Clinical Profile Of Hepatocellular Carcinoma-Experience At A Tertiary Care Hospital

Rafi ud din, Fauzia Anjum, Abdul Moueed Tariq, Abdul Latif Khattak, Rao Saad Ali Khan, Khawar Shabbir

ABSTRACT

Objective: To determine the characteristics of Hepatocellular carcinoma (HCC) in patients visiting PEMH Rawalpindi.

Study Design and Setting: Cross-sectional Study conducted at Department of Gastroenterology/hepatology in Pak Emirates Military Hospital Rawalpindi (PEMH) from Oct 2015 to Jan 2018.

Methodology: In this study total 100 patients, with HCC of both genders were included. All the cases were discussed in multidisciplinary team (MDT) meetings which were held once every week. A decision on the best possible management for the given case was arrived at in the MDT meeting. All the relevant features of each case were recorded in the Performa. Descriptive statistics were used to calculate mean, standard deviation and frequencies for gender, various presenting features, co-morbidities and clinical features. Data was analyzed on SPSS version 21. P value <0.05 was considered as statistically significant.

Results: Sixty seven men and 33 women with HCC were included in this study with a mean age of 58.23 years. The abdominal pain was the most common symptom present in 66 (66%) patients. Edema was seen in 30 (30%) and palpable splenomegaly in 26(26%). Diabetes mellitus was the most common co-morbidity found in 20(20%) patients. HCV was the commonest cause of HCC present in 79(79%) patients. Vascular involvement was seen in 15 (15%) patients. Most (62%) patients had a single HCC lesion and most belonged to Child –Pugh class A (68%) and BCLC stage B (42%). ECOG performance status was good in most patients with 49% patients scoring 0. The AFP levels were raised in 58 (58%) of the patients.

Conclusion: HCV was the most common underlying etiology. Most of the patients were asymptomatic at the time of diagnosis. Majority of subjects reported with the complaint of abdominal pain and had no underlying co morbidity. The metastasis was negative in majority of cases.

Key Words: Hepatocellular Carcinoma, Hepatitis C, Splenomegaly.

INTRODUCTION:

The Primary liver cancer is the 6th most common cancer world wide.[1] Hepatocellular carcinoma is one of the most common tumors involving the liver while it is the 2nd leading cause of cancer related death.[2] In year 2018; total of 841,000 (4.7%) new cases of liver cancers were reported and further incidences are increasing.[3,4] There are various risk factors associated with development of HCC including hepatitis B, hepatitis C, toxins exposure such as aflatoxins, lifestyle risk factors such as obesity, smoking and alcohol consumption. While 44% of HCC cases were attributable to chronic hepatitis B infection; Hepatitis C was responsible for 21% of cases.[5] Certain diseases such as hemochromatosis, Wilson and Alpha -1 anti trpysin deficiency are also associated with increased risk of HCC.[5]

The etiological factors are different in different populations. HCC is one of the commonly occurring tumors in Pakistan with age-standardized rate 7.64/100000 for men and 2.8/100000 for women.[5] The majority of cases occurred having the background of liver cirrhosis.[6,7] The etiology during last few decades has changed from a majority of HCC cases previously being positive for HBV to a clear majority now being positive positive for HCV infection. Though the incidence of HCC are on rise and the overall associated mortality is decreasing.[8]

Majority of HCC cases are identified in patients who are already diagnosed with Chronic liver disease secondary to any other cause. The patients may be asymptomatic at the time of diagnosis or they may present with worsening of their disease. Increased surveillance of patients with liver disease with Ultrasonography for HCC, has led to increased number of patients identified at an asymptomatic stage.

Rafi Ud Din
Classified Medical Specialist, Department of Gastroenterology,
Combined Military Hospital, Quetta
Email: rudin2005@gmail.com

Fauzia Anjum
Consultant Gynacologist,
Hameed Latif Hospital Lahore

Abdul Moueed Tariq
Registrar Medicine, Department of Gastroenterology,
Combined Military Hospital, Quetta

Abdul Latif Khattak
Classified Medical Specialist, Department of Gastroenterology,
Combined Military Hospital, Quetta

Rao Saad Ali khan
Classified Medical Specialist, Department of Gastroenterology,
Pak Emirates Military Hospital Rawalpindi

Khawar Shabbir
Classified Medical Specialist, Department of Gastroenterology,
Combined Military Hospital, Peshawar

Received: 31-Jul-2019
Accepted: 11-Dec-2019

Patients may present with variety of symptoms including abdominal pain, abdominal distension, appearance of or worsening of jaundice, weight loss, anorexia, sarcopenia, fatigue, vomiting. The treatment as well as prognosis of HCC depends on size, number of lesions, local as well systemic and extra hepatic spread and over all wellbeing of patient. The prognosis of untreated HCC is poor; overall median survival is 9 months. The main cause behind death was progression of tumor in these untreated patients.[9] As the Barcelona Clinic Liver Cancer (BCLC) stage worsened it resulted in progressive and significant decrease in median survival of the patients.[10]

Despite being a common tumor in our population, clinical features of this tumor have not been adequately described in local literature.[11] In Pakistan there is dearth of central cancer registries framework and data primarily comes from single center experiences. Several studies have been published describing one or more aspects of HCC but detailed clinical profile studies are limited.[5,8,11] Due to a paucity of published literature on HCC patients' profile, a need was felt to document the common clinical and laboratory features of HCC in Pakistani population for future use as a reference. Therefore; the aim of the study was to determine the characteristics of Hepatocellular carcinoma (HCC) among patients visiting to PEMH Rawalpindi.

METHODOLOGY:

It was a cross sectional study carried out from Oct 2015 to Jan 2018 at department of Gastroenterology, Pak Emirates Military Hospital (PEMH) Rawalpindi. The sample size was calculated using a prevalence of 5.2/100000 (7.6/100000 for males and 2.8/100000 for females) and keeping the confidence level at 95% and margin of error at 5%.[12] All patients diagnosed with HCC in PEMH and those coming with the diagnosis of HCC were enrolled in the study with non-probability convenience sampling. After taking consent and providing the rationale of the study; the history and clinical examination was performed; followed by investigations. Functional status of patients was recorded according to the ECOG scoring system. Investigation carried out for all cases included complete blood counts, Liver function tests including albumin, Prothrombin time and INR, renal function tests, hepatitis serology, Alfa fetoprotein (AFP) levels, ultrasonography and contrast enhanced CT scan of abdomen. Few investigations were only performed where indicated such as Upper GI endoscopy, PCR for HBV and/or HCV, MRI abdomen, liver biopsy, Doppler sonography for vascular involvement, tumor markers (CA-19-9, CEA). Patients were categorized according to BCLC and Child-Pugh classification systems. Data was analyzed in SPSS version 21. The descriptive statistics for gender and etiological factors for HCC such as frequency, percentage was calculated along with mean and SD for age. The frequency and percentages for various presenting features, associated co-morbid conditions were calculated. The descriptive statistics were used to calculate frequencies, means and standard deviation for various clinical, radiological and biochemical features of HCC. P value <0.05 was considered as statistically significant.

RESULTS:

Total one hundred patients were enrolled in the study. The gender distribution is shown in figure-1. The clinical presentation was varied as shown in table 1. Twenty seven (27%) patients were asymptomatic at presentation and were diagnosed as a result of screening or imaging for an unrelated problem. In symptomatic patients, abdominal pain was the most common symptom which was present in 66(66%) whereas haematemesis was the least common presenting symptom seen in only 5(5%) patients. Sixty three (63%) patients reported 2 or more symptoms at the time of diagnosis. Presenting features are tabulated in Table -1. Most patients (69%) had no other co-morbidities whereas diabetes mellitus was found in 20(20%) patients as shown in Table No 2. Other co-morbidities included hypertension and ischemic heart disease. HCV was the most common underlying etiology and was found positive in 79(79%) patients. Distribution of etiology of cirrhosis is given in figure-2. The Clinical profiling of the patients with HCC presenting to PEMH is shown in the Table No. 3. In an overwhelming majority (90%), no extra-hepatic metastatic deposits were identified. Vascular involvement was found at the time of diagnosis in 15(15%) patients with tumor most commonly involving a branch of portal vein. In most patients size of the tumor was more than 5 cm at the time of diagnosis. Most patients (62%) presented with a single tumor nodule and the size of largest lesion in most patients (60%) was more than 5 cm. Most patients (68%) were in Child-Pugh class A at the time of diagnosis and in majority (42%) BCLC tumor stage was found to be "B". Functional status of most patients (49%) was unimpaired at the time of diagnosis of HCC. The AFP levels were normal in 42% of patients while out of remaining 58% it was overwhelmingly raised to more than 1000 ng/ml in 19% of patients.

DISCUSSION:

The incidence and prevalence of HCC was high due to high prevalence of chronic viral hepatitis in our study sample. HCC more commonly affects men than women and this was reflected in the gender distribution of cases in this study with two thirds of patients being men.[13] The difference in the incidence of HCC in both genders has led to the hypothesis of a protective role of estrogens in female population.[13,14] As many as 27% patients were asymptomatic at the time of diagnosis which is a significantly high figure as other studies like Kumar et al[15] reported that 91.6% of patients with HCC were symptomatic at the time of diagnosis. The performance status as depicted by ECOG performance score 0 or 1 was seen in 87% of the patients. Studies have shown that those patients having better performance status had better survival rates.[16]

Table 1: Presentation of HCC

S NO	Parameter	Number of Patients (%)
1	Asymptomatic	27(27%)
2	Abdominal Pain	66(66%)
3	Ascites	15(15%)
4	Weight Loss	55(55%)
5	Haematemesis	5(5%)
6	Anorexia	43(43%)
7	Jaundice	9(9%)
8	Multiple symptoms	63(63%)
9	Palpable splenomegaly	26(26%)
10	Edema	30(30%)
11	Anemia(Hb<10g/dl)	24(24%)
12	Thrombocytopenia	21(21%)
13	Renal dysfunction	5(5%)

Figure 1: Gender Distribution

FEMALE   MALE
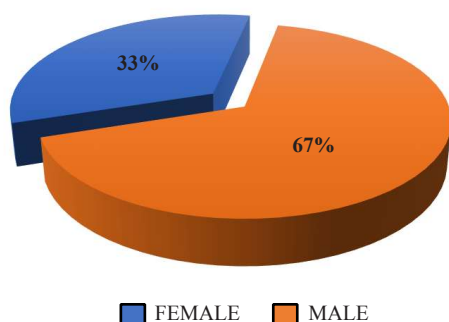
Table 2: Associated Co-morbidities

S NO	Condition	Number Of Patients(%)
1	No co-morbid illness	69(69%)
2	Diabetes mellitus	20(20%)
3	Hypertension	3(3%)
4	Ischemic heart disease	2(2%)
5	Diabetes mellitus & Hypertension	5(5%)

Figure 2: Distribution of Etiology

MALE   FEMALE
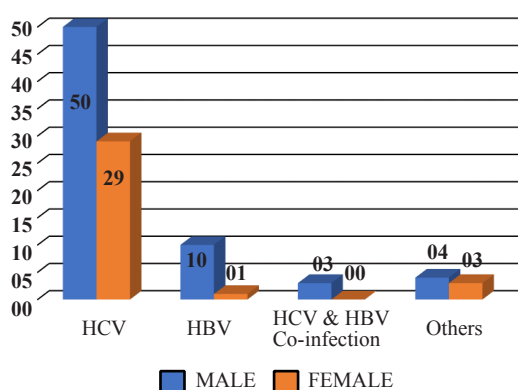
The effects of tumor size in HCC on clinical presentation and its role as a prognostic factor remain unclear .The 5-year mortality was higher in patients with tumor sizes more than 5 cm in comparison with those with sizes less than 5 cm,[18] Similarly, regardless of the tumor size in patients, the absence of vascular invasion or fibrosis was associated with better survival rates[19, 20, 21]. The AFP levels were normal in 42% of patients. The previous studies found that elevated AFP levels are associated with higher pathological grade, more advanced BCLC stage, and larger tumors.[22,23,24]

The vascular involvement was seen in only 15% of patients as compared to 35% in a study done in china.[25] Vascular involvement adversely affects the survival in HCCpatients independent of treatment modality being used. Patients with vascular involvement represent a distinct tumor phenotype of HCC. It is associated with younger age, aggressive tumor and poor performance status.[26] The majority of patients in our study had BCLC stage A or B tumor with a single tumor nodule with preserved functional status and few patients were asymptomatic as well at the time of presentation.[27] One possible explanation for high percentage of patients diagnosed before the development of symptoms and at an early stage may be the fact that majority of patients were known to have chronic liver disease due to chronic viral hepatitis and were also entitled to free medical treatment and hence were more likely to keep their appointments for surveillance of HCC. This could have led to an increasing number of patients being diagnosed at an earlier stage. Another possible reason for majority of patients falling in earlier tumor stages may be the referral bias; since PEMH is a tertiary care hospital and patients are referred to this center after being worked up at other hospitals in the country. It is possible that HCC patients with advanced stages of tumor were never referred to PEMH. Thus a referral bias cannot be excluded.

On the other hand, the size of tumor nodule in majority of patients was more than 5 cm which argues against the assumption that sticking to a surveillance program might have picked up patients at an earlier stage. It is therefore more likely that patients with more advanced disease did not report to this hospital.

The limitation of our study was possible referral bias. Another limitation was data being from a single center which might not necessarily be generalizable to the rest of country. It is recommended that future researches on HCC be carried out at multiple centers and referral bias be minimized. It is of critical importance for all the healthcare professionals involved in care of patients with HCC, to make themselves familiar with the common clinical features of this important tumor. Regular surveillance should be done in all at risk patients as per recommended guidelines to diagnose the HCC at an early stage, where the patients can be offered a treatment modality with favorable outcomes. If we are able to diagnose HCC at an early stage, outlook can be favorable

Table 3: Clinical Profiling of HCC Patients

		Number of patients(%)
Metastases	Nil	90(90%)
	Yes	10(10%)
Vascular involvement	Nil	85(85%)
	Main portal vein	4(4%)
	Branch of portal vein	9(%)
	Portal & Mesenteric veins	1(1%)
	Inferior vena cava & Portal vein	1(1%)
Tumor size (cm)	< 3	17(17%)
	3-5	23(23%)
	>5	60(60%)
Number of HCC lesions	1	62(62%)
	2	11(11%)
	3 or more	27(27%)
Child-Pugh Class	A	68(68%)
	B	30(30%)
	C	1(1%)
BCLC Stage	0	1(1%)
	A	34(34%)
	B	42(42%)
	C	18(18%)
	D	5(5%)
ECOG Score	0	49(49%)
	1	38(38%)
	2	7(7%)
	3	6(6%)
Alfa Fetoprotein Level (ng/ml)	<8.5	42(2%)
	8.6 – 100	24(24%)
	100.1 - 1000	15(15%)
	>1000	19(19%)

for these patients with potentially curative treatments now available

CONCLUSION:

HCV was the most common underlying etiology. Significant number of the patients were asymptomatic at the time of diagnosis. Majority of subjects reported with the complaint of abdominal pain and had no underlying co morbidity. No metastases were found in majority of cases.

REFERENCES:

1. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis. 2015;19(2):223-38.

2. Sia D, Villanueva A, Friedman SL, Llovet JM. Liver Cancer Cell of Origin, Molecular Class, and Effects on Patient Prognosis. Gastroenterology. 2017;152(4):745-61.

3. Rawla P, Sunkara T, Muralidharan P, Raj JP. Update in global trends and aetiology of hepatocellular carcinoma. Contemp Oncol (Pozn). 2018;22(3):141-50.

4. Hafeez Bhatti AB, Dar FS, Waheed A, Shafique K, Sultan F, Shah NH. Hepatocellular Carcinoma in Pakistan: National Trends and Global Perspective. Gastroenterology Research and Practice. 2016;2016:10.

5. Baecker A, Liu X, La Vecchia C, Zhang ZF. Worldwide incidence of hepatocellular carcinoma cases attributable to major risk factors. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). 2018;27(3):205-12

6. Butt AS, Abbas Z, Jafri W. Hepatocellular carcinoma in pakistan: where do we stand? Hepat Mon. 2012;12(10 HCC):e6023-e

7. Butt AS, Hamid S, Wadalawala AA, Ghufran M, Javed AA, Farooq O, et al. Hepatocellular carcinoma in Native South Asian Pakistani population; trends, clinico-pathological characteristics & differences in viral marker negative & viral-hepatocellular carcinoma. BMC research notes. 2013;6(1):137.

8. Hester D, Golabi P, Paik J, Younossi I, Mishra A, Younossi ZM. Among Medicare Patients With Hepatocellular Carcinoma, Non-alcoholic Fatty Liver Disease is the Most Common Etiology and Cause of Mortality. J Clin Gastroenterol. 2019.

9. Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology. 2015;61(1):184-90.

10. Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology (Baltimore, Md). 2015;61(1):184-90.

11. Khokhar N, Aijazi I, Gill ML. Spectrum of hepatocellular carcinoma at Shifa International Hospital, Islamabad. Journal of Ayub Medical College Abbottabad. 2003;15(4)

12. https://www.calculator.net/sample-size-calculator.html?type=1&cl=95&ci=5&pp=5.20&ps=&x=78&y=14

13. Liu P, Xie S-H, Hu S, Cheng X, Gao T, Zhang C, et al. Age-specific sex difference in the incidence of hepatocellular carcinoma in the United States. Oncotarget. 2017;8(40):68131-7.

14. Keng VW, Largaespada DA, Villanueva A. Why men are at higher risk for hepatocellular carcinoma? J Hepatol. 2012;57(2):453-4.

15. Kumar R, Saraswat MK, Sharma BC, Sakhuja P, Sarin SK. Characteristics of hepatocellular carcinoma in India: a retrospective analysis of 191 cases. QJM : monthly journal of the Association of Physicians. 2008;101(6):479-85.

16. Nishikawa H, Kita R, Kimura T, Ohara Y, Sakamoto A, Saito S et al. Clinical implication of performance status in patients with hepatocellular carcinoma complicating with cirrhosis. J Cancer 2015; 6:394-402

17. Wu G, Wu J, Wang B, Zhu X, Shi X, Ding Y. Importance of tumor size at diagnosis as a prognostic factor for hepatocellular carcinoma survival: a population-based study. Cancer Manag Res. 2018;10:4401-10.

18. Dai CY, Lin CY, Tsai PC, Lin PY, Yeh ML, Huang CF, et al. Impact of tumor size on the prognosis of hepatocellular carcinoma in patients who underwent liver resection. Journal of the Chinese Medical Association: JCMA. 2018;81(2):155-63.

19. Truant S, Boleslawski E, Duhamel A, Bouras AF, Louvet A, Febvay C, et al. Tumor size of hepatocellular carcinoma in noncirrhotic liver: a controversial predictive factor for outcome after resection. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2012;38(12):1189-96

20. Nishikawa H, Kita R, Kimura T, Ohara Y, Sakamoto A, Saito S, et al. Clinical implication of performance status in patients with hepatocellular carcinoma complicating with cirrhosis. J Cancer. 2015;6(4):394-402.

21. Hsu CY, Lee YH, Hsia CY, Huang YH, Su CW, Lin HC, et al. Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the Barcelona Clinic Liver Cancer system. Hepatology (Baltimore, Md). 2013;57(1):112-9

22. Sauzay C, Petit A, Bourgeois AM, Barbare JC, Chauffert B, Galmiche A, et al. Alpha-foetoprotein (AFP): A multi-purpose marker in hepatocellular carcinoma. Clinica chimica acta; international journal of clinical chemistry. 2016;463:39-44.

23. An SL, Xiao T, Wang LM, Rong WQ, Wu F, Feng L, et al. Prognostic Significance of Preoperative Serum Alpha-fetoprotein in Hepatocellular Carcinoma and Correlation with Clinicopathological Factors: a Single-center Experience from China. Asian Pacific journal of cancer prevention : APJCP. 2015;16(10):4421-7

24. ai D-S, Zhang C, Chen P, Jin S-J, Jiang G-Q. The prognostic correlation of AFP level at diagnosis with pathological grade, progression, and survival of patients with hepatocellular carcinoma. Sci Rep. 2017;7(1):12870-.

25. Lee YH, Hsu CY, Huang YH, Hsia CY, Chiou YY, Su CW, et al. Vascular invasion in hepatocellular carcinoma: prevalence, determinants and prognostic impact. Journal of clinical gastroenterology. 2014;48(8):734-41.

26. Hsieh C-H, Wei C-K, Yin W-Y, Chang C-M, Tsai S-J, Wang L-Y, et al. Vascular invasion affects survival in early hepatocellular carcinoma. Mol Clin Oncol. 2015;3(1):252-6.

27. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver international: official journal of the International Association for the Study of the Liver. 2015;35(9):2155-66.

••••★••••