Original Article

Prevalence of Hepatocellular Carcinoma in Cirrhotic Patients of Northern Sindh Attending Liver Clinics at Ghulam Mohammad Mahar Medical College Hospitals Sukkur and Khairpur

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ABSTRACT

Despite bearing the main burden of Hepatocellular carcinoma, prospective studies from developing countries particularly Pakistan are lacking. This prospective observational study was designed to estimate the prevalence of HCC among Northern Sindh patients with hepatic cirrhosis.

OBJECTIVE: To assess the prevalence of hepatocellular carcinoma in cirrhotic patients of Northern Sindh attending liver clinics at Ghulam Mohammad Mahar Medical College Hospitals Sukkur and Khairpur

STUDY DESIGN: Prospective observational study

PLACE & DURATION OF STUDY: Liver clinic Ghulam Mohammad Mahar Medical College Hospitals Sukkur and Khairpur, between April 2008 and November 2010

METHODOLOGY: Between April 2008 and November 2010, we enrolled 301 patients with liver cirrhosis. Patients found to be free of hepatocellular carcinoma (HCC) using baseline abdominal ultrasound, computed tomography (CT) Scan of abdomen in selected cases and serum alpha-fetoprotein (AFP) levels. Patients were followed up prospectively for detection of HCC using ultrasound and AFP every 6 months, liver biopsy and CT scan of abdomen in selected cases when required.

RESULTS: Among the 194 patients (mean age [SD] 45.1±13.1 years; male: female 6.1:1.0) followed up, 154 had Child's A and 40 had Child's B disease. The causes of cirrhosis were: hepatitis B in 71 (36.6%), hepatitis C in 54 (27.8%), dual infection with hepatitis B and C in 12 (6.2%) and others including autoimmune, alcoholic and cryptogenic cirrhosis in 57 (29.4%) cases. During a cumulative follow up period of 563.4 person-years, 9 cases of HCC were detected, with an incidence rate of 1.60 per 100 person-years.

CONCLUSION: In our study, the prevalence of HCC among patients with liver cirrhosis was intermediate, being lower than that in Japan but higher than that reported from Europe.

KEY WORDS: Hepatocellular Carcinoma, Cirrhosis, Incidence, Northern Sindh.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem, being the fifth most common neoplasm in the world, and the third most common cause of cancer-related deaths. More than 500,000 new cases are currently diagnosed annually, with an age-adjusted incidence of 5.5-14.9 per 100,000 population worldwide[1]. Age-adjusted incident rates for liver cancer in developing countries are two to three-fold higher than those in the developed countries[2]. Approximately 80% of liver cancers occur in Asia and Africa[3]. The incidence is comparatively lower in Middle East[4].

HCC almost always occurs in a histologically abnormal liver and the presence of chronic liver disease represents a potential risk factor for its development. In large series, more than 80% of patients developing HCC had liver cirrhosis. Though cirrhosis of any etiology may be complicated by HCC, persistent HBV or HCV infections account for over 80% of HCC cases worldwide[2]. HCC is a complication of liver cirrhosis with an annual incidence of 2.0%-6.6%[5]. Studies from Europe and Japan indicate that 1.0% to 5.8% patients of cirrhosis develop HCC each year[6]. However, such estimates from low and middle-income countries are not available. The rate of occurrence of HCC in patients with cirrhosis in Pakistan has not been well studied. The current study was undertaken to address this issue.

METHODS

The present prospective study was conducted from April 2008 to November 2010 at the liver clinics, Ghulam Mohammad Mahar Medical College Hospitals Sukkur and Khairpur, after approval by the institutional ethics committee.

The study population consisted of new and previously diagnosed cases of liver cirrhosis of any etiology reporting to the Liver Clinics at the Department of

Medicine of our institute. Patients of Child A or B class cirrhosis were enrolled into the study after obtaining consent. Patients with Child C cirrhosis, those having severe co-morbidity such as coronary artery disease, chronic renal failure, respiratory disease or any other prolonged illness where the expected survival was less than a year, and those unable to visit the hospital every six months were excluded.

A detailed history was obtained from each patient and physical examination was done. Investigations included complete blood count, liver function tests, upper gastrointestinal endoscopy (in selected cases), viral markers for hepatitis B and C, and autoimmune markers, HBsAg and anti-HCV were tested using commercial ELISA. HBV DNA and HCV RNA were first detected by using qualitative PCR[7-9] and if they were positive, they were quantitated using quantitative PCR[9]. The sensitivity of qualitative PCR for HBV DNA was 100 copies/mL and HCV RNA 500 copies/mL[9-10]. These tests were done at initial presentation and every three months thereafter in patients treated with antiviral drugs. Serum alpha-fetoprotein (AFP) was estimated using a particle enzyme immunoassay (normal range <20 ng/mL).

The abdominal ultrasonogram (US) was done at the time of enrolment. Abdominal CT scan was done in selected cases. Features of chronic liver disease and characteristics of any mass lesion in liver were noted. The US and CT Scan of abdomen were interpreted together along with serum AFP levels to arrive at a final diagnosis regarding the presence of absence of HCC[11]. Liver biopsy was done for mass lesions, for the histological confirmation of the diagnosis[12].

Patients found to be free of HCC at enrollment were followed up prospectively for the occurrence of HCC using US and AFP measurement every six months, and CT scan annually (in selected cases). Regular follow-up was ensured through phone calls, letters and scheduled appointments for the tests. The follow up period was estimated from the date of diagnosis of cirrhosis to either end of study (November 2010), death, or development of HCC. Follow up duration was expressed in person-years and incidence rate as events per 100 person-years.

Sample size of the follow-up cohort was calculated so that incidence of HCC could be measured with a precision of 15% (α=0.15) at a confidence level of 95%[13]. This yielded a sample size of 170 subjects. Addition of 10% dropouts and loss to follow up led to a final sample size of 187.

Diagnosis of cirrhosis was made on the basis of clinical, biochemical and endoscopy findings. Liver biopsy was done whenever considered necessary. Patients were classified as freshly-diagnosed cirrhosis if the duration of cirrhosis was less than 3 months at enrolment in the study, the rest were classified as having previously diagnosed cirrhosis.

HBV cirrhosis was diagnosed when detectable HBsAg in serum was present. HCV cirrhosis was diagnosed with detectable anti-HCV and/or HCV RNA or both in serum. Replicating HBV infection was considered when these patients of cirrhosis had detectable HBeAg and/or HBV DNA in sera. Replicating HCV infection was diagnosed with detectable HCV RNA in the sera.

Diagnostic criteria followed for HCC were the modified European Association for study of Liver (EASL) criteria[14]. These consisted of (a); either fine needle aspiration cytology (FNAC) or (b); any two of the following three criteria:(i), AFP level > 300 ng/mL, (ii), arterialization of the mass on CT scan or (iii), arterialization of the mass on MRI. HCC was staged according to the Barcelona Clinic Liver Cancer (BCLC) staging.

RESULTS

Three hundred and one patients with liver cirrhosis were screened for HCC during the study period. Of these, 107 were found to have HCC. The remaining 194 patients who were free of HCC at enrollment constituted the follow-up cohort. Among the 194 patients, 154 belonged to Child class A and 40 to class B. The mean (SD) age of these patients was 45.1 (±13.1) years with a male-female ratio of 6.1:1. Ninety six patients were newly diagnosed cases whereas 98 had previously diagnosed cirrhosis.

The distribution of etiology was: HBV 71 (36.6%), HCV 54 (27.8%), dual infection with HBV and HCV 12 (6.2%), and other causes 57 (29.4%) including autoimmune, alcoholic or cryptogenic cirrhosis). Viral replication was observed in 59/83 (71%) patients with HBV infection and 38/66 (58%) patients with HCV infection. Mean AFP level of the cohort at enrolment was 17.5 (45.7) ng/mL (median 5.1; interquartile range 2.9-9.6). At the time of enrollment, 85% of the patients had AFP levels below 20 ng/mL, where as 1% had a level >300 ng/ml.

These 194 patients were followed up during the study period by US and AFP every 6 (±1.6) months and CT scan every 12 (± 2) months, if required. A cumulative follow up of 563.4 person-years (mean 34.9 months, median 25.5 months) was accomplished. Nine patients (age range 43-71 years, all men) developed HCC on follow up. The incidence of HCC among patients with liver cirrhosis was 1.60 (95% CI 0.55-2.64) per 100 person-years **(Table I)**. The incidence of HCC among the newly diagnosed cases of cirrhosis was 3.53 per 100 person years (95% CI 0.07-6.99). All the remaining patients of cirrhosis in the cohort continued to be free of HCC till the end of the study or death.

Four of nine patients who developed HCC were newly

TABLE I: INCIDENCE RATE (PER HUNDRED PERSON YEARS) BASED ON DURATION SINCE THE DIAGNOSIS OF CIRRHOSIS (n=194)

Patients	Number	Follow up			Developed HCC	Incidence
		Cumulative (Years)	Mean (Months)	Median(Range) (Months)	(n)	(95% CI)
Newly diagnosed	96	113.33	14.2	9.5 (0 – 44)	4	3.53(0.07 – 699)
Previously diagnosed	98	450.09	55.1	46 (4 – 181)	5	1.11 (0.14 – 2.08)
Total	194	563.4	34.9	25.5 (0 – 181)	9	1.60 (0.55 – 2.64)

TABLE II: INCIDENCE RATE (PER HUNDRED PERSON YEARS) ACCORDING TO ETIOLOGY OF CIRRHOSIS

Etiology of Cirrhosis	Number	Follow up			Developed HCC	Incidence
		Cumulative (Years)	Mean (Months)	Median(Range) (Months)	(n)	(95% CI)
Hepatitis B	71	166.25	28.1	24	4	2.41 (0.05 – 4.76)
Hepatitis C	54	168.83	36.4	23	4	2.44 (0.05 – 4.83)
HBV + HCV	12	29.83	34.9	25.5	1	3.35 (0.0 – 9.92)
Others	57	203.50	42.8	32	0	0

diagnosed cases of cirrhosis (median [range] duration 16 [9-26] months), while five were known cirrhotic for a variable duration (66 [44-152] months). Four patients had HBV and HCV infection each and one had dual infection with HBV and HCV. All these patients had replicating HBV/ HCV infection and were in Child A cirrhosis at the time of detection of HCC. Incidence of HCC was similar among patients with HBV and HCV infection **(Table II)**. These 9 HCC cases picked up on surveillance had a baseline AFP level ranging from 2.5- 40.1 ng/mL. At the time of detection of HCC, the AFP level of only one case was >300 ng/mL while the remaining 8 HCC cases had levels of 4.1, 5.4, 7.0, 10.3, 11.8, 13, 102 and 135 ng/mL, respectively.

Six patients (single lesion 4, multiple 2) had small sized (≤5 cm diameter) HCCs, detected at 11, 13, 22, 29, 36 and 37 months after enrollment, respectively. Three patients (single 1, multiple 2) had large (>5 cm) HCCs, detected at 6, 8 and 13 months after enrollment, respectively. Three patients in whom the HCC was detected at a period less than a year the tumors were picked up on US. They subsequently underwent CT scan. These patients were definitely free of HCC at US at the time of enrollment. In the remaining 6 patients, HCC was detected both on US and CT scan. Of these 9 HCC patients, 4 were found to be at BCLC-A stage and two patients were at BCLC-B stage. The remaining 3 patients were at BCLC-C stage.

DISCUSSION

Ghulam Mohammad Mahar Medical College is the premier institute of North Sindh in public sector. It covers districts; Sukkur, Ghotki, Khairpur, Noshehro Feroz, Shikarpur, Jacobabad, Kashmore- Kandh kot & certain Parts of Balochistan. In Pakistan, particularly in Northern Sindh the incidence of HCC in cirrhotic patients is yet not well known, however, in India the mean incidence of HCC (per 100,000 population) in the four population based cancer registries in the nineties was 2.77 for males and 1.28 for females[15]. HCC accounted for 1.9% of the 24.975 cases of cancers recorded at 6 registries put together; the proportion ranging from 1.1% (94/8763) in Delhi to 5.3% (10/187) in Barshi rural registry[16].

In the present study, the incidence rate has been estimated to be 1.60 per 100 person-years. The incidence in the newly diagnosed patients of cirrhosis was 3.53 per 100 person-years. The lower incidence in the previously diagnosed patients (1.1) per 100 person years indicates possibly a survival bias, as they represent the 'survivors' of the 'original cohort' whose counterparts may have developed HCC and died.

In the 9 HCC patients detected on surveillance, 3 patients were diagnosed to have HCC at less than a year (6, 8 and 11 months). All these cases like others had undergone baseline US, AFP and CT scan at enrollment and were free of HCC at that stage. However, imaging techniques have a known fallacy of having very low sensitivity for tumors <1 cm, but for all

practical purposes the cohort was free of HCC at enrollment; therefore tumors detected at these periods of follow up should be viewed as detection on surveillance.

In various studies on HCC surveillance among patients of cirrhosis from different countries, the reported annual incidence ranged from 1.0% to 5.8% per year[17,18]. Thus, the incidence of HCC in Indian subcontinent is somewhat lower than European and other Asian countries. Studies among immigrant populations in Singapore and Australia also indicate that South Asians, in comparison to Malay and Chinese populations, are less prone to HCC[19].

Risk of HCC is higher in patients of cirrhosis caused by viral infections compared to non-viral causes. In different Indian studies, almost half of HCC patients have underlying HBV infection; while over a quarter have HCV infection. The attributable fraction of HCC for HBV and HCV infections in Japan and Europe / US are 20%-22% and 60% 63%, respectively[20]. In recent years, an improved understanding of viral genotypes has helped in explaining differential progression of HBV and HCV infections to HCC in different populations. Genotypes of HBV (A and D) and HCV (2, 3, 5 and 6) predominantly prevalent in Indian Subcontinent are less virulent and are associated with less frequent progression to HCC than other genotypes[21,22]. This may be a critical additional reason for a relatively low risk of HCC among South Asian patients of liver cirrhosis[23]. Additionally, host characteristics might also be responsible for lower incidence of HCC among cirrhotic patients of Indian Subcontinent.

We found an equal proportion of case of HBV and HCV cirrhosis developing HCC. Persistent HBV and HCV infections are the most important causes of HCC worldwide and have a variable geographical distribution. Various Indian studies have reported HBV infection as the predominant risk factor of HCC[24,25]. Hepatitis B surface antigen (HBsAg) positivity in Indian HCC patients varies from 36% to 74%, with an average of 47%[26]. It is estimated that nearly 42.5 million people in India are HBsAg positive[26]. The prevalence of anti HCV antibody in the South Asian population varies from 0.3% to 1.8%[27]. In our region, HBV transmission is a combination of mainly horizontal (75%) and vertical modes (25%), occurring mostly in childhood[28]. HCV is an adult disease acquired mainly through the parenteral route.

CONCLUSION

In conclusion, the present prospective cohort study reveals the HCC incidence among Northern Sindh patients of cirrhosis is 1.6% per year. Using this estimate of the incidence of HCC, the cost effectiveness of the surveillance program employing six monthly US and AFP with annual CT (in selected cases) has also been estimated. This cost per HCC case detected is exorbitant for low / middle income countries like Pakistan.

Our study has some limitations. Due to small number of HCC cases detected, the risk factors of HCC could not be ascertained. Secondly, this being a hospital-based study, a referral bias leading to high prevalence of HCC in cirrhosis was unavoidable. However, it may be noted that on account of a very large population (approximately I60 million), the number of HCC patients in Pakistan would still be enormous, despite the low incidence.

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