International Journal of Research in Medical Sciences
Tariq M et al. Int J Res Med Sci. 2015 Jul;3(7):1594-1598
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20150235

Research Article

Frequency of hepatocellular carcinoma in cirrhotic patients with hepatitis-C virus positive patients in Karachi-Pakistan

Muhammad Tariq*, Wajeeha Ahad, Muhammad Tahir, Ayaz Ahmed, Hafeez Muhammad Shafique

Department of Medicine, Civil Hospital, Karachi, Pakistan

Received: 12 March 2015
Accepted: 10 April 2015

***Correspondence:**
Dr. Muhammad Tariq,
E-mail: mtarique@yahoo.com

ABSTRACT

Background: Hepatocellular Carcinoma is the 5th most common neoplasm in the world and 4th most common cancer death. Most patients with HCC have an underlying chronic liver disease (often cirrhosis), resulting mainly from chronic infection by Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), excessive alcohol consumption, and often an association of these causes. HCC has recently gained more interest due to its increasing incidence in industrialized countries. Objective: To determine the frequency of hepatocellular carcinoma in hepatitis C reactive cirrhotic patients.
Methods: Place and duration of study: Department of medicine, civil hospital Karachi. Duration: Six months from 16-12-2012 to 15-6-2013. Subjects and methods: Patients admitted in medical wards of civil hospital Karachi with liver cirrhosis due to hepatitis C virus were included in the study. Investigation relevant to hepatocellular carcinoma like alpha fetoprotein and ultrasound was performed. If the Alpha fetoprotein is greater, then 200 ng/ml in the setting of a mass in a cirrhotic liver the likelihood of hepatocellular carcinoma is greater then 90% and biopsy is not required.
Results: Overall mean age was 41.1 ± 7.1 years with Male:Female = 4.2:1. Out of 141 cases; hepatocellular carcinoma was diagnosed in 8 (5.7%) of patients with HCV related cirrhosis with mean age 48.6 ± 6.4 years. Proportion of hepatocellular carcinoma was high 7 (6.1%) in male. 7 (6.4%) cases had child pugh-C, 1 (5%) case had child pugh-B and while no HCC was seen in child pugh-A.
Conclusion: In this study hepatocellular carcinoma was 5.7% in cases with hepatitis-C induced cirrhosis. Older age (>54 years), male sex and child pugh-C were predominant factors leading to hepatocellular carcinoma.

Keywords: HCV, Cirrhosis, Hepatocellular carcinoma, Alpha fetoprotein

INTRODUCTION

Pakistan carries one of the world highest burdens of chronic hepatitis and mortality due to liver failure and hepatocellular carcinoma.[1] In a study in Pakistan 16% cases were found to be positive for anti HCV positive.[2,3] HCV is a major cause of hepatocellular carcinoma worldwide due to high prevalence of HCV infections.[4] It has been demonstrated that nearly 50% cases with hepatocellular carcinoma in Pakistan are anti HCV positive.[5] Various researchers from Pakistan have reported variable figures about prevalence of hepatocellular carcinoma in cirrhosis ranging from 3.7%[6] to 16.7%.[6] Hepatitis B Virus (HBV) infection has been identified as a cause of hepatocellular carcinoma in the non-cirrhotic liver and HBV can be directly oncogenic, leading to hepatocellular carcinoma through integration of the viral genome into the host genome.[7] In addition, the X protein of HBV is a potent transactivator that can interact with p53, interfering with its tumor-suppressor activity.[8] Cirrhotic patients have a higher risk than non-cirrhotic patients with annual HCC incidences 2-6.6% and 0.4% respectively. Worldwide, 380 million individuals are infected with hepatitis B and 170 million

with hepatitis C.[9] It is estimated that 2-6.7% of all patients with HCV induced cirrhosis will develop HCC over 10 years and the annual risk is 1 to 4 percent.[10] Both HCV and Hepatitis B Virus (HBV) infections are the leading causes of HCC in Pakistan and co-infection with HCV and HBV account for 7% of HCC.[11] While early detection is highly desirable, patients with early disease are often asymptomatic[12] and consequently HCC is frequently diagnosed late, by which time it is often untreatable.[13] Suspicion of disease may first arise in patients with liver cirrhosis who develop ascites, encephalopathy or jaundice. Some patients initially present with upper abdominal pain, weight loss, early satiety or a palpable mass in the upper abdomen.[12] Other symptoms include obstructive jaundice, diarrhoea, bone pain, dyspnoea, intraperitoneal bleeding, paraneoplastic syndromes (e.g. hypoglycemia, erythrocytosis, hypercalcemia), severe watery diarrhoea, or cutaneous features (e.g. dermatomyositis).[14]

METHODS

Setting

This cross-sectional study was conducted at the department of medicine, civil hospital Karachi from December 2012 to June 2013 after approval from ethical committee of the institute. Patients of either gender of more than 18 years of age admitted in medical wards of civil hospital Karachi with diagnosis of cirrhosis (all child pugh classes i.e. A, B and C) due to hepatitis C virus (more than five years of duration) were included in the study by non-probability consecutive sampling. Patients with cirrhosis due to causes other than hepatitis C virus like hepatitis B virus, alcoholic liver disease, haemochomotosis, Wilson disease, end stage liver disease.

A total of 141 patients admitted in medical wards of civil hospital Karachi of liver cirrhosis with hepatitis C virus were included in the study. Informed written consent was taken from all patients and approval of ethical committee was sought. Investigation relevant to hepatocellular carcinoma like alpha fetoprotein and ultrasound was performed. If the Alpha fetoprotein is greater then 200 ng/ml in the setting of a mass in a cirrhotic liver the likelihood of hepatocellular carcinoma is greater then 90% and biopsy is not required.[15] Performa specially designed for the study was used to documents findings, confounding variable like hepatitis B virus, Alcoholic liver disease, haemachromatosis, Wilson disease were controlled by following a strict exclusion criteria. To minimize the bias all labs were send to same laboratory of civil hospital Karachi.

Data was entered and analyzed by Statistical Package of Social Sciences version 16 (SPSS Inc, Chicago, IL). Categorical variables were computed in the form of number and percentages like gender, size of liver mass in ultrasound abdomen (hepatocellular carcinoma). Continuous variables were computed in the term of mean and standard deviation like age and alpha fetoprotein. Risk stratification technique was used to control effect modifiers like age, duration, gender and severity of disease.

Sample size

$$n = z^2 p(1-p)/e^2$$

Where;

- "p" is prevalence of hepatocellular carcinoma (3.7% to 16.7%[6]) average 10.2%
- "Z" is significant value at 95%
- Confidence interval = 1.96
- "e" margin of error = 5%
- n=141 patients

RESULTS

A total of 141 cases with hepatitis-C induced liver cirrhosis were included in this study. Average age of patients was 41.1 ± .1 years (Min-Max = 25-58 years). Majority 79 (56%) of cases had age between 40-54 years (Figure 1).

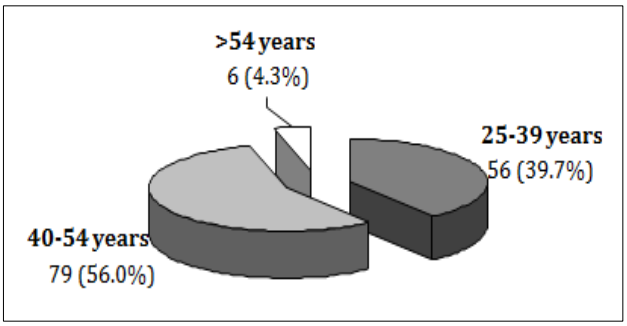

Figure 1: Age distribution (n=141).

Gender distribution showed male preponderance (male:female = 4.2:1), 114 (80.9%) were males and 27 (19.1%) were females (Figure 2).

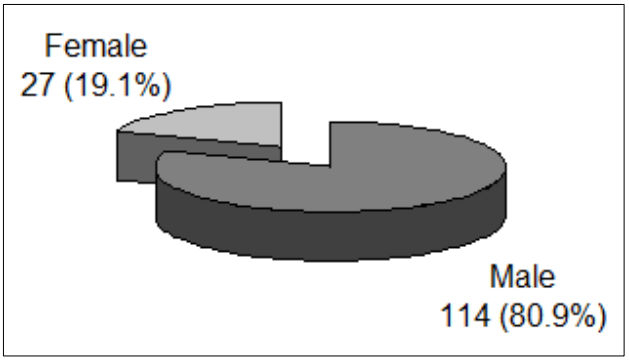

Figure 2: Gender distribution (n=141).

Average duration of disease was 15.3 ± 8.6 years (Min-Max = 5-20 years). Majority 92 (65.2%) of cases duration of cirrhosis was >10 years (Figure 3).

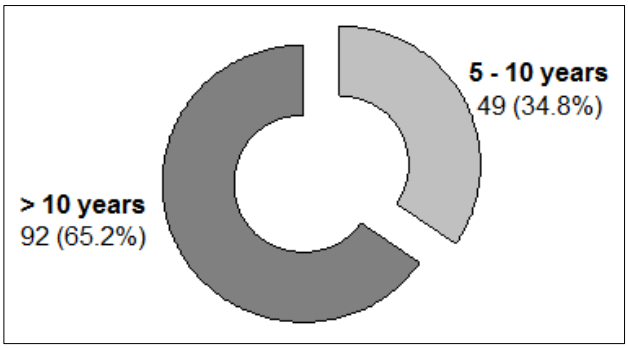

Figure 3: Duration of liver cirrhosis (n=141).

Severity of liver cirrhosis was assessed by child pugh's classification (A, B and C). Out of 141 cirrhotic cases, 110 (78%) cases had C-class, 20 (14.2%) cases had B-class while 11 (7.8%) patients had A-class (Figure 4).

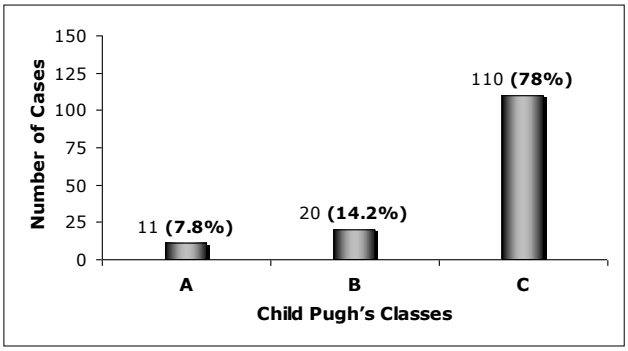

Figure 4: Severity of liver cirrhosis on child pugh's classes (n=141).

Out of 141 cases with hepatitis-C induced liver cirrhosis, hepatocellular carcinoma was diagnosed in 8 (5.7%) cases (Figure 5). Mean Alpha Fetoprotein (AFP) was 299.9 ± 118.6 ng/ml.

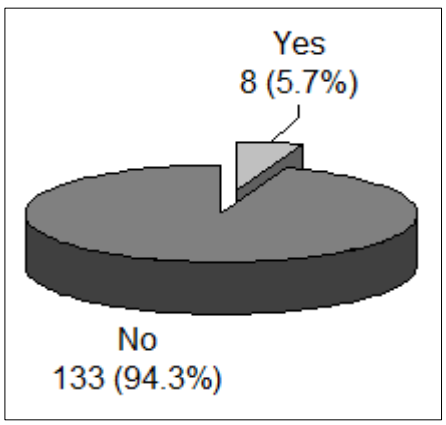

Figure 5: Hepatocellular carcinoma in patients with hepatitis-C related liver cirrhosis (n=141).

Average age of patients with hepatocellular carcinoma was 48.6 ± 6.4 years (Min-Max = 35-55 years). Proportion of hepatocellular carcinoma was high 4 (66.7%) in age >54 years (Table 1).

Table 1: Hepatocellular carcinoma in different age groups (n=141).

Age (years)	Total	Hepatocellular carcinoma	Percentage
25-39	56	1	1.8%
40-54	79	3	3.8%
>54	6	4	66.7%

Proportion of hepatocellular carcinoma was high 7 (6.1%) in male (Table 2).

Table 2: Hepatocellular carcinoma in gender (n=141).

Gender	Total	Hepatocellular carcinoma	Percentage
Male	114	7	6.1%
Female	27	1	3.7%

Hepatocellular carcinoma in patients with cirrhosis raised in order of grades A, B and C of liver dysfunction assessed by child pugh classification. 1 (5%) cases had child pugh-B and 7 (6.4%) cases had child pugh-C while no HCC was seen in child pugh-A (Table 3).

Table 3: Hepatocellular carcinoma and severity of cirrhosis (n=141).

Duration	Total	Hepatocellular carcinoma	Percentage
B	20	1	5.0%
C	110	7	6.4%

Duration of disease and hepatocellular carcinoma is shown in Table 4. Mean duration of cases with hepatocellular carcinoma was 17.9 ± 7.6 years (Min-Max = 8-20 years).

Table 4: Hepatocellular carcinoma and duration of cirrhosis (n=141).

Duration (years)	Total	Hepatocellular carcinoma	Percentage
5-10	49	2	4.1%
>10	92	6	6.5%

DISCUSSION

Hepatocellular carcinoma (HCC) affects approximately half a million persons each year worldwide making it the fifth most common malignancy in men and the ninth

most common in women.[16] Most patients with HCC have an underlying chronic liver disease (often cirrhosis), resulting mainly from chronic infection by Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), excessive alcohol consumption, and often an association of these causes. HCC has recently gained more interest due to its increasing incidence in industrialized countries.[17,18]

Liver cirrhosis can evolve to hepatocellular carcinoma, and the presence of comorbidities, exposure to hepatitis B or C virus, as well as alcohol consumption and age, can influence the terminal event. In fact, liver cirrhosis is well known to consist of a diffuse alteration of the liver structure resulting from protracted processes of liver inflammation and necrosis of different natures. The main causes of liver cirrhosis are chronic viral hepatitis B or C and the consumption of alcohol. In particular, alcohol abuse can halve the time of onset of cirrhosis in a patient already affected by chronic viral hepatitis (from about 20-30 years to 10-15 years). Hepatocellular carcinoma occurs at a rate of 1% to 4% per year after cirrhosis is established[19] and cirrhosis underlies HCC in approximately 80%-90% of cases worldwide.[20]

In this study a total of 141 cases with liver cirrhosis due to HCV were included. Average age of patients was 41.1 ± 7.1 years and gender distribution showed male preponderance (male:female = 4.2:1). Seventy eight percent cases had C-class, 14.2% cases had B-class while 7.8% patients had A-class. The more commonly identified predictive factors of HCC are age higher than 50, male sex, advanced cirrhosis, high basal alpha-fetoprotein (AFP) serum levels.[21,22] A study from India examine 301 patients with liver cirrhosis with mean age± SD = 45.1 ±13.1 years and male:female = 6.1:1.[23]

Proportion of hepatocellular carcinoma in hepatitis-C Induced cirrhosis was found 5.7% in this study. It has been demonstrated that nearly 50% cases with hepatocellular carcinoma in Pakistan are anti HCV positive.[5] various researchers from Pakistan have reported variable figures about prevalence of hepatocellular carcinoma in cirrhosis ranging from 3.7% to 16.7%.[6] In general, the incidence rates for HCC in patients with HCV-related cirrhosis are higher than those reported for HBV or alcohol-related cirrhosis. It is less certain whether alcohol consumption may further increase the risk for HCC in HCV-related cirrhosis. Imberti D et al. studied 200 cases of liver cirrhosis in 8 years and found HCC 5.1% yearly.[24] The incidence of hepatocellular carcinoma worldwide varies according to the prevalence of hepatitis B and C infections. Areas such as Asia and sub-Saharan Africa with high rates of infectious hepatitis have incidences as high as 120 cases per 100000.[7]

Once cirrhosis is established, it becomes more difficult to discern the effects of additional risk factors for HCC because cirrhosis seems to be the common pathway by which several risk factors exert their carcinogenic effects. Nevertheless, male sex (2 to 3 times), older age, as well as the severity of the underlying cirrhosis has been shown consistently to increase the risk for HCC even further.[25] In this study Average age of patients with hepatocellular carcinoma was 48.6 ± 6.4 years. High proportion 66.7% was seen in age >54 years with male preponderance (M:F = 7:1). Hepatocellular carcinoma in patients with cirrhosis raised in order of grades A, B and C of liver dysfunction was assessed by child pugh classification. 5% cases had child pugh-B and 6.4% cases had child pugh-C while no HCC was seen in child pugh-A. In the United States, 74% of hepatocellular carcinoma cases occur in men. In high-risk areas (China, sub-Saharan Africa, Japan), the difference in incidence between the sexes is more pronounced, with male-to-female ratios as high as 8:1.[7] Another study reported the percentage of HCC was statistically higher (P <0.01) in patients in Child's B and C than in Child's A class.

Age at diagnosis varies widely according to geographic distribution. In the United States and Europe, the median age at diagnosis is 65 years. Hepatocellular carcinoma is rarely diagnosed in persons younger than 40 years. However, between 1975 and 1998, the 45- to 49-year age group had the highest rate, a 3-fold increase in the incidence of hepatocellular carcinoma. In Africa & Asia, age at diagnosis is substantially younger, occurring in fourth and fifth decades of life, respectively.[7] Diagnosis at a younger age is thought to reflect natural history of hepatitis B and C related hepatocellular carcinoma.[26]

In the West, as in Asia, patients with cirrhosis of the liver are at substantial risk for hepatocellular carcinoma, with a yearly incidence rate of 3 percent. In brief cirrhosis, which is associated with genetic alterations predisposing to cancer, is the main risk factor for HCC occurrence. Virtually all HCV-related HCC cases occur among patients with cirrhosis. With the exception of areas in the world where hepatitis B is endemic, it is uncommon to find HCC in the absence of cirrhosis. Cases of HCC with chronic hepatitis without cirrhosis have been reported but remain very scarce.

CONCLUSIONS

In this study hepatocellular carcinoma was 5.7% in cases with hepatitis-C induced cirrhosis. Older age (>54 years), male sex and child pugh-C were predominant factors leading to hepatocellular carcinoma.

It is concluded that HCC is a common complication of cirrhosis, especially HCV associated cirrhosis. Early diagnosis is mandatory for management and reducing mortality.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Ali SA, Donahue RM, Qurashi H, Vermund SH. Hepatitis B and hepatitis C virus in Pakistan: prevalence and risk factors. Int J Infect Dis. 2009;13:9-19.
2. Ahmad N, Asgher M, Shafique M, Qureshi JA. An evidence of high prevalence of hepatitis C virus in Faisalabad, Pakistan. Saudi Med J. 2007;28:390-5.
3. Waheed Y, Shafi T, Safi SZ, Qadri I. Hepatitis C virus in Pakistan: a systemic review of prevalence, genotypes and risk factors. Wolrd J Gastroentrol. 2009;15:5647-53.
4. Trinchet JC, Ganne-Carrie N, Nahon P, Kontchou G, Beaugrand M. Hepatocellular carcinoma in patients with hepatitis C virus related chronic liver disease. Wolrd J Gastroentrol. 2007;13:2455-60.
5. Chohan AR, Umar M, Khaar B, Khurram M, Zahid M, Shah SF, et al. Demographic features of hepatocellular carcinoma. A study of 30 cases. J Rawal Med Coll. 2001;5:81-3.
6. Farooqi JI, Farooqi RJ. Prevalence of hepatocelllar carcinoma in patients of liver cirrhosis. J Coll Physicians Surg Pak. 2000;10:54-5.
7. Bosch FX, Ribes J, Diaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004;127:5-16.
8. Giordano TP, Kramer JR, Souchek J. Cirrhosis and hepatocellular carcinoma in HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992-2001. Arch Intern Med. 2004;164:2349-54.
9. WHO. Hepatitis C: global prevalence. Wkly Epidemiol Rec. 1997;72:341-4.
10. Sharieff S, Burni I, Salim A, Siddiqui T. Hepatocellular carcinoma. J Coll Physicians Surg Pak. 2002;12:264-7.
11. Choo QL, Vinor AJ, Overby LR, Kuo G, Houghton M, Bradley DW. Hepatitis C virus. The major causative agent of non-A non-B hepatitis. Br Med Bull. 1990;46:423-41.
12. Kew MC, Dos Santos HA, Sherlock S. Diagnosis of primary cancer of the liver. Br Med J. 1971;4:408.
13. The Cancer of the Liver Italian Program (CLIP) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology. 1998;28:751-5.
14. Tietge UJ, Scholf C, Ocran KW, Wagner S, Böker KH, Brabant G, et al. Hepatoma with severe non-islet cell tumor hypoglycemia. Am J Gastroenterol. 1998;93:997-1000.
15. Sherman M. Chronic hepatitis and screening for hepatocellular carcinoma. Clin Liver Dis. 2006;10(4):735-52.
16. El-Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. Hepatology. 2002;36:74-83.
17. McGlynn KA, London WT. Epidemiology and natural history of hepatocellular carcinoma. Best Pract Res Clin Gastroenterol. 2005;19:3-23.
18. Sherman M. Hepatocellular carcinoma: epidemiology, risk factors, and screening. Semin Liver Dis. 2005;25:143-54.
19. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Hepatology. 1997;26:34-8.
20. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127:35-50.
21. Ikeda K, Arase Y, Saitoh S, Kobayashi M, Someya T, Hosaka T, et al. Prediction model of hepatocarcinogenesis for patients with hepatitis C virus-related cirrhosis. Validation with internal and external cohorts. J Hepatol. 2006;44:1089-97.
22. Velazquez RF, Rodriguez M, Navascues CA, Linares A, Perez R, Sotorrios NG, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology. 2003;37:520-7.
23. Paul SB, Sreenivas V, Gulati MS, Madan K, Gupta AK, Mukhopadhyay S, et al. Incidence of hepatocellular carcinoma among Indian patients with cirrhosis of liver: an experience from a tertiary care center in northern India. Indian J Gastroenterol. 2007;26:274-8.
24. Imberti D, Fornari F, Sbolli G, Buscarini E, Squassante L, Buscarini L. Hepatocellular carcinoma in liver cirrhosis: a prospective study. Informa. 1993;28:540-4.
25. Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, et al. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. Gut. 2000;47:131-6.
26. Di Bisceglie AM, Carithers RL Jr, Gores GJ. Hepatocellular carcinoma. Hepatology. 1998;28:1161-5.

Cite this article as: Tariq M, Shafique HM, Muhammad Nadir S, Ahad W. Frequency of hepatocellular carcinoma in cirrhotic patients with hepatitis-C virus positive patients in Karachi-Pakistan. Int J Res Med Sci 2015;3:1594-8.