

HEPATOCELLULAR CARCINOMA AT INITIAL PRESENTATION AND ITS SUBSEQUENT THERAPEUTIC OPTIONS OFFERED: A TERTIARY CARE HOSPITAL EXPERIENCE

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ABSTRACT

Objective: To determine the important clinical features at the initial presentation of Hepatocellular carcinoma and the treatments offered thereby.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Gastroenterology, Pak Emirates Military Hospital, Rawalpindi, from Jan 2017 to Dec 2017.

Methodology: A total of 157 patients were studied. Their history, examination and relevant investigations were carried out at initial presentation to find all required details including age, gender, etiology of HCC, number and size of hepatic lesions, Child Pugh class, performance status, BCLC scoring, vascular invasion of tumor, lymph nodal involvement and metastasis; at time of diagnosis of hepatocellular carcinoma. Treatment was offered based on all these parameters, as per latest AASLD guidelines. Data were entered in SPSS version 24 for statistical analysis.

Results: Of the total 157 patients, 117 (75%) were males and 40 (25%) were females. Mean age was 60.4 ± 8.67 years. Majority of HCC cases (84%) were HCV infected. Performance status was 0 or 1 in 87% cases. Around 52% patients had huge size of lesion, >5cm, at presentation. Child Pugh score was A for 68% patients. BCLC score was B, C or D in 70% cases which implies intermediate or advanced disease where curative treatments could not be performed. TACE was the most frequent treatment offered (33% cases), followed by Sorafenib (29% cases).

Conclusion: Hepatocellular carcinoma was found to be on the rise in our setup as a consequence of the huge prevalence of HCV infection. Most patients were males presenting at intermediate or advanced stage disease where curative treatments were not possible.

Keywords: Hepatocellular carcinoma, Hepatitis C, Sorafenib, Transarterial chemo-embolization (TACE).

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INTRODUCTION

Hepatocellular carcinoma (HCC) is increasing in Pakistan, secondary to the huge burden of Hepatitis B and C¹. It is the fifth commonest malignancy worldwide². In Pakistan, estimates suggest that around 6.8% of the general population is infected with hepatitis C making it the second highest prevalence in the world and this number might be higher due to the scarcity of data³. Similarly, up to 4.3% of the general population is infected with Hepatitis B⁴. Together, these two are the most important risk

factors for development of hepatocellular carcinoma and are responsible locally for 68% and 22% of the cases respectively⁵. Besides these, alcohol consumption, aflatoxins, autoimmune hepatitis, alpha 1 antitrypsin deficiency, non alcoholic steatohepatitis (NASH), hereditary hemochromatosis and Wilson's disease are amongst the other risk factors¹.

Most of the patients present with advanced unresectable disease. The prognosis of HCC is generally poor despite the recent advances in diagnostic and therapeutic modalities. Incidence of HCC is expected to rise more in the coming years owing to the increasing prevalence of HCV and HBV in the country. Screening the population at risk for HCC is very important to

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be able to diagnose the disease at an early stage⁶. Triphasic CT remains the gold standard for establishing the diagnosis. Arterial phase enhancement followed by loss of enhancement (washout) in the portal venous and delayed phases is highly indicative of HCC⁷. Image guided biopsy is recommended for establishing the diagnosis in lesions <1 cm in size or having atypical imaging features.

Various treatment modalities exist for the treatment of HCC including surgical resection, radio frequency ablation (RFA), percutaneous ethanol injection (PEI), transarterial chemo-embolization (TACE) and chemotherapeutic agents such as Sorafenib. The choice of treatment modality depends on the stage of disease, patient performance status and liver function reserve. In this regard, Barcelona Clinic Liver Cancer (BCLC) staging system is most widely used and is the best predictor of survival for HCC patients⁸. RFA, TACE and Liver transplant are only available at few centres in the country. Majority of the patients present at a very advanced stage and hence only receive supportive therapy. Very few local studies have explored the stage at initial presentation of HCC. Butt *et al*⁹ in a recent study showed that around 86% of the patients belonged to Okuda class II or III and less than 15% patients were fit to receive any form of definitive treatment. We decided to conduct this study with the primary objective of determining the stage of HCC at initial presentation with regards to BCLC staging system and accordingly the therapeutic options offered.

METHODOLOGY

This cross-sectional study was conducted at department of Gastroenterology, Pak Emirates Military Hospital, Rawalpindi, from January 2017 to December 2017, after approval from institutional ethical committee. The sample size was calculated using Open Epi calculator with the statistical assumptions of 95% confidence interval, taking prevalence of Hepatocellular carcinoma to be 10.7%¹ of all cancers and sample size came out 145 patients for this study. A total

of 157 patients were included in the study, using consecutive sampling. All patients who were diagnosed to have HCC for the first time, were included in the study, irrespective of age and gender. The patients who were already diagnosed cases of HCC undergoing various treatments, or visiting for follow up, were not included in the study.

A detailed history, physical examination and investigations were carried out in all patients to study their features at initial presentation. Patients' age and gender were documented. Their performance status was graded from 0-5 as per WHO criteria¹⁰. All patients were tested for Hepatitis B and C to find the etiology of HCC. Ultrasonography was done to find the number of hepatic lesions as well as their sizes. Child Pugh score was noted as A, B or C, taking into account the required parameters including bilirubin and albumin levels, PT/INR, ascites and hepatic encephalopathy¹¹. Lymphatic and vascular involvement as well as metastasis was assessed by appropriate scans and/or histopathology, as appropriate. The Barcelona Clinic Liver Cancer (BCLC) staging classification was used, that comprises five stages (O,A,B,C,D) that select the best candidates for the best therapies currently available¹². Considering all these important parameters of HCC at presentation, various treatments were planned and offered. Curative surgical options like tumor resection and hepatic transplant; curative intervention radiological procedures like PEI and RFA were offered for early stages (BCLC-0,A). TACE was offered for intermediate stage HCC (BCLC-B). For more advanced disease (BCLC-C) only Sorafenib was advised while just terminal care could be offered for BCLC-D. Managements were planned according to latest American Association for the Study of Liver Diseases (AASLD) guidelines.

The data was entered in SPSS version 24 for statistical analysis. Descriptive statistics were calculated for both qualitative and quantitative variables. For quantitative variables, mean and standard deviation (SD) was calculated. For

qualitative variables frequencies and percentages were calculated.

RESULTS

Of the 157 patients studied, 117 (75%) were males and 40 (25%) were females (3:1). The mean age was 60.4 ± 8.67 years. Majority of HCC cases i.e 132 were HCV infected (84%), followed by 18

Table: Hepatocellular carcinoma propositata.

	Frequency of Patients	Percentage (%)
Etiology		
HCV infection	132	84
HBV infection	18	11.5
HBV/HCV co-infection	4	2.5
Both HBV/HCV negative	3	2
Number of lesions		
Single lesion	67	43
2-3 lesions	63	40
4-5 lesions	22	14
>5 lesions	5	3
Size of lesions		
2 cm	20	13
3-5 cm	56	35.7
5-10 cm	57	36.3
>10 cm	24	15
Vascular Invasion		
Present	48	31
Absent	109	69
Lymph Nodal Invasion		
Present	25	16
Absent	132	84
Metastatic Disease		
Present	19	12
Absent	138	88

who were HBV infected (11.5%). Majority of our patients presented with solitary lesions in the liver, however, the size at presentation was quite large in almost half of the cases. Table shown summarizes the etiology, number and size of lesions, as well as the extent of disease patients presented with.

The performance status was generally well enough at presentation with 87% patients spending their day to day activities either

normally or with only little difficulty. Fig-1 showed the performance status at presentation.

The Child Pugh score which assesses the prognosis of cirrhosis was found to be A for 68% patients, B for 27% patients while only 5% patients presented at Child Pugh score C. The BCLC scores calculated for our patients were as depicted in fig-2.

Majority of our patients (70%) presented at intermediate and advanced stages of disease (BCLC-B,C,D). Fig-3 showed the various treatments that were offered to patients based on their respective stages at presentation of HCC.

TACE was most frequent treatment planned for 52 patients (33%) followed by Sorafenib for 45 patients (29%). These two treatments combined covered 62% of our patients. These were followed by RFA, PEI, hepatic transplant and terminal care, and finally, tumor resection which could be done in just 4 (2.5%) of our patients.

DISCUSSION

Hepatocellular carcinoma is worldwide the fifth most common cancer in men and the seventh one in women, and it represents the overall third most frequent cause of cancer death¹⁵. In men, it is the second most common cause of cancer related death¹⁴. Liver cancer rates are highest in our part of the world, east and south-east Asia¹⁵, reason being our high prevalence of chronic HCV and HBV infection.

Liver cancer is much more common in men than in women. Rates of both incidence and mortality are 2 to 3 times higher in men, in most parts of the world¹⁴. In a latest worldwide estimation of cancers in 2018, in south-east Asia, the age adjusted incidence rates for liver cancer are 21 per 100,000 for men and 6.6 per 100,000 for women¹⁴. This is identical to the results of our study where male to female ratio was 3:1. The exact mechanism is unclear but a tumorigenic effect of androgens is suggested¹⁶. A comprehensive worldwide systemic review conducted to assess the etiology of HCC found HCV and HBV to be the topmost causes

worldwide¹⁷. The same study, for Pakistan, assessed the data from 1987 to 2010 and found that before the year 2000, around 30% cases of HCC in Pakistan were attributable to HBV and around 50% to HCV. However, after 2000, the proportion of HBV positive HCC cases fell to around 20% while HCV positive HCC cases rose to around 60%¹⁷. In our study, the proportion of HCV positive cases is even greater, reaching 84%, while HBV positive cases are further dropped to 11.5%.

At the time of presentation, most of our patient population had solitary lesions (43%) or 2-3 lesions (40%) but the tumor sizes were significantly large (>5cm in 52% cases). These presenting features are comparable with various previous studies from Pakistan from 1998 to 2011 where mean tumor sizes ranged from 5-10cm¹⁸. The reasons for this late diagnosis include lack of a proper surveillance system and hepatitis control program in the country, despite being at a high risk, where the HCV prevalence among general population of the country is 6.8%³. Then majority of the sonologists in Pakistan are not fully trained to pick up early lesions and hence they go unaddressed¹⁸. Since the disease does not have an acute onset and progression, patients generally carry on with their routines well enough till the time large enough lesions are formed and diagnosed. This explains why performance status of the majority (87%) was either normal or they had only mild difficulty in daily activities. Also, the presenting symptoms are similar to those of chronic liver disease such as yellowing of the skin and sclera, pain in the right hypochondrium, swelling of the abdomen, weakness, weight loss and fever¹⁹.

BCLC scoring was done to grade the disease, which takes into account tumor stage (number and size of lesions, portal invasion, metastasis, Okuda), liver functional status (bilirubin, Child Pugh, portal hypertension) and patient's performance status¹². The important feature of this staging system that is lacking in other staging systems is that it also guides regarding treatment options. BCLC stage 0 and A are early stage

diseases, suitable for radical therapies¹⁴. These patients are asymptomatic and have a good prognosis. Surgical option is beneficial in such patients with solitary lesions <2cm (BCLC-0) or a

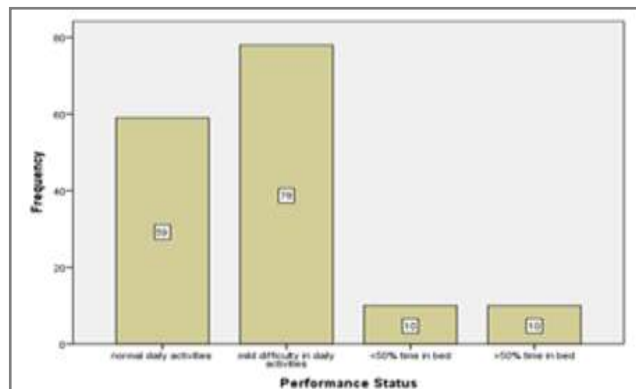


Figure-1: Frequency of performance status at presentation of HCC.

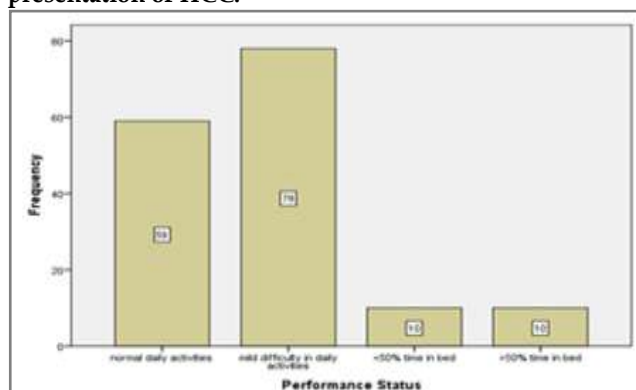


Figure-2: Frequency of BCLC Stage at presentation of HCC.

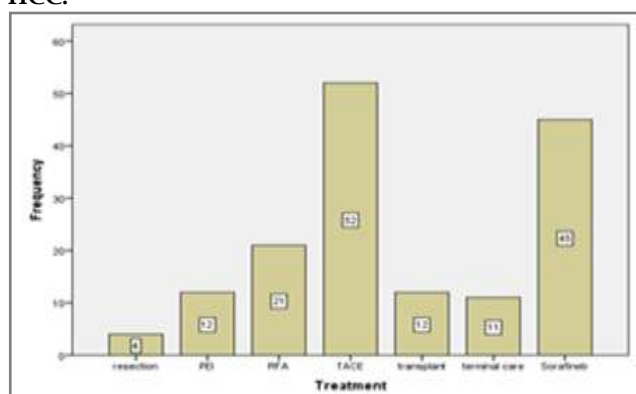


Figure-3: Various treatments offered to patients of HCC.

moderate size single lesion or multiple small lesions (BCLC-A) and preserved liver function. RFA and PEI are recent advances optimal for those patients who are unfit for surgical resection or liver transplant. Nearly one fourth of our

patients at presentation fell into this category. BCLC stage-B indicates intermediate disease, such patients are also often asymptomatic, have good performance status and multinodular HCC²⁰. They are unfit for resection. TACE is recommended for these. A significant proportion (34%) of our patient population presented at this stage. BCLC-C patients have advanced disease, they are symptomatic patients, often have vascular invasion and/or extrahepatic spread. Sorafenib is the only approved therapy for them². Around 31% of our patients were at this stage on presentation. Patients with stage-D disease have very advanced disease, have extremely poor prognosis and symptomatic control is all that can be done for them²⁰. We had 4.5% patients diagnosed at this stage. Overall, majority of patients (70%), presented at intermediate or advanced stages (BCLC-B,C,D) where curative treatments could not be done. This reflects the result of not having a good surveillance system in vogue.

As evident from the BCLC stages, TACE was the most frequent treatment (33%) offered to patients. Overall, 31% patients were offered curative treatments, of which resectable cases were just 2.5%, rest being RFA, PEI and transplant. Sorafenib and terminal care combined, were offered to 36% patients. The prognosis of HCC is generally poor with survival after diagnosis ranging from 6 to 20 months²⁰. However, studies have shown that if diagnosed early and surgical treatments done, both overall and disease-free survival can be significantly increased²¹. After early diagnosis and surgical resection, the median survival for HCC patients was 59.4 months and 1, 3 and 5-year overall survival rates were 82%, 62% and 49% respectively, in a study conducted at China²¹.

As the etiology of HCC is mainly infective (HCV and HBV), it is largely a preventable malignancy. In the US, the incidence of HCC almost tripled between 1975 and 2011 due to high HCV prevalence in IV drug abusers in 1960s and 1970s¹⁵. In contrast, the incidence of HCC is decreasing in some high risk areas like China and

Japan, due to measures against HBV and HCV, and in Taiwan after HBV vaccination¹⁵. This clearly indicates that this high mortality cancer is very much preventable if appropriate control measures are taken against the etiologic viral agents. Therefore, in a high risk country like ours, there is a dire need for prevention against hepatitis B and C and also, to have a good surveillance system to pick HCC at an early stage where curative measures could be taken. The hepatitis B vaccination program for newborns was started in Pakistan in 2002 and its coverage according to WHO and UNICEF estimates 2017 was 75%²². Well, HBV related HCC cases are decreasing, but HCV is still on the rise, perhaps due to unawareness and also, a lot many mal-practices in the country. HCV is preventable by easy prevention steps like avoiding reuse of medical devices, proper sterilization etc. All these must be strictly implemented in true letter and spirit to curb the rising trends of HCV and in turn, HCC. Surveillance programs for HCC must be carried out effectively, for high risk patients, which for our population include male gender, age >40 years, HBV or HCV positive, with or without cirrhosis. Additional risk factors may include obesity, diabetes mellitus, HBV/HCV co-infection, co-infection with HIV. The impact of surveillance has been established in various studies. It facilitates early diagnosis and hence more chances of a curative treatment. The overall mortality reduced to 38% due to pre-diagnosis HCC surveillance, in a study conducted in US²³. The latest surveillance guidelines now recommend ultrasound every 6 months, rather than both AFP levels and ultrasonography combined²⁴.

RECOMMENDATION

In the light of our study, it is recommended to start effective Hepatitis B and C prevention and control programs in the country and HCC screening program of high risk population.

CONCLUSION

Hepatocellular carcinoma was on the rise in our setup as a consequence of the huge

prevalence of HCV infection. Most patients were males presenting at intermediate or advanced stage disease where curative treatments were not possible.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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