Original Article

Prognostic factors of Survival in Patients with Non-Resectable Hepatocellular Carcinoma: Hepatitis C versus miscellaneous etiology

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Abstract

Objective: To identify prognostic determinants of survival in patients with non-resectable hepatocellular carcinoma (HCC), determine the effect of transarterial chemoembolization (TACE) on prognosis, compare hepatitis C related HCC with mixed etiologies and evaluate the prognostic value of different staging systems.

Methods: This cohort study included129 patients (male = 97, 75%) with non-resectable HCC. Data was collected from 2002 until August 2006. A series of demographic, clinical and biochemical and radiological data were collected. Cases were staged according to the Child's, Okuda, Cancer Liver Italian program (CLIP), Barcelona Clinic Liver Cancer (BCLC) and Chinese University Prognostic Index (CUPI) systems. Survival analysis was performed. Any effect of TACE on prognosis was recorded.

Results: Median age of patients was 52 years (range 18 - 82). Median follow-up 11 months (range 2-36). At the time of analysis, 102 patients had died (79%). Etiology of HCC was hepatitis C virus (HCV) in 66 (51.2%), hepatitis B virus (HBV) 31 (24%), HBV + HCV 10 (7.8%), HBV + delta hepatitis 02 (1.6), and non-B non-C 20 (15.4%). Forty-one patients (31%) were offered TACE. Univariate analysis for HCV related HCC showed that age > 52 years ($p<0.05$), bilirubin >1.17 mg /dl ($p<0.01$), INR > 1.3 ($p<0.01$), alpha fetoprotein > 400 ng / ml ($p<0.05$), splenomegaly ($p<0.01$), ascites ($p<0.001$), portal vein thrombosis ($p<0.01$), splenic varices ($p<0.01$), and TACE not offered ($p<0.01$) were the prognostic factors while in miscellaneous etiology female sex ($p<0.05$), haemoglobin < 11.0 gm/dl ($p<0.01$), alkaline Phosphatase > 169 IU/L ($p<0.05$), ascites ($p<0.05$) and multifocality ($p<0.05$) were adversely effecting prognosis. Overall independent determinants were Hepatitis C etiology, female sex and multifocality of tumour (Hazard ratios 3.0, 3.0 and 1.9 respectively). Mean survival was 17.2 vs. 12.8 months for patients offered vs. not offered TACE respectively (p value = 0.015). Okuda, CLIP, BCLC, CUPI and Child's staging systems retained their performance as judged by chi square values in regression analysis. Discriminatory ability for death evaluated by receiver operating characteristic curve was better for Okuda system in the first year.

Conclusion: Hepatitis C as the etiology of HCC, female sex and multi-focality are associated with poor prognosis. HCV related HCC may differ in prognostic factors from non-HCV HCC. Simple staging system by Okuda predicts prognosis effectively in non-resectable HCC (JPMA 58:602; 2008).

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common tumour worldwide.[1-3] Approximately one million deaths annually are caused by HCC worldwide and its incidence appears to be gradually increasing.[1] The overall survival of patients with HCC has not improved over the last 20 years, with the incidence rate almost equal to the death rate.[4] The causes of the underlying liver disease differ according to the geographical distribution. Common etiological factors for HCC include infection with hepatitis B virus (HBV), hepatitis C virus (HCV), cirrhosis of any cause, alcoholic liver disease, and inherited metabolic diseases such as haemochromatosis and α 1-antitrypsin deficiency. Cirrhosis is the strongest underlying risk factor, being present in more than 80%of HCC cases.[5,6] With the shift in etiology, HCV has replaced HBV as the major cause of HCC in many countries. In Pakistan most HCC patients still present with advanced disease and symptoms directly related to the tumours or to hepatic decompensation. This was the scenario in 1970s in the West.[7]

Small HCCs can be cured with an appreciable frequency.[8] However, patients with intermediate/advanced HCC are candidates only to palliative treatment. In some cases, survival can be improved, as it was demonstrated with trans-arterial chemoembolization (TACE).Therefore, it is important to understand the factors that predict survival even in such cases. The prognostic factors for survival in patients with HCC have been identified in previous studies and sub-classified into 3 groups: (1) demographic characteristics including age and gender; (2) factors related to HCC such as tumour size, the number of nodules, vascular invasion, the presence of a tumour capsule or

metastasis; and (3) factors related to underlying liver disease severity and synthetic function, including ascites, encephalopathy, or serum bilirubin.

Several prognostic staging systems have been proposed for HCC.[9-14] Factors that may affect the prognosis of patients with HCC include performance status of the patient, tumour stage at diagnosis and hepatic synthetic function.[9] There has been debate on which is the best staging system. In case of HCC we deal with two diseases as tumour usually occurs in the setting of cirrhosis of liver. The Child-Pugh classification, used in patients with cirrhosis, only considers liver disease and not the tumour characteristics. The Cancer of the Liver Italian Program (CLIP) score[15] is a staging system that has been validated in case series from various parts of the world.[16,17] Although its predictive power has been found to be superior to that of the Okuda system in most cases, doubts have been raised regarding its value in certain populations.[14] A second alternative is the Barcelona Clinic Liver Cancer (BCLC) staging system,[10] which, in theory, has certain advantages. Among the prognostic variables considered in BCLC staging are the performance status (PS)[18] and portal hypertension, which are not taken into account in either the CLIP or Okuda system. These additional criteria should make it especially suitable for staging HCCs diagnosed early in patients with well compensated cirrhosis. The lack of a consensus on an HCC staging system in part may be related to the heterogeneity in diagnostic criteria of HCC, differences in the etiological factors prevailing in different countries, lack of standardization regarding the tests needed to determine tumour burden and extent of spread of HCC, and liver function itself.

In Pakistan patients with HCC are mostly having HCV related cirrhosis and advanced unresectable disease.[19] Moreover, the facility of liver transplantation is not available in this country. The aim of the present study was to identify prognostic determinants of survival in patients with non-resectable hepatocellular carcinoma (HCC), determine the effect of transarterial chemoembolization (TACE) on prognosis, compare hepatitis C related HCC with mixed etiologies and evaluate and compare the prognostic value of different staging systems including Cancer Liver Italian program (CLIP),[11] Barcelona Clinic Liver Cancer (BCLC),[10] Okuda,[14,16] Chinese University Prognostic Index (CUPI)[12] and Child-Pugh score.

Patients and Methods

Included in this cohort study were 129 patients with HCC followed prospectively. Data was collected from 2002 until August 2006 to complete a minimum follow-up term of 3 months. According to the conclusions of the consensus conference of the European Association for the Study of Liver Disease, diagnosis of HCC was based upon histological confirmation, or 2 imaging studies including triphasic computed tomography (CT), or one imaging study in addition to an alpha fetoprotein level greater than 400 ng/ml.[9] To assess the size, number and location of tumours, and the existence of portal vein thrombosis, abdominal CT was performed in each case. According to the tumour characteristics, and following the strategies recommended in the EASL consensus conference, therapeutic option of trans-arterial chemoembolization (TACE) was offered to patients without portal thrombosis and preserved liver function (22 patients with HCV HCC and 19 patients with miscellaneous etiology).

A series of demographic, clinical, biochemical and radiological data were collected at the time of diagnosis including age, sex, presence and etiology of cirrhosis, presence of ascites or hepatic encephalopathy, serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline Phosphatase (ALP), gamma glutamyl transferase (GGT), albumin, prothrombin time, international normalized ratio (INR) and alpha fetoprotein. Presence of underlying cirrhosis was assessed via clinical and radiological evidence (nodular liver, splenomegaly, low platelets < 150000/microlitre, dilated portal vein and ascites). The morphological characteristics of the tumour were evaluated with the help of triphasic CT scan of abdomen: number of lesions, lobar distribution, diameter of the largest nodule and presence of portal vein thrombosis. Tumours were defined as unresectable or advanced, if the size of the mass was greater than > 5cm, multicenteric, Child Class B or C and vascular invasion. Performance status of patients was scored according to Eastern Cooperative Oncology Group scale.[20] MELD (Model for end stage liver disease) score was calculated. Cases were staged according to the Okuda, CLIP, CUPI, BCLC systems. In order to facilitate statistical analysis of the different scoring classifications, group A of the BCLC score were not subdivided further into stages A1-A4. For CLIP system, patients in categories 0-1 were taken in group A, 2-3 in group B and 4-6 in group C. The date of death was determined by hospital records or by contacting the family members.

Statistical analysis

Overall survival was the only end point used in the analysis. Survival time was defined as the difference (in months) between the diagnosis of HCC and death, or the finalization of the follow-up period (August 2006). Lost patients during the follow-up period (n=3) were censored at the last outpatient visit or the last known episode of hospitalization.

A univariate analysis to identify predictors of

survival at the time of HCC diagnosis (baseline) was performed using the Kaplan -Meier method of survival function by log rank test. Median values of continuous variables were taken as cut-off to compare survival. Hazard ratio i.e. the estimate of relative risk in the survival analysis was mentioned. Significant variables were then included in a multivariate analysis (Cox proportonal hazard model) in order to establish the relation with prognosis and survival. Survival of HCV related HCC was compared with the miscellaneous etiology group. Patients with concurrent infection of hepatitis B and C were analyzed in the miscellaneous group as their prognosis may differ from pure HCV related HCC.

The chi square values and likelihood ratio (LR) related to a Cox's proportional hazard regression model was used to evaluate the performance within categories of each classification system. The discriminatory ability of the staging systems was quantified using ROC curves. The study was conducted with the approval of the Institutional Ethics Committee. Informed consent was obtained from each patient.

Results

Included in this study were 129 patients with unresectable and advanced HCC. Males were 97 (75.1%). Median age of these patients was 52 years (range 18 - 82). Etiological factor for HCC was hepatitis C in 66 (51.2%) patients and miscellaneous in 63 (48.8%). The latter category included hepatitis B 31 (24%), HBV + HCV 10 (7.8%), HBV plus HDV 02 (1.6%), non-B non-C 20 (15.4%). All patients had clinical cirrhosis except one with hepatitis B etiology. At the time of analysis of data, 102 patients had died (79%). Cumulative deaths were 22 (21.6%) at six months, 62 (60.8%) at one year and 93 (92.2%) at two years. Median follow up of all patients (including deaths) was 11 months (range 2-36). Three patients were lost to follow-up with last follow-up at 4, 5 and 10 months each. Forty-one (31%) patients underwent TACE. Alpha fetoprotein level was normal i.e. less than 20 ng/ml in 40 (31%) and greater than 400 in 46 (37.5%) patients. Baseline characteristics comparing hepatitis C etiology versus miscellaneous group have been described in Table 1.

Univariate Analysis of variables predicting poor survival in all 129 HCC patients using log rank test is given in Table 2. The significant factors found were hepatitis C as etiology, female sex, presence of ascites, splenomegaly, presence of splenic varices, INR > 1.3, total bilirubin > 1.17 mg/dl, direct bilirubin > 0.4 mg/dl, alkaline phosphatase > 169 IU/L, MELD Score >12, Child Class B & C, multifocal tumour and chemoembolization not offered.

Table 1: Baseline characteristics of 129 patients with Hepatocellular Carcinoma

	HCV (n=66)	Misc. (n=63)	P Value
Age (yr ± S.D.)	52.7 + 10	52 + 13	NS
Sex (M:F)	41 vs 25	56 vs 7	<0.001
Haemoglobin (g/dl)	11.0+ 2	11.1+ 2	NS
Platelets (109 / L)	152+ 87	213+ 144	<0.01
Creatinine (mg/dl)	0.77 + 0.28	0.83 + 0.35	NS
Albumin (g/dl)	3.2+ 0.65	3.1+ 0.8	NS
Total bilirubin (mg/dl)	1.6+ 1.6	2.7+ 4.0	0.05
ALT (IU/L)	75+ 50	80+ 59	NS
AST (IU/L)	94 + 104	109 + 86	NS
GGT (IU/L)	107 + 114	166 + 181	<0.05
INR	1.31+ 0.3	1.3+ 0.4	NS
ALP IU/L	197+134	318 + 442	0.05
Alpha fetoprotein (ng/ml)	3712 + 10077	10838 + 46339	NS
AFP <400 / >400	45/21	41/22	NS
Liver size on U/S			
Normal/increased/decreased	20/29/17	15/31/17	NS
Tumour focality: multifocal	32	33	NS
No of tumours: solitary/2-3/>3	32/23/11	28/10/15	NS
Liver involvement (>50%)	15	21	NS
Size of largest Lesion 1-3/3-5/>5cm	6/30/30	5/25/33	NS
Splenomegaly Y/N	46/20	36/27	NS
Splenic Varices on U/S Y/N	46/20	36/27	NS
Portal patency Y/N	44/22	43/20	NS
Presence of Ascites	40	31	NS
CHILD A/B/C	22/31/13	30/15/18	NS
MELD Score (median)	7	10	NS
OKUDA I/II/III	14/42/10	21/31/11	NS
CUPI low/inter/high risk	13/42/11	18/27/18	NS
CLIP Stage A/B/C	5/50/11	7/49/7	NS
BCLC A/B/C/D	8/32/11/15	18/22/4/19	NS
TACE Offered	22	19	NS

ALT= Alanine aminotransferase, AST= aspartate aminotransferase, ALP= Alkaline Phosphatase , GGT= gamma glutamyl transferase, INR= International normalization ratio, TACE= Transarterial chemoembolization. MELD= Model for end stage liver disease, CLIP =Cancer Liver Italian program, BCLC = Barcelona Clinic Liver Cancer, CUPI= Chinese University Prognostic Index. p-values by Pearson chi-square, Fisher's exact test or T test. NS= not significant

Comparing HCC in hepatitis C patients with mixed etiology patients, age > 52 years (p<0.05), bilirubin >1.17 mg /dl (p<0.01), INR > 1.3 (p<0.01), alpha fetoprotein > 400 ng/ ml (p<0.05), splenomegaly (p<0.01), ascites (p<0.001), portal vein thrombosis (p<0.01), splenic varices (p<0.01), alpha, and TACE not offered (p<0.01) were the prognostic factors while in miscellaneous etiology female sex (p<0.05), haemoglobin < 11.0 gm/dl (p<0.01), alkaline Phosphatase > 169 IU/L (p<0.05), ascites (p<0.05) and multifocality (p<0.05) were adversely effecting the prognosis.

Forty-one patients (31%) were offered TACE; 24 patients were in Child's A, 15 in B and 2 in C. Twenty two (male = 13) patients had HCV while 19 (all males) had miscellaneous etiology. Overall median survival was 14.0 months vs. 9.5 months for patients offered vs. not offered TACE respectively (p<0.05). A beneficial effect

Table 2: Potential predictors of survival by univariate analysis in 129 patients with HCC (p values using log rank test and hazard ratio by Cox regression).

Variable		n=129	Median Survival (months)	P Value	Hazard ratio (95%CI)
Etiology	Hep C / Misc	66/63	11/17	<0.001	2.3 (1.5-3.6)
Sex	M / F	97/32	16/10	<0.01	2.0(1.3-3.3)
Ascites	Yes/no	71/58	11/18	<0.001	2.1 (1.4-3.2)
Splenic varices on U/S	Yes/no	72/57	12/17	<0.01	1.8 (1.3-2.8)
Splenomegaly	Yes/No	79/50	12/17	<0.01	1.8 (1.2-2.7)
Tumour Focality	Multifocal / Unifocal	65/64	13/16	0.05	1.5 (1.0-2.2)
INR	>1.3 / <1.3	55/74	12/16	<0.05	1.6(1.0 - 3.4)
Serum ALP (IU/L)	>169/<169	61/68	13/16	<0.05	1.5(1.0-2.3)
Total Bilirubin (mg/dl)	>1.17/<1.17	66/63	13/16	0.05	1.5(1.0-2.2)
Direct Bilirubin (mg/dl)	>0.4 / <0.4	65/64	12/16	<0.05	1.4 (1.0-2.2)
MELD Score	>12 / ?12	45/ 84	10/15	<0.01	1.7 (1.1-2.5)
Child Class	B & C vs. A	77/52	10/16	<0.001	2.2(1.5-3.3)
TACE offered	Yes / No	41/88	17/12	<0.05	1.6 (1.1-2.5)

INR= International normalization ratio, ALP= alkaline phosphatase, TACE= Transarterial chemoembolization, MELD= Model for end stage liver disease. Hazards ratios by Cox proportional hazards model.

of TACE on survival was seen: Odds Ratio 1.63, 95% confidence interval 1.07-2.48. There was improved one-year survival from those not offered (70% vs. 50%). In the sub group analysis of patients who were offered TACE, there was no significant difference in the age, Child class and Okuda stage of hepatitis C versus miscellaneous group (p values > 0.05 in each case). Survival of patients who were offered TACE was more in both HCV and miscellaneous HCC groups. In HCV group median survival was 14.0 months who were offered TACE versus 7.0 months who were not offered TACE. These values were 18.0 months versus 12 months respectively in the miscellaneous group.

Table 3: Performance evaluation of the Child's, Okuda, MELD Score, CLIP, CUPI and BCLC staging systems.

Staging system	X^2 Value	-2 Log likelihood	P Value
	All patients		
Okuda	66.485	752.666	0.000
BCLC	21.315	778.178	0.000
Chlid's	15.223	784.391	0.000
CLIP	11.694	789.565	0.003
CUPI	6.588	792.690	0.037
MELD Score	6.140	793.621	0.130
	Hepatitis C HCC		
Okuda	60.636	297.302	0.000
Chlid's	32.421	308.449	0.000
BCLC	29.386	308.678	0.000
MELD Score	21.66	314.228	0.000
CUPI	12.695	321.000	0.002
CLIP	7.938	323.910	0.019
	Misc. HCC		
Okuda	32.564	318.905	0.000
BCLC	10.051	331.520	0.018
Chlid's	6.548	335.507	0.038
CLIP	4.131	338.468	0.127
CUPI	3.184	338.656	0.204
MELD Score	2.018	339.839	0.155

BCLC = Barcelona Clinic Liver Cancer, CLIP =Cancer Liver Italian program, CUPI= Chinese University Prognostic Index, MELD= Model for end stage liver disease.

Cox regression model for multivariable analysis included factors which had a significant correlation with survival by the log rank test identified in Table 2. Independent predictors of survival were hepatitis C etiology, female sex, multifocality and TACE not offered: p values 0.00, 0.001,and 0.020: hazard ratios 3.0 (1.7-5.3) , 3.0 (1.6-5.6) and 1.9 (1.1-3.1) respectively. In a subgroup multivariable analysis comparing hepatitis C related HCC with miscellaneous etiology patients no statistically significant difference was found. However, TACE not offered (p = 0.06) and alpha fetoprotein > 400 (p=0.09) in hepatitis C related HCC, and female sex (p= 0.07) and ascites (p=0.08) in the miscellaneous group were found to have a borderline significance.

As expected, all classification models (Child's, Okuda, CLIP, CUPI & BCLC) showed a significant relationship to survival according to the Kaplan-Meier method. X2 values that were obtained by Cox model were better for Okuda and BCLC systems (Table 3). Discriminatory ability for death at 12 and 24 months was evaluated by receiver operating characteristic (ROC) curve area. Though different staging systems retain their performance evaluation, Okuda staging system predicted prognosis better up to one year (Table 4). For first year deaths (62 / 102), ROC curve areas with 95% confidence interval were Okuda 0.804

Table 4: Discriminatory ability for death at 12 and 24 months, evaluated by receiver operating characteristic (ROC) curve area for Okuda, CLIP, CUPI & BCLC scores.

Staging systems	Overall		HCV patients		Misc patients	
	ROC curve area	95% CI	ROC curve area	95% CI	ROC curve area	95% CI
1st year Deaths	**(62 / 102)**		**(37/49)**		**(25/53)**	
Okuda	0.804	0.716- 0.891	0.694	0.554- 0.885	0.789	0.678-0.901
BCLC	0.767	0.671 - 0.684	0.802	0.691-0.913	0.746	0.624-0.869
CUPI	0.632	0.522-0.742	0.612	0.470-0.754	0.613	0.474-0.753
CLIP	0.631	0.522 - 0.740	0.660	0.518-0.803	0.585	0.444-0.726
2nd year Deaths	**31/ 102**		**(12/49)**		**(20/53)**	
CLIP	0.400	0.284 - 0.515	0.340	0.197-0.482	0.470	0.321-0.618
CUPI	0.377	0.267-0.488	0.338	0.246-0.530	0.402	0.261-0.543
Okuda	0.263	0.161 - 0.365	0.306	0.165-0.446	0.337	0.201-0.473
BCLC	0.247	0.149- 0.334	0.198	0.087-0.309	0.309	0.178-0.440

BCLC = Barcelona Clinic Liver Cancer, CLIP =Cancer Liver Italian program, CUPI= Chinese University Prognostic Index.

(0.716- 0.891), BCLC 0.767 (0.671 - 0.684), CUPI 0.632 (0.522-0.742), CLIP 0.631(0.522 - 0.740) (Figure).

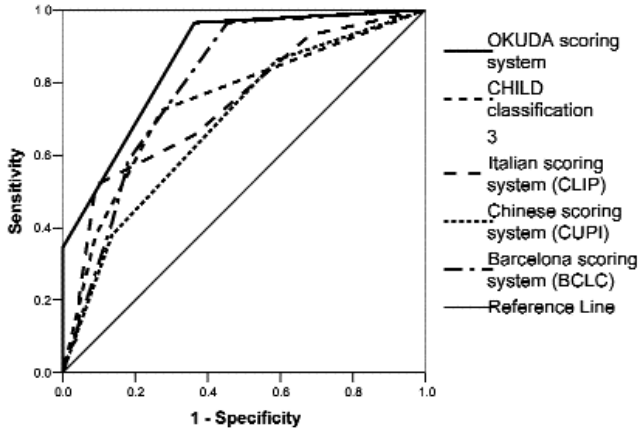

Figure: Discriminatory ability for death at 12 and 24 months was evaluated by receiver operating characteristic (ROC) curve area.

Discussion

The etiology of hepatocellular carcinoma varies worldwide and it is still not known whether HCCs of different etiologies have different prognosis. With the shift in etiology, HCV has replaced HBV as the major cause of HCC in Pakistan[20] and many parts of the world. Multivariate analysis in our study showed that independent pretreatment predictors of survival were hepatitis C as etiology, female sex, multifocality and TACE not offered. Comparing HCC in our hepatitis C patients with miscellaneous (predominately HBV) patients, it appears that HCV related HCC behaves in a different way. Usually men are thought to be more susceptible to HCC than women. They tend to consume more alcohol and cigarettes, and have increased iron stores. Androgenic hormones and increased genetic susceptibility have also been proposed as the contributing factors. The reason for the male predominance in previously reported studies may be due to higher prevalence of hepatitis B as the etiological factor.[12,21] In our series, males were in a larger proportion in the HCC of miscellaneous etiology (predominately HBV related HCC) than in HCV related HCC.

Transarterial chemoembolization (TACE) has been shown in recent meta-analysis of randomized controlled trials to be associated with longer 2-year survival in ideal candidates that is patients with preserved liver function, without vascular invasion or extrahepatic dissemination.[22] Our study showed a beneficial effect and improved survival in patients who were offered TACE. Survival of patients who were offered TACE was more in both HCV and miscellaneous HCC groups. In HCV group median survival was 14 months who were offered TACE versus 7 months who were not offered TACE. These values were 18 months versus 12 months respectively in the miscellaneous group.

In our study we compared the usefulness of different scoring systems to assess prognosis in patients with HCC. The prognosis and the median survival is lower compared to the western studies in our cohort of patients[15,23] and hepatitis C has become an important etiological factor. Therefore survival data generated from studies conducted in different parts of the world may not be necessarily applicable to other countries or areas and each staging system should be validated locally. We have found Okuda, CLIP, CUPI and BCLC classifications useful to predict survival in patients with non-resectable HCC. When comparing the efficacy of predicting values of all prognostic systems by means of Cox's regression analysis, Okuda and BCLC offered better results. However, discriminative ability for death evaluated by ROC curve was better for Okuda system. The merit of the Okuda staging lies on the four simple parameters; tumor size less than or more than 50% of liver, ascites absent or present, serum albumin < or

> 3 g /dl and bilirubin < or > 3 mg /dl. The later three parameters are from the Child's staging for cirrhosis. Our patients were of advanced liver disease so Okuda did very well. However, it may be less accurate than CLIP and BCLC, in the prediction of survival in early stage disease.[6,24] CLIP scoring system takes into account Child stage, tumour morphology, alpha fetoprotein levels and portal vein involvement, while BCLC staging depends on the tumour size, morphology, vascular invasion, liver function status and performance evaluation of the patient.

The Child-Pugh score is the most commonly used prognostic classification in patients with cirrhosis and becomes an important prognostic indicator when HCC is being developed in the advanced decompensated disease. This is especially true for the HCC developing in the HCV cirrhosis patients, where advanced liver disease itself predicts the poor survival. This was the reason that we kept this variable while prognosticating HCC. Value of performance status included in BCLC becomes important only when dealing with patients having early Child-Pugh score. BCLC at this stage becomes a more accurate prognostic model for exploring therapeutic possibilities. Alpha fetoprotein has not been included in BCLC but has been retained in CLIP. In our study, alpha fetoprotein was not elevated significantly in many cases of HCV related HCC. However, when elevated >400, it showed poor prognosis in HCV related HCC but not in the miscellaneous etiology HCC.

In conclusion, the prognosis of cirrhotic patients developing HCC, continues to be poor. Despite the existence of several validated staging systems, our study reinforces the importance of baseline liver function, as assessed by Child-Pugh classification and simple staging by Okuda as valuable tools in assessing the prognosis of patients with non-resectable HCC. As prognosis of HCV related HCC patients differs from other etiologies, we suggest that this factor should also receive due consideration.

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