B and C viruses should be informed about the benefits of strict surveillance, appropriate treatment options available for the B and C viruses and the different treatment modalities available for HCC. It requires the attention of basic healthcare policy makers to educate the people to control this outbreak with great efficiency.

5. Conclusion

Among the chronic viral hepatitis, hepatitis C is most common in our setup with female preponderance. In hepatitis B and C patients, incidence of DCLD and HCC is high. Majority of the patients develop DCLD within 0 to 5 years, earlier in the course of chronic hepatitis. Within 6-10 years of hepatitis B and C seropositivity, most of the DCLD patients develop HCC.

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