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ORIGINAL ARTICLE

Evaluation of Co-Relation between BCLC Stage of HCC and Alpha-Fetoprotein Levels

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ABSTRACT

Background: One of the leading cancers worldwide is the hepatocellular carcinoma, ranked as the 6th most common cancers.
Aim: To evaluate the co-relation between BCLC staging of HCC and alpha fetoprotein levels.
Study design: Cross-sectional study.
Methodology: Patients (n=90) of either gender irrespective of age who were diagnosed with hepatocellular carcinoma were included into the study. Clinical examination was performed and findings were noted. Eastern cooperative oncology group ECOG scoring system was used to identify the functional performance status of the patients. Hepatocellular carcinoma staging was done using the BCLC scoring system. Complete blood counts, Liver function tests (LFTS), INR, alpha fetoprotein levels, viral serology for hepatits and ultrasonography of abdomen were performed for all the patients. Data was analyzed using SPSS version 26. Results were presented as frequency and percentage. Age was presented as mean± SD.
Results: Mean AFP levels were 400.7±305.4 IU/ml with a range of 8.50- 1015 IU/ml. 3(3.3%) patients were in BCLC stage 0, 23(25.6%) were in stage A, 33(36.7%) in stage B, 15(16.7%) in stage C and 16 (17.8%) in stage D. Results showed significant positive correlation between BCLC staging and AFP levels (r=o.834, p=0.001).
Conclusion: It was concluded that Hep C followed by Hep B was the main cause of HCC. AFP has a significant diagnostic and prognostic value with positive co-relation with HCC.
Keywords: Alpha-Fetoprotein, BCLC Staging, HCC and Liver Disease.

INTRODUCTION

One of the leading cancers worldwide is the hepatocellular carcinoma, ranked as the 6th most common cancers[1]. It has a rapid clinical course which makes its diagnosis and treatment a major challenge for the oncologists. In Pakistan Hepatitis C virus has become endemic. Incidence of cancer and related mortality is increasing in the developing countries day by day. The prevalence of hepatocellular carcinoma varies from 3.7% to 16% in our population[2]. Viral hepatitis B, C and D are attributed as the most common etiological cause of HCC[3]. Male population is more at a risk of developing HCC (7.6 per 1 lac in males and 2.8 for females)[4].

Alcohol consumption, Hepatitis B and C chronic infections, hereditary hemochromatosis, Wilson disease and deficiency of alpha 1 anti trypsin are among the noted risk factors of HCC. 58% of the cases in Pakistan present with chronic hepatitis C as an underlying cause of HCC and 25.3% have hepatitis B[5]. There are many reasons like sedentary lifestyle, obesity and diabetes that have contributed in increased prevalence of non hepatitis HCC[6].

Proper screening and early detection can make way to potential cure. Various guidelines have been developed in the western countries about screening and diagnosis of HCC. Ultrasonography and estimation of serum alpha fetoprotein levels seem to be the only first line screening options available for diagnosing and staging HCC. After every 6 months, ultrasound abdomen has been recommended by Pakistan society among cirrhotic patients with liver disease as revealed by literature review[7].

Common serological marker for diagnosis of HCC is α-fetoprotein. The sensitivity and specificity of AFP has remained controversial due to differences in study designs and patient characteristics. Various staging systems are operational for classification of HCC but Barcelona clinic liver cancer (BCLC) staging is considered the most appropriate among all systems[8,9].

The objective of the study was to evaluate the co-relation between BCLC staging of HCC and alpha fetoprotein levels.

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METHODOLOGY

Present study was conducted in the Department of General Medicine, CMH Kharian after IRB permission. This institute receives patients coming in from all over the country and is one of the biggest tertiary care hospital in the country. Total of patient (n=90) were enrolled. Patients of either gender irrespective of age who were diagnosed with hepatocellular carcinoma were included into the study. Clinical examination was performed and findings were noted. Eastern cooperative oncology group ECOG scoring system was used to identify the functional performance status of the patients. Hepatocellular carcinoma staging was done using the BCLC scoring system. Very early stage (0) with single tumor ≤ 2cm, Early stage (A) with single or ≤ 3 nodules each ≤3cm, Intermediate stage (B) multinodular, Advanced stage (C) portal invasion or extrahepatic spread and Terminal stage (D).

Complete blood counts, Liver function tests (LFTS), INR, alpha fetoprotein levels, viral serology for hepatits and ultrasonography of abdomen was performed for all the patients. Upper Gastrointestinal endoscopy, ST scan, PCR for hepatitis B and C, liver biopsy, Doppler scan and tumor markers were performed only where required. Patients were divided into 3 groups based on levels of alpha fetoprotein. Group 1 (normal AFP ≤20 IU/ml), group 2 (mildly elevated 20-399 IU/ml) and group 3 (markedly elevated ≥ 400 IU/ml).

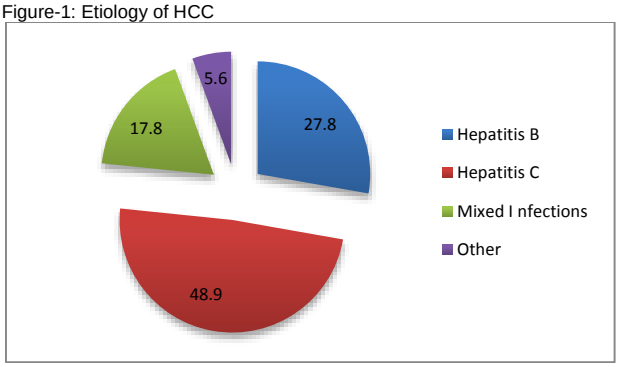
Statistical Analysis: Data was analyzed using SPSS version 26.0. Results were presented as frequency and percentage. Mean and SD presented Age and AFP levels. One way ANOVA was used to assess association between AFP levels and BCLC stages. Pearson correlation was used to assess correlation of BCLC staging and AFP levels. Chi square test was used to assess association of gender and BCLC stages with different groups based on AFP levels with p-value of ≤0.05 as significant.

RESULTS

Among enrolled subjects, males were 65 while females were 25. Mean age of patients was 57.05±14.65 years with a range of 28 to 86 years. Mean AFP levels were 400.7 ± 305.4 IU/ml with a range of 8.50-1015 IU/ml. Results showed that 03(3.3%) patients were in BCLC stage 0, 23(25.6%) were in stage A, 33(36.7%) in stage B, 15(16.7%) in stage C and 16(17.8%) in stage D. 7(7.8%) had their AFP levels ≤20 IU/ml, 42(46.7%) had AFP levels between 20-399

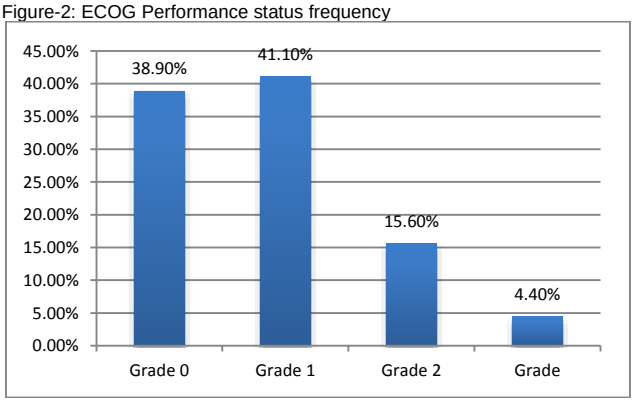
IU/ml and 41 (45.6%) had markedly elevated AFP levels. Etiology of hepatocellular carcinoma was shown in figure-1.

Figure-1: Etiology of HCC



Mostly patients had good ECOG performance status in this study as shown by figure-2.

Figure-2: ECOG Performance status frequency



Comparison of AFP levels among various stages of HCC revealed that as the disease progresses the AFP levels increase significantly as shown by table-1.

Table 1: Comparison of AFP levels among BCLC stages of HCC

BCLC stage	Mean AFP levels IU/ml	Minimum AFP levels	Maximum AFP levels
Stage 0	20.9 ± 16.1	8.5	39.2
Stage A	80.6 ± 77.5	10.2	323.0
Stage B	387.1 ±151.7	89.4	826.0
Stage C	553.2 ± 277.8	29.4	995.0
Stage D	817.0 ± 170.8	472.0	1015.0

P value 0.001* *Statistically significant

Table 2: Post Hoc Tukeys analysis among groups

Groups by BCLC staging	P value
0 vs A	0.9
0 vs B	0.004*
0 vs C	0.001*
0 vs D	0.001*
A vs B	0.001*
A vs C	0.001*
A vs D	0.001*
B vs C	0.017*
B vs D	0.001*
C vs D	0.001*

*Statistically significant

Post Hoc tukeys test for multiple comparison revealed the following results as shown in Table-2. There was a statistically insignificant difference of AFP levels between BCLC stage 0 and Stage A. Results showed that males were found to have greater AFP levels and advanced stage disease than females with p-value of 0.04 as shown in table-3. BCLC stage A and B patients showed mildly elevated AFP levels where as stage C and D patients showed markedly elevated AFP levels.

Table-3: Association of gender and BCLC staging with groups based on AFP levels

BCLC staging	AFP groups			P-value
	Group 1 (n=7)	Group 2 (n=42)	Group 3 (n=41)	
Male	6	25	34	0.04*
Female	1	17	7	
0	2	1	0	0.001*
A	5	18	0	
B	0	19	14	
C	0	4	11	
D	0	0	16	

DISCUSSION

During gestation the hepatocytes of the fetus and the yolk sac secrete a glycoprotein which is known as Alpha Fetoprotein. It has also been an important tumor marker for various malignancies which include gastric carcinoma, gonadal tumors and hepatocellular carcinoma. There has been a lot of debate in the past whether there is any correlation between the basic tumor characteristic such as size, stage etiology etc. Kumar et al reported that there is no correlation where as Abbasi et al, Gill et al in their studies conducted in Pakistan showed a significant correlation between increased AFP levels and poor prognosis[10-12]. Similar results were shown in our study depicting positive correlation of AFP levels and BCLC stages.

Zhang et al in his study revealed that AFP levels can accurately diagnose HCC. Sensitivity and specificity for 400ng/ml AFP was better than 200ng/ml[13]. Rafi ud din et al showed a weak but positive correlation between them for HCC (r= 0.203, p= 0.04).[14] BCLC staging is dependent on the patients performance status and degree of liver functionality. It seems very logical that increasing AFP levels would be seen in patients having advanced stage HCC.

Muqadas et al suggested in her study that as the AFP levels increase there is worsening in levels of serum bilirubin, number of lesions/tumors, BCLC stage and other pathological parameters[15]. Shabbir et al in his study found raised AFP levels in only 64.5% of the HCC patients with no association between them[16]. This was significantly higher from our results which showed markedly elevated AFP levels in only 45.6% of the cases. Abbasi et and Samiullah et al in their studies found AFP levels to be raised in 77.5% and 77.7% of the HCC patients[11,17].

In our study only 01 patient in BCLC stage showed markedly elevated serum AFP levels. Hepatitis C was the main etiological cause of HCC found in our study population. This could be attributed to rising disease burden of Hep C in Pakistan. Javeria et al also attributed Hep C as a cause of HCC in 77.3% of her study population.[18] HCV related HCC usually presents with cirrhotic morphology of liver. Munaf et al reported an overall prevalence of Hep C and Hep B related HCC to be 66% and 34% respectively. He also showed that patients with Hep C virus related HCC were more likely to transform into HCC at an advanced age and with increased AFP levels[19]. Sarwar et al in his study revealed that use of AFP can be taken under consideration for screening of HCC patients as it has a 72% sensitivity and 86% specificity when the cutoff value of 20.86 ng/ml was used[20].

Every 6 monthly an ultrasound should be done with or without determining serum AFP levels. Multiphasic CT scan or multiphasic MRI can also be used for diagnosis due to similar diagnostic accuracy. Patients with Child Pugh class C should not be screened as there is a very low survival rate of these patients. The only possible treatment left for such cases is the liver transplant[21].

HCC is a preventable disease if prompt screening and diagnosis is carried out. 66.4% of the patients suffering from HCC

are diagnosed at a stage (usually a tumor size of greater than 5cm) where no treatment can be given to cure the disease. There is a dire need of developing proper guidelines in diagnosis and screening of cases with signs and symptoms of HCC in Pakistan. Measures should be taken to prevent the spread of hepatitis (B and C) which can ultimately decrease the sudden rise of HCC in our setup. Further studies should be conducted to check association of AFP level and patient survival rates (mortality and morbidity).

Limitations: Our study had limitations like financial constraints, lack of resources, genetic workup and short duration of study.

CONCLUSION

It was concluded that Hep C followed by Hep B was the main cause of HCC. AFP has a significant diagnostic and prognostic value with positive co-relation with HCC.

Authors' Contribution: AH,SAAG&NKN: Conceptualized the study, analyzed the data, and formulated the initial draft. **SHT&IR:** Contributed to the proof reading, **RS&TL:** Collected data.

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Conflict of Interest: None to declare

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