

## RESEARCH ARTICLE

# Roles of Ethnicity in Survival of Hepatocellular Carcinoma Patients in Malaysia

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### Abstract

The incidence of hepatocellular carcinoma (HCC) in Malaysia for the year 2001 was 2.8 per 100,000 people. The mortality rate is increasing. A retrospective cohort study measuring the survival of HCC patients who received treatment in Selayang Hospital was conducted from 1 January 2003 to 31 December 2006. The main objectives of the study were to measure the survival of the patients and to understand the influencing factors, especially ethnicity. The subjects were newly diagnosed cases of HCC by CT scan and histopathological assessment who underwent further investigations and treatments in Hospital Selayang (inception cohort). The survival time was measured from the date of diagnosis until the subjects died, or failed to follow-up at the end of the study period (31 December 2007). A total of 299 patients were selected with 95 patients dying, the majority among Chinese (39.1%). Subgroup analysis according to ethnicity proved significantly that Chinese patients who had smaller tumor, less number of nodules, low AFP level, Child Pugh Class A and received surgical treatment had a better median survival rate compared to other ethnic groups. Malay (cHR: 1.3, 95% CI; 0.89-1.85) and Indian (cHR: 1.3, 95% CI; 0.74-2.26) patients had a poor survival compared to Chinese patients, but not in the final model. Therefore ethnicity may play a role in survival of HCC patients, but not as a main hazard prognostic factor.

**Keywords:** Ethnicity - survival - HCC - prognostic factors - Malaysia

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### Introduction

Hepatocellular carcinoma (HCC) accounts for 6% of all cancers worldwide and the fifth commonest cancer in the world. Morbidity and mortality rate trend is equivalent to its incidence trend (Bosch et al., 2004). About 80% of the cases worldwide arise in the developing countries i.e. Southeast Asia and sub-Saharan Africa. The estimated number of people who develop HCC is 564,000 cases per year worldwide (Parkin, 2001). In North America and some European countries, HCC is less occurring and mortality rate is less than 5 for every 100,000 residents each year (Ramsey et al., 1995; Bosch and Ribes, 2000).

In Malaysia, HCC is one of the commonest malignancies, with an age-standardised annual incidence of 2.8 cases per 100,000 populations. It accounts for 5.6% of all cancers and 8.1% of all cancer related deaths in this country. HCC is twelve commonest cancers in men and ranked eighteenth amongst women in Malaysia as reported by National Cancer Society, 2004.

There are variations in the cases of HCC based on ethnic group, with the rate in the nation among black and Hispanic America are more compare with white people (Shea et al., 1990; Trapido et al., 1990). Somewhat interesting, the difference in the survival rate in overall of

white people and the minority people in the United States have been reported, and the difference in the survival rate has been attributed to various factors, including the distinction of treatment, the mortality rate is proceeding from natural sources and biological changes in cancer itself (Clegg et al., 2002).

Meanwhile, HCC cases in the United States continues to increase (El Seraq et al., 1999), the age standardized rate for HCC patients in the nation of black and America Hispanic is twice compare with white patients. The same distinction in the rate of HCC patients between black and white, also found significance in New Jersey. Additional to the distinction of cases, ethnic background can also predict the results of the HCC patients. Chin (1999) compared the results of patients in Asia with others ethnic, the HCC has diagnosed in institutions in the West. They report the status of ethnic is independent of these results, with patients from other ethnic, the survival rate were better than Asian patients.

One study in Australia found a different reduction in risk of death among immigrants in the immigrant-east and Southeast Asia, according to the determination of their period: 12.1 years set for 0.9, 11.9 for 10-19 years, 5.0 for between 20 and 29 years, and 3.1 for more than 30 years (Lam et al., 2005). The National Cancer in Malaysia,

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in 2004 reported a higher risk to develop HCC among Chinese compare of many other ethnic group, namely the Malay and Indian. As a result, the mortality rate is also might be higher among the Chinese community, it also found the same effect among Chinese Singapore to other ethnic group in Singapore (Lim et al., 2002).

The objective of the study was to measure the survival of HCC patients and to identify ethnicity as one of predictors in HCC patients.

## Materials and Methods

A retrospective cohort study measuring the survival of HCC patients who received treatment in Selayang Hospital was conducted from 1 January 2003 to 31 December 2006. It was a universal sampling from case notes of HCC patients. The subjects were newly diagnosed cases of HCC by CT Scan and confirmed by histopathological who underwent further investigations and treatments in Selayang Hospital from 1 January 2003 to 31 December 2006. The survival time was measured from the date of diagnosis until the subjects died, failed to follow up or still alive at the end of the study period which was 31 December 2007.

Factors studied included demography background such as age, gender, marital status and ethnic; risk factors towards HCC which are smoking, alcohol intake and hepatitis status; AFP level during diagnosis in which divided into 3 groups of less than 20 ng/L, 20-1,000 ng/L and more than 1,000 ng/L; Child Pugh Class of A, B or C; cancer characteristic based on Ct Scan findings divided into cancer size (<3 or ≥3 cm) and number of nodules (<4 or ≥4 cm); types of treatment which was divided into surgical, non-surgical or palliative treatment.

Analysis of data was using the SPSS version 15.0. Division of the survival of 1, 3, 5 years will be computed using the Kaplan-Meier (with a median months) and the difference in the survival rate among the factors was tested using log-Rank test. Survival of the various variables was analysis using Cox regression analysis. Significant value was determined using 95% confidence interval, with a value of p<0.05 (2 tails). All of the patients who not completed follow up treatment during this study or the outcome did not know, it will put as a censored cases. All the censored cases was contacted through the phone to know the status of their survival.

## Results

### Descriptive

A total of 299 patients were selected with 204 patients alive/censored case and 95 were died. Out of 204 patients, 211 patients (70.6%) received treatment whether surgical, non surgical or combination of both. A balance of 88 patients (29.4%) did not receive any treatment in which they were in late stage. Most of patients received first treatment of non surgical (54% or 114 patients) and 97 patients (46%) received surgical treatment. Among Chinese ethnic who had HCC, 39.1% of them died compare to others ethnic (X<sup>2</sup>=13.15, p<0.001) (Table 1).

Majority of Chinese or Malay ethnic involved were

age less than 60 years old except for Indian. Most of them were male with tumor size more than 4 cm, number of nodules less than 3 and moderate level of AFP (20-999 ng/L). Among Chinese, 54.5% were smoker while for Non-Chinese majority of them a non-smoker. Indian consumed alcohol more compared to others ethnic with majority of them without Hepatitis (57.9%). Chinese had Child Pugh Class A (55.7%) more while Malay (45.5%) and Indian (5.9%) had more Child Pugh Class B. Surgical treatment was offered most to Chinese (45.3%) while most of Non-chinese coming with late stage and offered palliative treatment (Table 2).

### Survival analysis

**Overall Survival Analysis for HCC Patients Regardless of Types of Treatments:** The overall cumulative survival rate for HCC patients (n=299) regardless of whether they received treatments or not for 1, 3, and 5 years was 52%, 29% and 14% respectively with survival median of 14 months at 95%CI (10.5, 17.5).

**Table 1. Survival Status (died/alive) among Chinese, Malay and Indian**

Ethnic	Status	
	Died (n=95)	Alive (n=204)
Chinese	75 (39.1)	117 (60.9)
Malay	17 (19.3)	71 (80.7)
Indian	3 (15.8)	16 (84.2)

\*X<sup>2</sup>(df)=13.24(2); p=0.001

**Table 2. Demographic, Risk Factors, Clinical Characteristic and Type of Treatment between Ethnicity**

Variables	Ethnic			Total	
	Chinese (n=192)	Malay (n=88)	Indian (n=19)		
Age	<60	62(70.5)	115(59.9)	8(42.1)	185(61.9)
	≥60	26(29.5)	77(40.1)	11(57.9)	114(38.1)
Gender	Male	66(75.0)	157(81.8)	236(78.9)	236(78.9)
	Female	22(25.0)	35(18.2)	63(21.1)	63(21.1)
Smoking	Yes	48(54.5)	78(40.6)	7(36.8)	133(44.5)
	No	40(45.5)	114(59.4)	12(63.2)	166(55.5)
Alcohol consumer	Yes	92(47.9)	24(27.3)	11(57.9)	127(42.5)
	No	100(52.1)	64(72.7)	8(42.1)	172(57.5)
Hepatitis status	Yes	158(82.3)	68(77.3)	8(42.1)	234(78.3)
	No	34(17.7)	20(22.7)	11(57.9)	65(21.7)
Size of tumor	<4cm	67(34.9)	26(29.5)	6(31.6)	99(33.1)
	≥4cm	125(65.1)	62(70.5)	13(68.4)	200(66.9)
No. of nodules	<3	147(76.6)	56(65.9)	10(52.6)	215(71.9)
	≥3	45(23.4)	30(34.1)	9(47.4)	84(28.1)
AFP	<20	68(35.4)	20(22.7)	7(36.8)	95(31.8)
	20-999	82(42.7)	35(39.8)	10(52.6)	127(42.5)
	>1000ng/L	42(21.9)	33(37.5)	2(10.5)	77(25.8)
Child Pugh Class	A	107(55.7)	25(28.4)	5(26.3)	137(45.8)
	B	70(36.5)	40(45.5)	11(57.9)	121(40.5)
	C	15(7.8)	23(26.1)	3(15.8)	41(13.7)
Types of treatment	Surgical	87(45.3)	23(26.1)	4(21.1)	114(38.1)
	Non-surgical	72(37.5)	19(21.6)	6(31.6)	97(32.4)
	Palliative	33(17.2)	46(52.3)	9(47.4)	88(29.4)

**Table 3. Median Survival Duration (months) among Chinese and Non-Chinese**

Variable	Median (months)			Log rank(df)	p value
	Chinese (n=192)	Malay (n=88)	Indian (n=19)		
Age					
<60	21	6	6	0.25(1)	0.614
≥ 60	20	6	20		
Gender					
Male	20	6	20	0.37(1)	0.544
Female	21	5	3		
Smoking					
No	25	8	14	0.79(1)	0.374
Yes	15	5	7		
Alcohol consumer					
No	22	6	14	0.42(1)	0.519
Yes	20	5	3		
Hepatitis status					
No	21	8	16	1.61(1)	0.204
Yes	15	5	6		
Size of tumor					
<4	45	10	20	16.70(1)	<0.001
≥ 4	14	6	3		
Number of nodules					
<3	29	15	16	36.61(1)	<0.001
≥ 3	10	4	6		
AFP(ng/L)					
<20	26	23	20	24.19(2)	<0.001
20-999	22	8	6		
≥ 1000	12	3	3		
Child Pugh Class					
A	44	21	43	59.68(2)	
B	12	6	7		<0.001
C	3	5	2		
Types of treatment					
Surgical	44	25	34	87.52(2)	<0.001
Non-surgical	22	12	20		
Palliative	3	4	2		

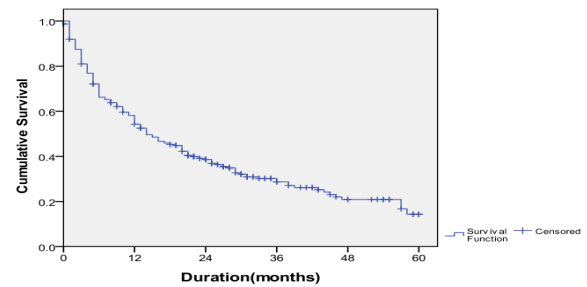
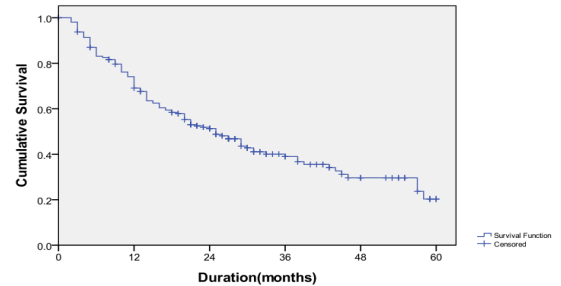
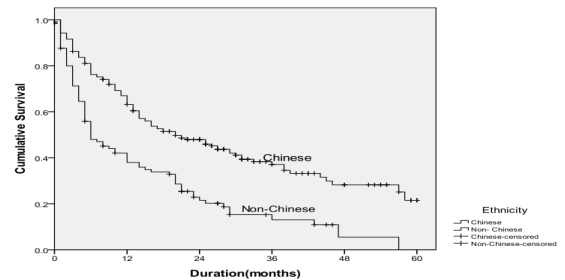
**Table 4. Negative Prognostic Factors among HCC Patients**

	B	p value	cHR*	95%CI	B	p value	aHR**	95%CI
Negative Prognosis Factors								
Malay vs Chinese	0.25	0.167	1.3	0.89-1.85	-			
Indian vs Chinese	0.26	0.359	1.3	0.74-2.26	-			
Tumor size ≥4cm	0.37	<0.001	1.9	1.39-2.60	0.41	0.011	1.5	1.10-2.08
Number of nodules ≥3	0.62	<0.001	2.5	1.85-3.30	0.63	<0.001	1.9	1.38-2.53
AFP > 1000ng/L	0.87	<0.001	2.3	1.63-3.33	0.79	<0.001	2.2	1.55-3.25
Child Pugh Class B vs A	0.77	0.001	2.1	1.52-2.98	0.78	<0.001	2.2	1.56-3.05
Child Pugh Class C vs A	0.69	0.015	1.9	1.13-3.08	0.68	0.006	2	1.22-3.21
Non-Surgical treatment	0.42	0.031	1.8	1.29-2.65	0.56	0.003	1.7	1.21-2.52

\*Simple Cox regression, \*\*Multiple Cox regression; final model was based on backward stepwise. Final model fits well with no multicollinearity and interaction

**Analysis of Survival of HCC Patients Receiving Treatments:** The analysis of survival for HCC patients who received only treatments either surgical or non surgical (n=211) showed survival rate of 68% for 1 year, 38% for 3 years and 25% for 5 years with median of 25 months at 95%CI (20.00, 29.99).

**Analysis of Survival of HCC Patients According to ethnic:** The Chinese had survival rate of 60% for 1 year, 39% for 3 years, and 21% for 5 years with a median of 20 months (95%CI;12.92, 27.08). Meanwhile, the survival rates for Malay patients were 47% for 1 year, 13% for 3 years, and could not last for 5 years with a median of only

**Figure 1. Overall Survival Curve for HCC Patients Regardless of Treatment Types (n=299)****Figure 2. Survival Curve of HCC Patients Receiving Only Treatments (n=211)****Figure 3. Survival Curve Among HCC Patients By Ethnicity (n=299)**

6 months (95%CI; 4.02, 7.98). Indian had median survival of 14 months with 47% for first year, 15% for 3 years and could not survive till five years as shown in Figure 1.

Subgroup analysis according to ethnicity as shown in Table 3, proved significantly that size of tumor, number of nodules, AFP level, Child Pugh Class and types of treatment affected survival by ethnicity. Chinese patients had a good median survival in view of smaller size of tumor (45 months), less nodules involved (29 months), low AFP level (26 months), Child Pugh Class A (44 months) and surgical treatment (44 months) compare to others ethnic.

**Prognostic factor of HCC patients:** The final model of prognostic factor of HCC patients were tumor size, number of nodules, AFP level, Child Pugh Class and types of treatment as shown in Table 4. Malay ethnic with crude HR was 1.3 times to have poor survival compare to Chinese ethnic (95%CI; 0.89, 1.85) while Indian also 1.3 times to have poor survival compared to Chinese (95%CI;0.74, 2.26). It proved that ethnicity was not the main hazard in the prognostic factors among HCC patients as a final model.

## Discussion

Results of the analysis for overall survival for HCC patients either those who had treatment or otherwise was

52% for 1 year, 29% for 3 years, and 14% for 5 years. Survival of those who had only treatment were 68% for 1 year, 38% for 3 years, and 25% for 5 years, implying that treatment resulted better survival. A study conducted in Bologna (Marco et al., 2004) showed the same results with surgery had a better survival (1 and 3 year survival rate; 83%, 65%) while non surgical (radiofrequency ablation) with 78% for 1 year and 33% for 3 year survival rate. It implies that even though Malaysian HCC patients had a better survival rate when seek for the treatment but still lower compare to develop country.

Among Chinese patients, it showed significantly ( $\chi^2=13.15$ ,  $p<0.001$ ) that they survived longer compare to non-Chinese patients. Majority of HCC cases was among Chinese when we compare to other ethnic (192 vs 107 HCC patients) however Chinese had a good survival rate of median 20 months compare to non-Chinese patients. It might due to Chinese patients more aggressive in seeking treatment and coming early with a good Child Pugh Class and Non-Chinese patients prone to delay and came with poor Child Pugh Class as we can see in Table 2. Therefore Chinese ethnic was offered for surgical treatment (45.3%) while non-Chinese more palliative treatment. It explains why Chinese patients had a better survival in which 44 months of survival who had surgical compare to Indian (34 months) and Malay (25 months).

There are marked differences in rates of HCC in different ethnic and racial groups worldwide (Bosch et al., 1999). A study conducted among black Americans and white in Alaska (Dana et al., 2006) showed that black Americans had a lower survival rate compared to white in which majority of black Americans presented with late stage as similar to non-Chinese patients in this study. Asians people had poor survival compared to non-Asians.

Philip et al. (1999) in which become a non-Asians will predict to better survival ( $p=0.007$ ). It's also proved resectable tumors ( $p=0.001$ ) will give a good survival as in this study majority of Chinese undergone surgery.

Non-Chinese, especially the Malays are often keen to delay in visiting hospitals even at bad HCC level, worsening their rate of survival. The Chi Square test did not show any significant difference among ethnic groups with AFP level ( $\chi^2=0.513$ ), Child Pugh Class (Fisher Test=0.218), cancer size ( $\chi^2=0.456$ ) and nodule count ( $\chi^2=0.469$ ). Thereby, we cannot really clearly conclude that the Chinese often seek early treatment. A follow up study such as ethnic based behavioral study or qualitative study, must be conducted to determine why the Chinese patients have better survival compared with the non-Chinese. Not that many research were conducted on HCC patients in multicultural society like Malaysia, making it difficult to make comparisons with other studies.

Even though Chinese had a better survival compare to others ethnic in which 1.3 times better however it is not a predictive factors towards a good survival among HCC patients. Therefore ethnicity is not the main roles in predictive towards better or poor survival in which a little big different with others study (Philip et al., 1999). A study in United States (Avo et al., 2010) found ethnicity was the predictive factor towards survival among HCC patients in which black race had poor survival (HR 1.2)

compare to Asian race.

In conclusion, this study showed that ethnic seems not play a major role in predicting survival of HCC patients. It was instead risk factor which is related to being Chinese. The tolerance towards the treatment or disease itself may influence the survival for different ethnic. However further study need to be done such as qualitative study, behavioral or genetic study so we can get more information in view ethnicity and survival of HCC patients. By knowing that, we may practise the information in promoting good survival of HCC.

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