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A STUDY TO DETERMINE HEPATOCELLULAR CARCINOMA PREVALENCE IN CIRRHOTIC PATIENTS

Dr Muhammad Awais[1], Dr Syeda Rubbab Naqvi[2], Dr Hidayatullah[3]

[1]Abbottabad International Medical College, Abbottabad, [2]Alnafees Medical College Isra University, Islamabad, [3]Rokhan Institute of Higher Education, Nangarhar.

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Abstract:

Objective: *To evaluate the hepatocellular carcinoma prevalence in patients with cirrhosis.*

Study design: *A prospective observation study.*

Place and duration: *In the Gastroenterology department of Mayo Hospital Lahore for two year duration from May 2017 to May 2019.*

Methods: *301 patients with liver cirrhosis were included. Basal abdominal ultrasound, abdominal computed tomography (CT), alpha-fetoprotein (AFP) show hepatocellular carcinoma (HCC) were not detected in selected patients and those were 194 cases and was the final sample size. Patients were prospectively followed up in selected cases for detection of HCC by ultrasonography and AFP, liver biopsy and abdominal computed tomography every 6 months.*

Results: *The total patients were 194 with 45.1 + 13.1 years mean age; men: women 6.1: 1.0), 154 had type A child's disease, 40 with B disease. The cause of cirrhosis in 54 (27.8%) was hepatitis C, 71 (36.6%) with hepatitis B, in 12 (6.2%) cases both hepatitis B and C and others including alcoholic, cryptogenic cirrhosis and autoimmune in 57 (29.4%) subjects.*

Conclusion: *In our analysis, the prevalence of HCC in liver cirrhosis patients was found to be moderate, lower than Japan, but advanced than those stated in Europe.*

Key Words: Incidence, cirrhosis, hepatocellular carcinoma.

Corresponding author:

Dr. Muhammad Awais,

Abbottabad International Medical College, Abbottabad.

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INTRODUCTION:

In the world; the fifth most common disease is Hepatocellular carcinoma (HCC) and the 3rd most usual reason of cancer-associated mortality[1-2]. Annually, above 500,000 new cases are identified with a 5.5-14.9 per 100,000 people frequency globally. In developing countries; Age-related liver cancer incidence rates are 2 to 3 times more than in established countries[3]. In Africa and Asia; 80% of liver cancers occurs approximately. The incidence in the Middle East is relatively low. HCC is constantly seen in the abnormal liver histologically, and the chronic liver disease presence is a probable risk factor for its progress[4]. The liver cirrhosis developed in more than 80% of patients with HCC. Although the liver cirrhosis can be complicated by HCC, insistent hepatitis B & C infections make up more than 80% of HCC cases[5-6]. Globally, the most usual complication of liver cirrhosis is HCC with a frequency of 3.0% - 6.5%. Studies from Japan and Europe show that 2.0% to 6.08% of cirrhosis patients progress to HCC every year[7-8]. However, the data of under developed countries is not presented. In Pakistan; the HCC prevalence in cirrhosis patients has not been studied well[9-10]. This work was done to fix this problem.

MATERIALS AND METHODS:

In this study all new and earlier liver cirrhosis diagnosed cases of the etiology reported to the Gastroenterology department of Mayo Hospital Lahore for two year duration from May 2017 to May 2019. Patient with Child Class A or B cirrhosis were included in the analysis after agreement. The subjects with severe comorbidity, such as cirrhosis, coronary heart disease, respiratory disease, chronic renal failure or other long-term illnesses with a life expectancy of less than one year and patients who cannot came to the hospital every 6 months were not included. Every patient detailed history of each patient was taken and physical inspection was performed. CBC, LFTS, viral markers, upper GI endoscopy (in selected cases) and autoimmune markers for hepatitis B & C, HBsAg and anti-HCV were confirmed by ELISA. Hepatitis B DNA and C RNA were 1st identified by qualitative PCR and positively quantified by quantitative PCR. For HBV DNA; the qualitative PCR sensitivity was hundred copies / ml and 500 copies / ml for HCV RNA. These trials were performed in subjects managed with antiviral drugs at the first presentation and then every three months. Serum alphafetoprotein (AFP) was determined using an enzyme particle immunoassay (<20 ng / ml normal range). The ultrasound of abdomen was performed during various time periods. Abdominal computed tomography was performed in designated subjects. The characteristics of any mass in liver and chronic liver disease were observed. Computed tomography and abdominal computed tomography were inferred collectively with serum AFP levels to make a definitive diagnosis in the absence of HCC. In massive lesions, liver biopsy was performed to confirm the diagnosis histologically. Patients who did not contain HCC at the time of registration were prospectively followed to determine the HCC progression using US measurements. Annual computed tomography and AFP every six months were done (in selected cases). Regular follow-up with letters, scheduled appointments and phone calls were performed for the test. Follow-up time was stated as year incidence as events per 100 person year. The cohort study sample size was planned so that the HCC incidence can be determined with 95% confidence level and a sensitivity of 15% (a = 0.15). 170 was the sample size. The 10% drop in follow-up and the inclusion of losses led to 194 subjects as final sample size. The cirrhosis diagnosis was based on biochemical, endoscopy findings and on clinical basis. If necessary, performed with liver biopsy. If the duration of cirrhosis at the time of registration was less than 3 months, the patients were categorised as newly detected cirrhosis and the rest as earlier detected cirrhosis. HBV cirrhosis was detected in the presence of detectable HBsAg serum. Serum HCV cirrhosis was detected in anti HCV. The HBV infection replication was deliberated when HBeAg DNA and / or serum detectable HBV was found in these cirrhosis patients. With HCV RNA detectable in serum; HCV replication infection was identified. The HCC diagnostic criteria was modified criteria of the European Liver Studies Association (EASL). To these); fine needle aspiration cytology (FNAC) or (b); Two of the following three criteria: (i) > 300 ng / ml AFP level, (ii) mass arterialization on MRI or mass arterialization on CT or (iii). The HCC is regulated by the Barcelona Clinic (BCLC) classification of liver cancer.

RESULTS:

301 liver cirrhosis patients underwent HCC screening tests during the study period. 107 of them were found to be HCC. During follow-up, 194 patients without HCC formed the cohort follow-up. From 194 cases, in class A there were 154 patients and in class B 40 cases. 45.1 (± 13.1) was the mean age with 6.1. 1 M: F ratio. 96 patients were recently diagnosed, and previously detected cases of cirrhosis were 98. The etiology distribution was 54 (27.8%) HCV, 71 (36.6%) HBV cases and both B and C in 12 (6.2%) and other cirrhosis causes in 29.4% (57) were alcoholic, cryptogenic and autoimmune. In HBV infection of 59/83 (71%) cases; viral replication was noted and with HCV infection, 38/66 (58%) patients have

replication. 17.5 (45.7) ng / mL was the mean AFP level of the cohort at the time of recording (interquartile range 2.9-9.6, median 5.1). The 85% of patients had below 20 ng / ml AFP levels on registration and above 300 ng / ml in 1 percent of cases. In 563.4 person, during cumulative follow up period, HCC were diagnosed in 9 cases, with 1.60 per 100 person-years an incidence rate. The incidence of HCC in patients with liver cirrhosis was 1.60 (95% CI 0.55-2.64) per 100 subjects (Table I).

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)

The 3.53 per person was the HCC incidence in recently detected cirrhosis cases per 100 years (96% CI 0.06-7.01). 4 of 9 patients with HCC had recently diagnosed cirrhosis (median [16 months [9-26] months) and five had variable time cirrhosis (66 [44-152]). Each of the 4 cases had hepatitis B and C infection, and 1 had bilateral infection. All of these cases had B and C infection replication and had childhood cirrhosis during HCC detection. The HCC incidence was similar in B and C infection (Table II).

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

Small HCC (<5 cm diameter) was detected in 6 cases (multiple lesion in 2 cases and single lesion 4), respectively, at 11, 13, 22, 29, 36 and 37 months after recording, respectively. Three patients (single 1, multiple 2) had a large HCC (> 5 cm) detected at 6, 8 and 13 months after recording, respectively. 3 cases with HCC were detected in less than a year. Then, a CT scan was performed. These patients certainly did not have HCC during registration. The remaining 6 patients had HCC on both ultrasound and CT. Four of these 9 patients with HCC were in BCLC-A and two in BCLC-B. The residual 3 cases were in the BCLC-C stage.

DISCUSSION:

Although the HCC incidence in cirrhosis patients in Pakistan is not studied well. In India, the average HCC incidence per 100,000 inhabitants is in four[11-12]. Together, the HCC accounted for 2.0% of the 24,890 cancer cases noted in 6 records; this rate ranges between 1.2% (95/8759) in Delhi and 5.4% (11/186) in the rural Barshi register[13]. In this study, the incidence rate was calculated to be 1.59 per hundred people. 3.53 was the newly diagnosed cirrhosis patient's incidence per 100 people. The lower incidence in pre-diagnosed patients (1.1) every 100 years tends to survive, as their colleagues represent "survivors" of the "original cohort who developed HCC and died[14]. Nine patients under surveillance were diagnosed with HCC in less than one year (6, 8 and 11 months). All of these patients underwent a basic examination as well as others. AFP and CT were not present during HCC recording. However, imaging techniques have a known error with very low

sensitivity for tumors <1 cm, but for all practical purposes, the cohort did not contain HCC at the time of recording; Therefore, tumors detected during these follow-up periods should be considered as screening tests[14]. In several studies on coronary heart disease surveillance in cirrhotic patients from different countries, the reported annual incidence ranges from 1.0% to 5.8% per year. Therefore, the HCC incidence in the Indian sub-continent is slightly lower than in the Asian and European countries. Studies between the immigrant population in Australia and Singapore show that South Asians are less prone to HCC than Malaysia and China[15].

CONCLUSION:

In conclusion, this prospective cohort study reveals that the incidence of HCC is 1.6% per year in patients with cirrhosis. Using this value of HCC incidence, the surveillance program cost effectiveness of 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.

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