FHCC-Pro: PROGNOSTIC STRATIFICATION INDEX OF FILIPINO PATIENTS WITH HEPATOCELLULAR CARCINOMA

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ABSTRACT

SIGNIFICANCE: The long-term prognosis of hepatocellular carcinoma (HCC) remains dismal of which prediction of survival is often difficult. A prognostic staging classification combining clinical and tumor-related variables is recommended and provides a guide for patient treatment and care. This study aims to develop a clinical prognostic scoring index predictive of survival for patients with HCC.

METHODOLOGY: A retrospective cohort of patients diagnosed with HCC from January 2003 to June 2011 was done. Demographic data such as age, sex, presence of diabetes, viral hepatitis, and alcohol consumption, and Child-Pugh class were taken. Tumor-related variables reviewed include tumor size, tumor #, presence of portal vein obstruction and elevated AFP. Frequencies and proportions were taken for categorical data, 1-year survival based on the number of months from the time of diagnosis up to the time of death. Kaplan Meier Survival Analysis was also used to determine and compare the survival rates per prognosis. A scoring index was devised and a validation study subsequently performed.

RESULTS: A total of 378 patients with HCC were included. Majority of patients were male (66%) and older than 40 years of age (97.4%). Hepatitis B infection was documented in 65.1% of cases. More than half of tumors were <3cm (53.7%), and solitary (80.4%). One-third of patients were Childs-Pugh B. Univariate analysis showed that presence of diabetes, history of alcohol intake, tumor size, tumor number, AFP levels and Child-Pugh class significantly correlated with survival (p-value 0.021, 0.001, 0.000 for tumor size up to Child-Pugh class, respectively). A contingency table was made with individual scores for each of the factors summed up to one final score. Cut-offs within the range of the final score are established and class widths computed based on mean and standard deviation. The scores are as follows: good prognosis 0-4.0 intermediate 5.0-8.0, poor prognosis >8.0. The overall survival rate was 68%. Kaplan-Meier survival analysis was done and showed that patients with scores <4.0 has a 94% 1-year survival rate; intermediate 60% survival rate; poor 17% survival rate. Further analysis done according to treatment intervention done showed the following survival rates: 100% for good prognosis, 69% for intermediate and 11% for poor prognosis. Validation of this index was performed in an ambispective cohort of patients. A total of 37 patients were included and categorized as good, intermediate and poor risk. The survival rates according to class are: good 87%, intermediate 50%, and poor 27%. Kaplan meier analysis was significant at p-0.032). Overall survival rates for those who received RFA and/or TACE was higher than those with supportive treatment alone (51% vs 48%).

CONCLUSION: Presence of diabetes, significant alcohol consumption, tumor size of >3cm, multiple tumors, elevated AFP and Child-Pugh classification correlate with poor survival. A scoring system such as this model may be used to predict survival of patients with HCC.

KEYWORDS: prognostication, hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC, also called malignant hepatoma) is the most common type of liver malignancy. It is the third leading cause of cancer mortality worldwide and. The incidence exceeds 30 cases/100,000/year in the east-Asian region. Worldwide, it accounts for almost 1 million deaths/year. The frequency of liver cancer is high among Asians because liver cancer is closely linked to chronic hepatitis B infection.5.6

In the Philippines, hepatocellular carcinoma ranks as the fourth most common cancer with an age-standardized rate of 6.7 per 100 000 persons in 2005. The incidence rates are 14 per 100 000 persons for males and 4.8 per 100 000 persons for females. It ranks 2nd among males and 9th among females. In 1977, the Liver Study Group of the University of the Philippines performed a demographic review of all cases of HCC. Among agents looked into were chemicals including sex hormones, hepatitis B virus (HBV), aflatoxin and alcohol.1

The detection of hepatocellular carcinoma is difficult as most patients are asymptomatic or present with advanced disease. The onset of abdominal pain, weight loss, early satiety, jaundice and a palpable mass in the upper abdomen usually indicate an advanced cancer.3-4 Most cases of HCC are secondary to chronic viral hepatitis infection (hepatitis B or C) or cirrhosis. There are other emerging risk factors that may play a role in the development of HCC such as diabetes mellitus, and significant alcohol intake.3-6 Demographic factors such as sex and age may also contribute to the the probabaility of developing HCC.7

In 1998, an estimated 5,249 new cases, 3,906 cases in males and 1,343 cases in females, and about 4,403 deaths are expected to occur every year. According to the statistics from the University of Santo Tomas, 2008, 55% of patients with HCC have CHB; 4.4% have CHC; 9.2% have chronic alcoholism; and 24.9% have cryptogenic cause. The mean age of development of HCC is 60 years. The male-to-female ratio is 3:1, and 74% of patients have a tumor size >5 cm at the time of diagnosis. As such, surgical resection or liver transplantation can be done in only 3.7% of these patients, and 24% of patients with HCC receive TACE. More than 50% of patients only receive symptomatic treatment.21 Most liver cancer patients die within a year of diagnosis and the 5-year survival rate for the disease is less than 5%. Even with treatment, the 5-year survival rate for liver cancer is still low at 35%.

In malignancy diseases, staging system is important because it defines prognosis and is a guiding tool for treatment options and also a research tool for comparison between different groups and trials. Traditionally, the prognosis of patients with HCC has been

assessed using Tumor-Node-Metastasis (TNM) Scoring to evaluate the tumor extension and Child-Pugh Classification (CPC).7,8 The Okuda staging system from Japan is an accepted and widely used classification system for HCC which consists of tumor load, ascites, albumin, and bilirubin. However, the Okuda staging system does not properly identify patients who may be suitable for certain therapeutic interventions. However, there is still no consensus on the staging system to use to predict prognosis.

The significance of this study is to propose a new scoring system for the prognostication of patients with Hepatocellular Carcinoma among Filipinos that is practical and easily assessable in clinical practice and help clinicians to discuss the treatment modalities to patients in terms of survival rates. This study aims to develop a clinical prognostic scoring index predictive of risk for advanced Hepatocellular Carcinoma (HCC) using both tumor-related variables and liver function. The specific objectives are:

1. ToanalyzethepresentdemographicsofHepatocellularcarcinomaamongFilipinos.

2.Todeterminetheriskfactorsassociatedwithpatientsurvival.

3. Todevelopaclinicalscoringindexpredictiveofsurvival

4. Tovalidatetheproposedclinicalscoringindex.

METHODOLOGY

A retrospective review of patients diagnosed with HCC from the period of January 2003 and June 2011 was performed. HCC was diagnosed based on imaging test and/or liver biopsy. Patients diagnosed with congenital liver pathology and other malignancies were excluded in this study. Chart review was done. The following data were collected for all patients: age, sex, history of Diabetes mellitus, significant alcohol consumption, tumor characteristics like size, number, presence of portal vein obstruction, level of alpha-feto protein (AFP), international normalized ratio (INR), albumin, bilirubin, presence of encephalopathy and ascites, Child-Pugh classification and duration of illness. Primary outcome

measured was 1-year survival. Statistical analysis used was frequencies and percentages for categorical data. Chi-square test of independence is performed to compare outcomes. Risk factors identified are combined to create a clinical scoring index. Kaplan Meier Survival Analysis is used to determine and compare the survival rates per prognosis. The scoring index was then used in an ambispective cohort validation study.

RESULTS

A total of 378 patients diagnosed with hepatocellular carcinoma were reviewed and analyzed in this study. Table 1 describes the baseline characteristics of the study population. Majority of HCC patients are male (66.1%), over 40 years old (97.4%), HBV-relates (65%), and without significant alcohol intake. About half (53.7%) had tumors measuring less than 3cm while 45.5% had tumor size about 3cm or bigger. Majority of patients (80.4%) had single tumor only. Few patients had presence of portal vein obstruction (2.6%). AFP levels were greater than 10ng/ml in most patients. Almost one third (63.2%) of patients belong in Child- Pugh Class B.

Table 1: Baseline Characteristics of the Study Population

PATIENT CHARACTERISTICS		Total Patients (N=378)	
		#	%
Sex	Male	250	66.1
	Female	128	33.9
Age group	<40	10	2.6
	≥40	368	97.4
Diabetes Mellitus	No	184	48.7
	Yes	194	51.3
Etiology	No	125	33.1
	HBV	246	65.1
	HCV	7	1.9
History of alcohol intake	No	305	80.7
	Yes	73	19.3
Tumor size	<3cm	203	53.7
	≥3cm	172	45.5
Tumor no.	1	304	80.4
	≥2	74	19.6
Portal vein obstruction	No	368	97.4
	Yes	10	2.6
AFP levels	<10	109	28.8
	≥10 ng/ml	269	71.2
Child-Pugh Class	A	80	21.2
	B	239	63.2
	C	59	15.6

There were a total of 120 deaths with an over-all mortality rate of 31.7%. Univariate analysis using Pearson's chi-square test was performed to compare the proportion of patients who survived and did not survive according to the demographic data (Table 2). The male:female ratio was almost equivalent in the study population.

The following factors were significantly correlated with survival: absence of DM (p=0.021), absence of significant alcohol intake (p=0.001), tumor size of <3cm (p=0.000), single tumors (p=0.000), low AFP (p=0.000) and CPC class A (p=0.000). Conversely, there were higher percentage of deaths among patients who are diabetics, alcohol drinkers, with bigger and multiple tumors, high AFP levels and Child C.

Table 2: Univariate Analysis of Risk Factors associated with Survival

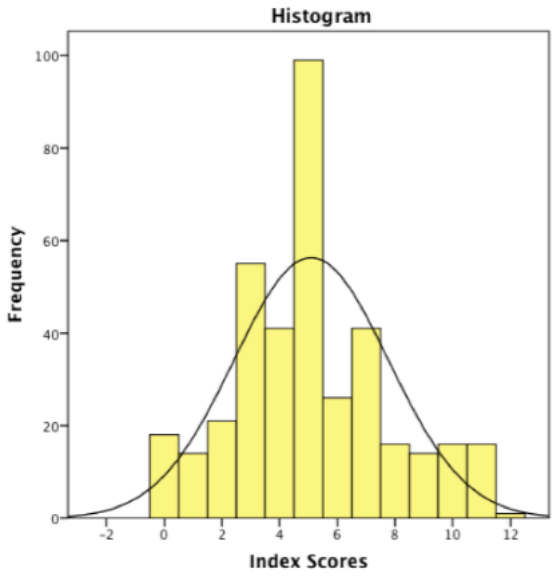
VARIABLES		Deaths		Survivor		P - value
		N	%	N	%	
Sex	M	86	34.4	164	65.6	0.121
	F	34	26.6	94	73.4	
Age group	<40	2	20.0	8	80.0	0.419
	≥ 40	118	32.1	250	67.9	
Diabetes Mellitus	No	48	26.1	136	73.9	**0.021**
	Yes	72	37.1	122	62.9	
Etiology	No	39	31.2	86	68.8	0.075
	HBV	76	30.9	170	69.1	
	HCV	5	71.4	2	28.6	
History of alcohol intake	No	85	27.9	220	72.1	**0.001**
	Yes	35	47.9	38	52.1	
Tumor size	<3cm	30	14.8	173	85.2	**0.000**
	≥ 3cm	90	51.4	85	48.6	
Tumor no.	Single	66	21.7	238	78.3	**0.000**
	Multiple	54	73.0	20	27.0	
Portal vein obstruction	No	115	31.3	252	68.7	0.362
	Yes	5	50.0	5	50.0	
AFP levels	<10	15	13.8	94	86.2	**0.000**
	≥ 10	105	39.0	164	61.0	
Child-Pugh Class	A	3	3.8	77	96.3	**0.000**
	B	83	34.7	156	65.3	
	C	34	57.6	25	42.4	

The significant risk factors identified were combined and a scoring index was devised where in a score of 0 was given to those significantly related to survival and 2 for those related to mortality (Table 3). A score of 1 was given to Child's B as an intermediate class. The maximum score is 12. The individual scores of the study population were measured and is shown in the histogram (Figure 1). The mean score was noted at 5.

Table 3: Proposed Clinical Scoring Index

VARIABLE		Score
Diabetes mellitus	No	0
	Yes	2
Alcohol intake	No	0
	Yes	2
Tumor size	<3cm	0
	≥3cm	2
Tumor number	Single	0
	Multiple	2
AFP (ng/ml)	<10	0
	≥10	2
Child-Pugh Classification	A	0
	B	1
	C	2

Figure 1: Frequency Distribution of Scores



Class widths were calculated to establish cut-offs within the range of the mean. The class scores are as follows: Good 0 – 4, Intermediate 5 – 8, and Poor risk 9 – 12. The patients were then classified according to the class scores shown in table 4.

Table 4: Proportion of Survivors in each prognostic class

Prognostic Class	Survivor N	% Survival Rate	Average Survival Time (mos.)
Good	144/153	94	11
Intermediate	106/177	60	10
Poor	8/48	17	7
Overall Survival		68.3	10

The over-all survival rate is 68.3% with an average survival time of 10 months. The survival rate according to prognostic class are as follows: good 100%, intermediate 60%, and poor 17% with an average survival time of 11 months, 10 months and 7 months respectively. Kaplan Meier analysis shows that the survival rates between the 3 classes were significantly different with p value of 0.000 (Figure 2). Figures 3-4 show the comparison of the survival of patients given treatment (TACE, RFA

or both) to those with supportive management alone. Kaplan meier analysis was significant with a log-rank test of p=0.000.

Figure 2: Kaplan-Meier Survival Curve according to Prognostic Class

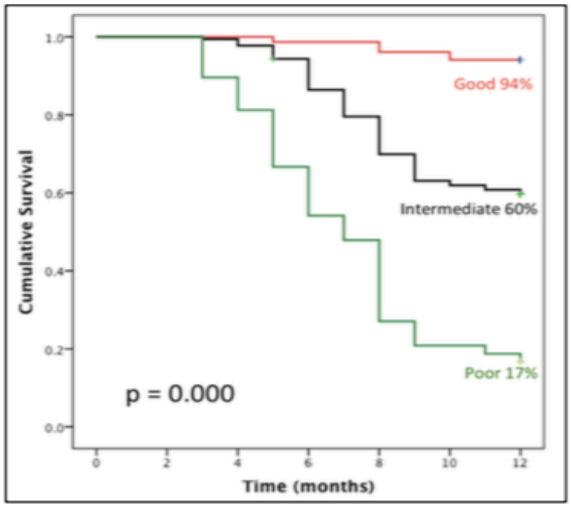
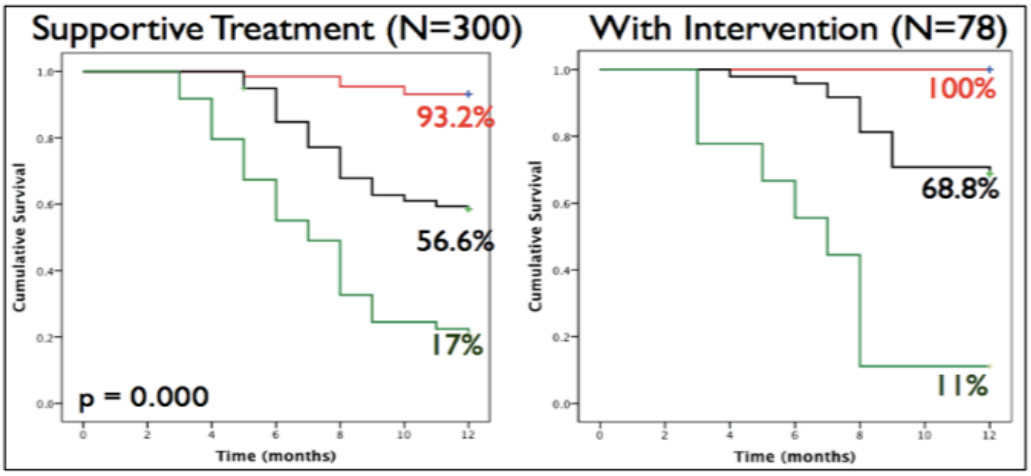


Figure 3-4: Kaplan-Meier Survival Curve sub-stratified according to treatment



To validate this proposed scoring index, an ambispective cohort of patients diagnosed with HCC from the period of June 2010 to August 2012 was done. A total of 37 patients were included and using the proposed scoring index, they were categorized as good (n=8), intermediate risk (n=18), and poor risk (n=11). The primary outcome measured was 1-year survival. Table 5 shows the distribution and proportion of patients in each prognostic class. The over-all survival rate was 51.4% with an average

survival time of 8 months. Kaplan meier analysis showed that the survival rates were significantly different with a p-value of 0.032 (Figure 5).

Table 5: Proportion of Survivors in each prognostic class

Prognostic Class	Survivor N	% Survival Rate	Average Survival Time (mos.)
Good	7/8	87.5	11
Intermediate	9/18	50	8
Poor	3/11	27	6
Overall Survival		51.4	8

Figure 5: Kaplan-Meier Survival Curve according to Prognostic Class

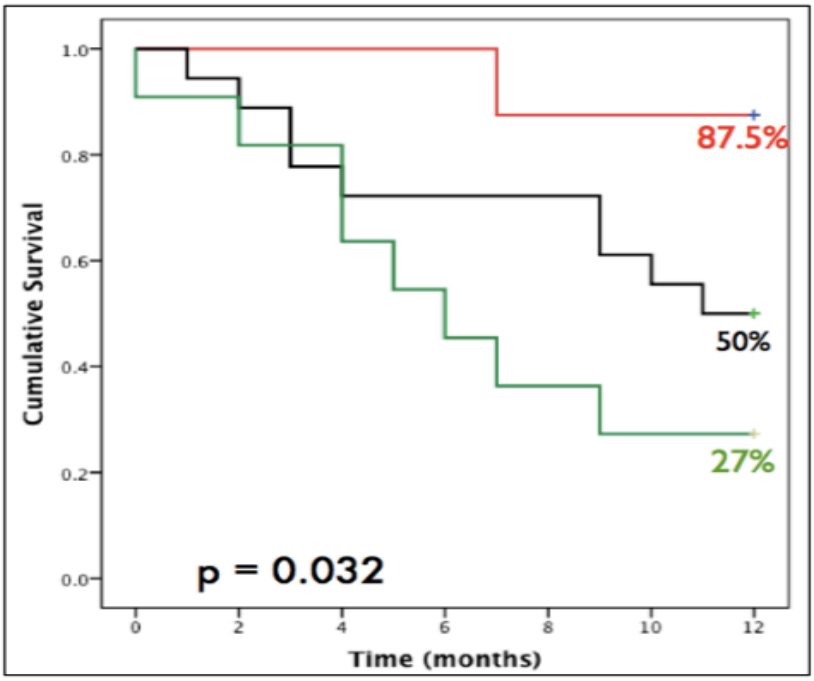


Table 6: Proportion of Survivors in each prognostic class stratified according to treatment

	Supportive Treatment		With Intervention	
Prognostic Class	**Survivor N**	**% Survival Rate**	**Survivor N**	**% Survival Rate**
Good	5/5	100	2/3	66.7
Intermediate	6/15	40	3/3	100
Poor	3/9	33.3	5/8	62.5
Overall Survival		48.3		51.4

Substratification of patients according to treatment showed that the over all survival rate for those with intervention was higher at 51.4% vs. 48.3& for those with supportive treatment. Further analysis however was not done due to a small number of subjects in each prognostic class.

DISCUSSION

The long-term prognosis of patients with Hepatocellular Carcinoma among Filipinos remains dismal of which prediction of survival is often difficult. At present, many scoring system for prognostication of Hepatocellular Carcinoma are available but there is no consensus on what to use worldwide. The short-term mortality in HCC patients remains high. An accurate prognostic stratification will certainly allow guidance on the therapeutic approach and will probably improve the survival of patients.

In recent years, various studies have investigated the usefulness of different prognostication system for HCC. Most studies include noninvasive parameters like demographic, biochemical and clinical. Here, we included demographics, risk factors, clinical, analytical, tumor characteristics and functional status of the liver that includes the Child Pugh's Criteria. In the original studies like MELD scoring system it does not allow the stratification of patients with good, intermediate and poor prognosis because the cut off value are still controversial. Another study like I-CLIP includes histologic features only while Ep- CAM includes biomarker only, hence was providing some limitations in the prognostication system.

In our study, we devised a scoring index that may be applied in the clinics. This scoring system is accessible and easy to perform and includes clinical data and tumor. The following factors significantly correlated with survival: absence of DM, absence of significant alcohol intake, tumor size of <3cm,

single tumors, low AFP and CPC class A (p=0.000). Conversely, there were higher percentage of deaths among patients who are diabetics, alcohol drinkers, with bigger and multiple tumors, high AFP levels and Child C. These risk factors have been observed individually and are related in the development of HCC. But in combination, the cumulative risk

In the study population, although majority of patients were HBV related it was not significantly related to survival. This may be explained by the fact that HBV-related HCC patients are commonly younger, and some may present with no underlying liver cirrhosis.

Diabetes mellitus was identified as an independent predictor or survival and is shown to be higher in the population who died and is due to the fact that with the presence of diabetes, patients may have other confounding factors, such as presence of comorbidities which increase their over-all risk. Further analysis is recommended to describe the reasons why diabetes alone decreases the survival of patients with concomitant HCC.

CONCLUSION

We therefore conclude that most patients with HCC were male, 40 years and older which was HBV related. The prognostic scoring index which include DM, alcohol intake, tumor size, tumor number, and Child-Pugh class correlates with survival risk. The scoring system : Good 0 – 4, Intermediate 5 – 8, and Poor risk 9 – 12 is accessible and easy to perform. Treatment intervention in the form of RFA and/or TACE improves over-all survival rates. We recommend a larger population to validate this tool.

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