Original Article

Clinical Characteristics of Primary Liver Cancer Patients Presenting to Mayo Hospital, Lahore

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Objective: To determine the clinical characteristics of patients with hepatocellular carcinoma and common risk factors associated with development of this disease.

Methods: In this cross-sectional study clinical data of 151 HCC patients was collected over one year Jan 2017-Dec 2017. Variables included age, sex, socioeconomic status, presence or absence of liver cirrhosis, tumor size, tumor stage, presence of portal vein thrombosis, hepatitis serology, serum AFP levels, and management received. SPSS 22 was used for statistical analysis. Mean and standard deviation was calculated for quantitative variables like age and size of tumor and frequency and percentage was calculated for qualitative variables like gender, socioeconomic status etc.

Results: Total 151 patients were included in the study. 106(70%) were males. Mean age of presentation was 57.1 ± 8.6 years. Patients with rural background were 115 (76.2%) and urban cases were 36 (23.7%). 136 (90%) patients belonged to lower socioeconomic strata while 15 (10%) were of middle social class. Most common cause found was viral hepatitis, with 104 (69%) patients were positive for Hepatitis C virus, 27 (18%) were positive for Hepatitis B virus, 6 (4%) were infected with both. Serum Alpha fetoprotein was raised more than 400 ng/ml in in 67 (44 %). Mean tumor size was 8.2 cm ± 2.9 cm. 32%, 47%, and 21% patients had Child class A, B and C respectively at the time of presentation. A total of 93(61.6%) received 5FU therapy, 7(4.7%) underwent surgery, 18(11.9%) received sorafenib therapy and only 1 patient (0.6%) opted for liver transplant.

Conclusions: Hepatitis C virus has been found the most prevalent cause for nurturing HCC in this study, and most of the patients present at advanced stages, with large tumor size and portal vein thrombosis, where only palliative therapies can be offered. There is a need to devise and implement an effective screening programs for prevention, early detection and treatment of viral hepatitis. In patients who have developed cirrhosis already, should be kept on close follow up so that early and curative intervention can be offered to save precious lives.

Keywords: cirrhosis, child-turcotte-pugh classification, hepatocellular carcinoma, serum AFP, viral hepatitis.

Introduction

Hepatocellular carcinoma (HCC) is the most common liver cancer (also called hematoma).[1] Liver cancer is second commonest cause of cancer death around the globe.[1] Worldwide incidence of HCC is 5.4%.[2] It is 5th most common cancer in men (7.5%) and 9th in women (3.4%) with highest incidence is found in Asian (China, Taiwan, Korea) and Sub-Saharan African countries because of Hepatitis B virus that is transmitted to infants through vertical transmission.[1,2] While in Japan and Europe most important causative agent is Hepatitis C virus [2]. Other important causative factors of HCC are metabolic toxins like aflatoxin and alcohol, hemochromatosis, alpha1 antitrypsin deficiency and steatohepatitis[2]. All these agents incorporate inside hepatocytes, disturb their structure, function and genomic material resulting in a vicious cycle of inflammation and regeneration of hepatocytes.[3] Hepatocytes try to repair the damage but become dysplastic and ultimately neoplastic as they accumulate structural and numeric chromosomal abnormality indicative of genomic instability.[3]

Developed countries like United States, HCC is relatively uncommon.[4] Pakistan being under-developed countryharbors great number of HCC patients. Many remain undiagnosed due to lack of proper health care facilities and unawareness to risk factors.[3,4] Pakistan has 2nd highest prevalence of chronic Hepatitis C infection in the world[4]. Approximately over 10 million people are infected with chronic Hepatitis virus in Pakistan[5]. Hepatitis C prevalence is 6%-13% while Hepatitis B prevalence is 2-3%. According to Punjab cancer registry, it is the fifth most

common cancer collectively in both genders (3.8%) and 3rd most common in men (6.6%).[5] Viral hepatitis and excessive alcohol consumption are the top most causes of HCC[6]. HCC can be treated by radioablation, chemoembolization, resection and transplant in advanced stages but has a dismal outcome.[7] The purpose of this study is to find out clinical characteristics of patients with HCC in local population so that proper screening methods can be planned for our population. This will help in early detection, treatment and decreasing the need for liver transplant.

Methods

This cross-sectional observational study enrolled 151 patients of hepatocellular carcinoma. The variables studied were age, sex, socioeconomic status(monthly income below 10,000 PKR = Low, or above =Middle class) underlying co-morbidity, presence or absence of liver cirrhosis, tumor size, single/multiple tumors, hepatitis serology, serum AFP levels, management received(standard management options include surgery, liver transplant, local ablation and systemic therapy with Sorafenib), portal vein thrombosis, Child classification (Classified as A, B and C depending upon serumbilirubin, albumin, prothrombin, ascites and encephalopathy) during one year i.e. between January 2017 till December 2017 were obtained from the patients presenting to Oncology Department and oncology outdoor of Mayo Hospital, Lahore with the help of participating investigators. All information was recorded in a predesigned proforma after informed consent. All data was analyzed by SPSS 22 and descriptive statistics were used for variables. Mean and standard deviation was calculated for quantitative variables. Frequency and percentage was calculated for qualitative variables like gender, socioeconomic status, cirrhosis, stage of tumor, causes of HCC, serum AFP, portal vein thrombosis and type of therapy received.

Results

Total151 patients were included in the study. Out of 151, 106(70%) were males and 45 (30%) were females. Mean age of presentation was 57.1 ± 8.6 years. Patients with rural background were 115 (76.2%) and urban cases were 36 (23.7%). 136 (90%) patients belonged to lower socioeconomic strata while 15(10%) were of middle social class. (Table I). According to this study 104 (69%)patients were positive for Hepatitis C virus, 27 (18%) were positive for Hepatitis B virus, 6 (4%)were infected with both viruses, 3 (2%) were alcoholic and 11(7%) patients had no known causative factor for HCC **(Fig-I)**.

Analysis of child-turcotte-pugh classification, this patient population showed that 48(32%) of patients had class A, 71 (47%) class B, and 32(21%) had class C. Levels of serum Alpha fetoprotein showed that 67(44 %) of patients had AFP more than 400 ng/ml, 48 (32%) had AFP level between 20-400ng/ml and 36 (25%) had AFP levels below 20 ng/ml. Mean tumor size was 8.2 cm ± 2.9 cm.

Tumor size was more than 10cm in 39(25.8%) patients. Multicentric tumor was present in 97(64.2%) and Portal Vein Thrombosis was seen in 56 (37%) of patients. Regarding stage of Hepatocellular carcinoma 3(1.9%) patients were at Stage I, 16 (10.7%) had stage II, 84 (55.7%) had stage III and 48 (31.7%) patients were at stage IV of disease. Outcome of therapy received by patients showed that 93(61.6%) received 5FU therapy, 7(4.7%) underwent resection/ local ablation/ surgery, 18(11.9%) received sorafenib therapy. While 32(21.1%) were of Child class C and hence could not receive any therapy and 1 patient (0.6%) opted for liver transplant **(Fig-II)**

Table-1: Demographic features of HCC.

Mean age ± SD	**57.1±8.6 Years**	
Gender Distribution	Male	106 (70%)
	Female	45 (30%)
Background	Rural	115 (76.2%)
	Urban	36 (23.7%)
	Lower Class	136 (90%)
	Middle Class	15 (10%)
Mean Tumor size±SD	**8.2cm±2.9cm**	
Alpha-feto Protein Level	Normal level (20ng)	55 (43.71%)
	Between 20-400ng	49 (32.45%)
	More than 400ng	36 (23.84%)
Functional Liver Reserves	Child class A	48 (31.79%)
	Child class B	71 (47.02%)
	Child Class C	32 (21.19%)

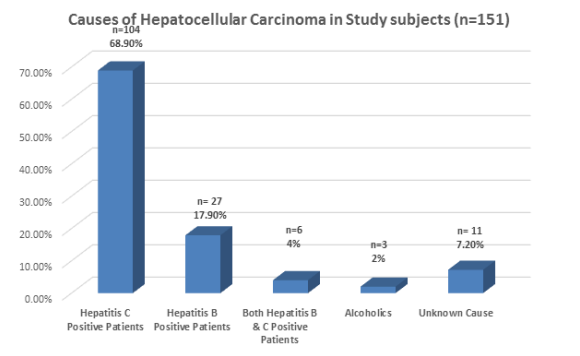

Fig-I: Causative agent of Hepatocellular Carcinoma.

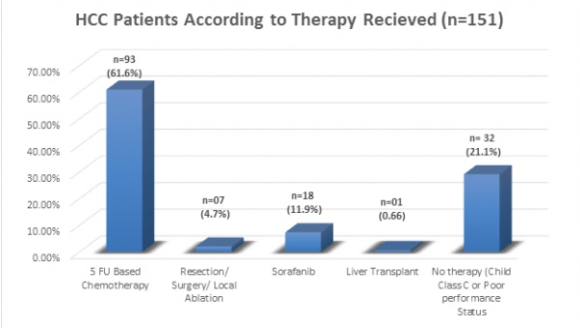

Fig-2: Therapy received by HCC patients.

Discussion

Hepatocellular carcinoma is life threatening condition with rising incidence worldwide. Despite improvement in HCC management multiple factors like lifestyle, metabolic syndrome, environmental factors, obesity, hepatitis viruses and many other are supporting its development[7,8]. It is diagnosed at advanced stage and has many complications during and after treatment[8]. Males and females are affected differently from it. Zheng et al stated that estrogen /androgen signaling pathway is associated with decreased/increased transcription and replication of HBV genes that promote development of HBV infection by up/down regulating RNA transcription of viruses which in turn slows the progression of HBV induced HCC. Estrogen and androgen can also effect HBV related HCC by induction of epigenetic changes. This could be the reason behind different incidence among males and females.[9] In this study, out of 151, 106(70%) were males and 45 (30%) were females. Kao conducted multivariate analysis on HCC patients and results showed that HCC was associated with poor prognosis when accompanied by factors like age older than 65 years, Alpha fetoprotein (AFP) greater than 20 and multiple tumors [10]. Similarly, poor survival was seen in older patients, with advanced tumor stage and multiple tumors [7]. Kotewall's group of patients had median age of 58.5 with age range of 25-78 years [11].In this study, mean age of presentation was 57.1 ± 8.6 years Egyptian population also had median age of 58 years at diagnosis of HCC while African patients presented at median age of 46 years. Hepatitis C was leading cause of HCC in Egypt while Hepatitis B was major cause in African population[12]. We concluded that most of our patients were from rural background 115 (76.2%) and urban cases were 36 (23.7%). 136 (90%) patients belonged to lower socioeconomic (income below 10,000 PKR/ month) strata while 15 (10%) were of middle social class (income above 10,000 PKR). Similarly, in United States lower socioeconomic strata harbored more cases of HCC than higher class.[13]

AFP level more than 400ng/mL is independent risk factor for overall survival, it is still not sensitive enough to predict the prognosis in patients with HCC diameter less than 3 cm [14]. Similarly, Kotewall found that AFP levels (more than 400ng/mL) were higher in HCV infected patients (78.2%) as compared to HBV infected group (67.1%) [12]. We found that (67) 44 % of patients had AFP more than 400 ng/ml, 48 (32%) had AFP level between 20-400ng/ml and 36 (24%) had AFP levels below 20 ng/ml. In this study, patient's tumor size was more than 3cm and still more than 50% of patients had AFP below 400ng/mL. It was concluded that AFP is not sensitive enough to detect HCC in local population as most of them are infected with HCV.

According to this study 104 (69%) of patients were positive for Hepatitis C virus, 27(18%) were positive for Hepatitis B virus, 6 (4%) were infected with both viruses. However in United States, HCV is more common in HCC patients as compared to HBV [15]. Munaf A and studies in United States showed prevalence of HCV to be 66% and HBV as 34%. Patients with HCV were more likely to develop HCC at advanced age of 52 years as compared to HBV infected who developed HCC at the age of 40 years[15, 16]. A study conducted in Iran on 1654 people (healthy) with mean age of 29.1 showed HCV infection in 0.42%(7/1654) of patient population. Among them 80% were males and 20% were females. Iran has very low prevalence of hepatitis virus infection [17]. Data of this study is consistent with these observations but different from China.

In our patients tumor size was more than 10cm in 39(25.8%) patients. Kotewall's patients had median tumor size of 2.7 cm [12]. Tumor size was larger; more than 5cm in HCV group (66%) while less than 5cm in HBV group (59.3%). In local population, tumor size

much larger than seen in other studies. It was found that multicentric tumor was present in 97 (64.2%) and Portal Vein Thrombosis was seen in 56 (37%) of patients. In contrast, Munaf states that portal vein thrombosis was seen in 8% of HCV patients and only 1% of HBV group. HCV-HCC group were more cirrhotic than HBV and had more than two times higher rate of solitary macro vascular involvement than HBV group (OR=0.245 and 2.533 respectively).Regarding stage of Hepatocellular carcinoma 3(1.9%) patients were at Stage I, 16 (10.7%) had stage II, 84 (55.7%) had stage III and 48 (31.7%) of patients were at stage IV of disease. Analysis of child-turcotte-pugh classification, study patient population showed that 32% of patients had class A, 47% class B, and 21% had class C. In West and China most patients are diagnosed with early respectable disease.[18] This probably is due to effective screening programs in high risk cirrhotic population which include ultrasound and serum AFP levels. While in local population no such facility is available for cirrhotic patients and rural population is unaware of disease signs and symptoms. Lack of awareness among masses and ineffective screening leads to late disease presentation and diagnosis resulting in high morbidity and mortality due to HCC.

In advanced HCC sorafenib is standard first line care and regorafenib as a second line option. Patients with portal vein thrombosis are offered radio embolization if they are infected with HBV and sorafenib if infected with HCV.[19] The results of therapy received by study patient population showed that 93 (61.6%) received 5FU therapy, 7 (4.7%) underwent resection/ local ablation/ surgery, 18(11.9%) received sorafenib therapy. While 32(21.1%) were of class C and could not receive any therapy and one patient (0.66%) opted for liver transplant. We are way behind the world in detecting and treating HCC.

Conclusion

In local population, Hepatitis C virus has been found the most prevalent cause for nurturing HCC in this study, and most of the patients present at advanced stages, with large tumor size and portal vein thrombosis, where only palliative therapies can be offered. There is a need to devise and implement an effective screening program for prevention, early detection and treatment of viral hepatitis. In patients who have developed cirrhosis already, should be kept on close follow up so that early and curative intervention can be offered to save precious lives.

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