Barcelona Clinic Liver Cancer and Hong Kong Liver Cancer staging systems for prediction of survival among Hepatocellular Carcinoma patients

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ABSTRACT

Introduction: We aimed to compare the Barcelona Clinic Liver Cancer (BCLC) and Hong Kong Liver Cancer (HKLC) staging systems.

Materials and Methods: This is a retrospective study on patients with newly diagnosed hepatocellular carcinoma (HCC) at the University Malaya Medical Centre between 2011 and 2014. Survival times were analysed using the Kaplan-Meier procedure and comparison between groups was done using the log rank test.

Results: The data of 190 patients was analysed. Chronic hepatitis B was the most common aetiology for HCC (43.7%), but a large proportion was cryptogenic or non-alcoholic steatohepatitis-related (41.6%). Only 11.1% were diagnosed early (BCLC Stage 0-A) while majority were diagnosed at an intermediate stage (BCLC Stage B, 53.7%). The median survival rate was significantly different between the different groups when either of the staging systems was used ($p<0.05$ for all comparisons). However, the two staging systems lacked agreement (weighted kappa 0.519, 95%CI: 0.449, 0.589) with significant difference in median survival rates between BCLC Stage A and HKLC Stage 2, and between BCLC Stage C and HKLC Stage 4.

Conclusion: Both staging systems were able to stratify patients according to survival, but they only had moderate agreement with significant differences observed in two groups of the staging systems.

KEYWORDS:
Classification; liver cancer; survival analysis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide. A total of 841,000 new HCC cases were diagnosed with 782,000 deaths in 2018.[1] HCC has an average five-year survival of <15%.[2] Clinically, determining the cancer stage is important for predicting prognosis of individual patients and when considering treatment options. It also helps in the communication among healthcare providers.[3] Over the last three decades, several HCC staging systems have been proposed. However, few have been validated and there is no single system that has been accepted universally.[4] Studies comparing their discriminatory ability have had conflicting results, in part related to differences in the study populations between Asia and the United States or Europe.[5] Various parameters, including liver function, tumour burden and biology as well as patient factors have been included in the development of staging systems for HCC.

Currently, the Barcelona Clinic Liver Cancer (BCLC) staging system, developed in 1999,[3] is widely used, especially in Europe and the United States of America as it has been validated externally and is endorsed by European Association for the Study of the Liver (EASL), European Organization for Research and Treatment of Cancer (EORTC) and American Association for the Study of Liver Diseases (AASLD).[6] BCLC includes tumour characteristics, liver function and overall physical status in prognostication of HCC patients. The BCLC has been shown to have lower ability for prognostication of advanced HCC.[7] The Hong Kong Liver Cancer (HKLC) staging system was developed in 2014 and was reported to have better prognostic value than the BCLC staging system.[8] Regarding the heterogeneity of the stages B and C in BCLC, HKLC is said to better stratify these patients and to result in better survival outcomes based on more aggressive treatment recommendations.[8,9]

In studies conducted in Korea,[10] Thailand[11] and India,[12] HKLC staging system was seen to predict overall survival (OS) better compared to the BCLC staging system. In a retrospective analysis of North American patients who underwent intra-arterial therapy for unresectable HCC, the HKLC staging system out-performed the BCLC system.[13] However, a study in Singapore showed that the BCLC staging system performed better in predicting OS compared to the HKLC staging system.[14] In this study, about 90% of the patients were of Chinese ethnicity. Furthermore, the capability of HKLC in European cohorts have been challenged.[15,16] In a recent study, the BCLC staging system was found to better predict OS for European patients than the HKLC staging system.[16]

In Malaysia, with a multi-ethnic Asian population, HCC is more prevalent among the Chinese compared to the Malays and Indians. Hepatitis B virus infection is the predominant

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aetiology among Malay and Chinese patients, while alcohol intake and cryptogenic causes, which are now recognized to be largely related to non-alcoholic steatohepatitis (NASH), are the most common among Indian patients.[17] Currently, the BCLC staging system is being used by clinicians in Malaysia. The suitability of the HKLC staging system is yet to be tested in Malaysia. The objectives of this study were to review the aetiology and presentation of HCC in recent years, to test the agreement between the BCLC and HKLC staging systems and to compare the survival times based on the BCLC and HKLC staging system in a cohort of patients with newly diagnosed HCC at a tertiary hospital in Malaysia.

MATERIALS AND METHODS

Patients and Methods

In this study, data of patients who were newly diagnosed with HCC at the University Malaya Medical Centre, Kuala Lumpur, Malaysia between 2011 and 2014 were retrospectively collected and analysed. Identification of patients was based on International Classification of Diseases (ICD) coding. Liver cancer was confirmed using the AASLD guidelines on a multiphasic computed tomography (CT) scan or a magnetic resonance imaging (MRI), where detected lesions had characteristic arterial hypervascularity and washout during the venous phase and raised α-fetoprotein (AFP) levels.[18] Demographic, clinical, laboratory, radiological, treatment, and survival information of each patient were collected. Survival time was defined as the time from the date of first diagnosis of HCC to the date of death or the date of data censoring (31 December 2016). The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the University of Malaya Medical Centre Medical Research Ethics Committee (MRECID No.: 201688-4126, Approval Date: 21 September 2016). Written informed consent was obtained from each participating subject.

Statistical Analysis

Data was analysed using IBM SPSS version 22. Continuous variables were presented as mean ± standard deviation or median (interquartile range) while categorical variables were presented as absolute number (percentage). Patients were grouped into the different stages according to the BCLC and HKLC staging systems. Weighted Kappa statistic was used to test the agreement between the two staging systems. Survival times were analysed using the Kaplan-Meier procedure while comparison between groups was done using the log rank test. Differences in the survival rates were compared using the log-rank test and p-value less than 0.05 was considered as statistically significant.

RESULTS

Patient characteristics

A total of 355 patients were diagnosed with HCC between January 2011 and December 2014. The medical records for all the patients were reviewed. Of these, 165 patients were excluded from the study (incomplete information, 98; liver metastases, 39; recurrent HCC, 20; other liver pathology, 8). The data for 190 patients were analysed. Patient characteristics are shown in Table I. The mean age of the study population was 61.7±12.3 years old and majority were males (73.2%). The study population was predominantly Chinese (64.2%) followed by Malays (23.2%) and Indians (12.1%). The most common aetiology for HCC was chronic hepatitis B virus (HBV) infection (43.7%) while chronic hepatitis C virus (HCV) infection, NASH and alcohol accounted for 8.4%, 7.4% and 6.3% of cases, respectively. Majority of patients (62.1%) had cirrhosis of liver. One third of patients had moderate or diuretic responsive ascites and 10.5% had severe or diuretic refractory ascites. Only 5.8% of patients had hepatic encephalopathy at the time of presentation. Majority of the patients were Child-Pugh A (43.7%) or B (41.1%) and were Eastern Cooperation Oncology Group (ECOG) 0 (55.3%) or 1 (29.5%). Majority of the patients (57.4%) had more than one tumour, and the median diameter of the largest tumour was 7.4 cm. Portal vein thrombosis was seen in 35.8%, while 28.9% had extrahepatic metastasis.

Median overall survival

At the time of data censor, 163 patients (85.8%) had died. The median overall survival was 4 months (95% Confidence Interval (95%CI): 2.8 months, 5.2 months). The number of patients in each stage according to the BCLC and HKLC staging systems are shown in Table II. The median overall survival rate based on BCLC staging is shown in Table III and the corresponding survival curves are presented in Figure 2a. There were no deaths among patients diagnosed as Stage 0. The median overall survival was significantly longer among patients diagnosed as Stage A compared with patients diagnosed as Stage B, among patients diagnosed as Stage B compared with patients diagnosed as Stage C, and among patients diagnosed as Stage C compared with patients diagnosed as Stage D ($p < 0.05$ for all comparisons). The median overall survival based on HKLC staging is shown in Table III and the corresponding survival curves are presented in Figure 2b. The median overall survival rate was significantly longer among patients diagnosed as Stage 2 compared with patients diagnosed as Stage 3, among patients diagnosed as Stage 3 compared with patients diagnosed as Stage 4, and among patients diagnosed as Stage 4 compared with patients diagnosed as Stage 5 ($p<0.05$ for all comparisons).

Comparison between the BCLC and HKLC staging systems

The comparison between staging based on BCLC and HKLC is shown in Table IV. There was moderate agreement between the two classifications with a weighted kappa value of 0.519 (95%CI: 0.449, 0.589). BCLC Stage 0 and HKLC Stage 1 could not be compared as there were no death in BCLC Stage 0. The median overall survival was not significantly different between BCLC Stage B and HKLC Stage 3, and between BCLC Stage D and HKLC Stage 5. However, the median overall survival was significantly longer among patients diagnosed as BCLC Stage A compared with patients diagnosed as HKLC Stage 2, and significantly shorter among patients diagnosed as BCLC Stage C compared with HKLC Stage 4 ($p<0.05$ for both comparisons).

DISCUSSION

In this study on 190 patients with newly diagnosed HCC at a tertiary hospital in Malaysia between 2011 and 2014, we found that most patients were Chinese and that chronic

Table I: Patients' characteristics

Overall population, n = 190	n (%)
Age (mean, SD)	61.7 ± 12.3
Gender	
Male	139 (73.2%)
Female	51 (26.8%)
Race	
Malay	44 (23.2%)
Chinese	122 (64.2%)
Indian	23 (12.1%)
Others	1 (0.5%)
Number of symptoms*	
Asymptomatic	46 (24.2%)
1	36 (18.9%)
2	37 (19.5%)
3	44 (23.2%)
4	20 (10.5%)
5	7 (3.7%)
Etiology	
Hepatitis B	83 (43.7%)
Hepatitis C	16 (8.4%)
Alcohol	12 (6.3%)
NASH-related	14 (7.4%)
Cryptogenic	65 (34.2%)
Cirrhosis	118 (62.1%)
Ascites	
No	106 (55.8%)
Moderate	64 (33.7%)
Severe	20 (10.5%)
Encephalopathy	
No	179 (94.2%)
Precipitant induced	10 (5.3%)
Chronic	1 (0.5%)
Site of metastasis (included multiple sites)	
Lung	29 (15.3%)
Lymph node	23 (12.1%)
Bone	12 (6.3%)
Adrenal	2 (1.1%)
Peritoneum	2 (1.1%)
Pancreases	1 (0.5%)
Cervix	1 (0.5%)
Stomach	1 (0.5%)
Full Blood Count	
Haemoglobin (g/dL)	12.2 (10.2 - 13.7)
White Blood Cells (×10^9/L)	7.9 (5.9 - 7.8)
Platelet (×10^9/L)	192 (132 - 268)
Liver Function Test	
Albumin (g/L)	32 (25 - 37)
Bilirubin (umol/L)	19 (12 - 37)
ALP (U/L)	163 (101 - 263)
ALT (U/L)	56 (34 - 82)
AST (U/L)	83 (39 - 163)
GGT (U/L)	220 (105 - 362)
Others	
INR	1.2 (1.1 - 1.4)
AFP (IU/ml)	130 (9 - 4329)
Creatinine (µmol/L)	79 (62 - 105)
ECOG	
0	105 (55.3%)
1	56 (29.5%)
2	25 (13.2%)
3	3 (1.6%)
4	1 (0.5%)
Number of tumours	
1	81 (42.6%)
2	23 (12.1%)
3	11 (5.8%)
Multiple	75 (39.5%)

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Child-Pugh Grade	
A	83 (43.7%)
B	78 (41.1%)
C	29 (15.3%)
Size of the largest tumour	7.4 (4.2 – 11.4)
Portal Vein Thrombosis	68 (35.8%)
Extrahepatic Metastasis	55 (28.9%)

*The symptoms asked included: Abdominal pain, Loss of weight, Loss of appetite, Jaundice, Abdominal distention, Variceal bleeding

Table II: The number of patients in each stage according to the BCLC and HKLC staging systems

BCLC staging system	HKLC staging system					Total
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	
Stage 0	5	0	0	0	0	5
Stage A	16	0	0	0	0	16
Stage B	9	35	28	23	7	102
Stage C	0	1	9	14	10	34
Stage D	0	0	0	0	33	33
Total	30	36	37	37	50	190

Table III: Median overall survival in months by BCLC and HKLC staging systems

	n	Estimate	95% Confidence Interval	
			Lower Bound	Upper Bound
BCLC staging system				
Stage 0	5	37	-	-
Stage A	16	30	7.5	52.5
Stage B	102	5	2.5	7.5
Stage C	34	2	0.7	3.3
Stage D	33	1	0.5	1.6
Overall	190	4	2.8	5.2
HKLC staging system				
Stage 1	30	42	16.2	67.8
Stage 2	36	10	5.3	14.7
Stage 3	37	4	2.1	6.0
Stage 4	37	3	2.1	3.9
Stage 5	50	1	0.4	1.6
Overall	190	4	2.8	5.2

Table IV: Summary of pairwise comparisons between BCLC and HKLC survival times

	Compared Pairs	No.	Median	95% CI	p-value	Conclusion
Comparison 1	BCLC Stage 0	5	37	-	-	
	HKLC Stage 1	30	42	-		
Comparison 2	BCLC Stage A	16	30	7.5, 52.5	<0.05	Not similar
	HKLC Stage 2	36	10	5.3, 14.7		
Comparison 3	BCLC Stage B	102	5	2.5, 7.5	>0.05	Similar
	HKLC Stage 3	37	4	2.1, 6.0		
Comparison 4	BCLC Stage C	34	2	0.7, 3.3	< 0.05	Not similar
	HKLC Stage 4	37	3	2.1, 3.9		
Comparison 5	BCLC Stage D	33	1	0.5, 1.6	>0.05	Similar
	HKLC Stage 5	50	1	0.4, 1.6		

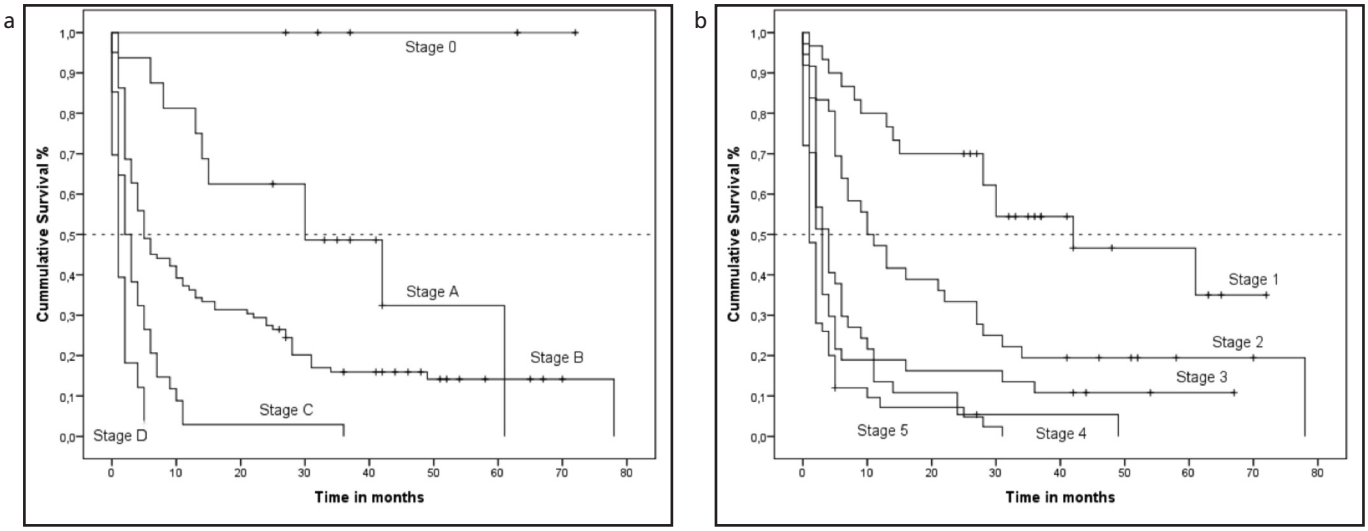

Fig. 1: Survival curves according to (a) BCLC, and (b) HKLC staging systems.

hepatitis B infection remained the leading aetiology, similar to an earlier study conducted at the same centre between 2006 and 2009.[17] This is consistent with the higher prevalence of chronic hepatitis B infection among the Chinese (4-7%) compared with the Malays (2-4%) and Indians (<1%) in the multi-ethnic population in Malaysia.[19] However, there was an over two-fold increase in the proportion of HCC patients with cryptogenic cause, from 16.4% in the earlier study to 34.2% in the current study. This is not including the 7.4% of patients who had a diagnosis of NASH prior to the diagnosis of HCC in the current study. Overall, this is reflective of the changing epidemiology of HCC, where NAFLD-related HCC is expected to increase in Asia, parallel to the increasing prevalence of NALFD in recent years.[20] The current study also found a larger proportion of patients presenting at BCLC Stage B compared with the previous study (53.7% vs. 21.6%). This is largely contributed by a decrease in the proportion of patients presenting at an earlier stage (11.0% in the current study compared with 34.5% in the previous study), which may be accounted for by the marked increase in proportion of HCC in patients with cryptogenic cause or NASH. The later presentation of NAFLD-related HCC may be due to lack of HCC screening because of previously undiagnosed cirrhosis, limitation of ultrasound to detect small tumours because of associated obesity or even the development of HCC in noncirrhotic NAFLD patients.[20]

BCLC and HKLC are the most commonly used staging systems to determine the prognosis and the best treatment modality for HCC patients. However, controversies exist as to which is a better staging system. The BCLC staging system was developed based on a cohort consisting of mainly HCV-infected patients, and most patients had more advanced liver disease.[3,10] In the cohort that the HKLC staging system was derived, the most common aetiology was HBV infection, and majority of patients had preserved liver function. These factors may partly explain the differences observed in the two staging systems.[8] To the best of our knowledge, this is the first study comparing the BCLC and HKLC staging systems in Malaysia. We found that both staging systems were able to stratify patients into distinct groups with significantly different overall survival rates that decreased with increasingly advanced stages. However, there was only a moderate level of agreement between the two staging systems, as indicated by a weighted kappa value of 0.519. Pairwise comparisons between the 5 stages of BCLC and HKLC staging systems showed significant dissimilarities in overall survival between BCLC Stage A and HKLC Stage 2, and between BCLC Stage C and HKLC Stage 4. These can be explained by inherent differences in the two staging systems. HKLC Stage 2 includes intermediate tumours defined as (1) ≤5 cm, either >3 tumour nodules or with intrahepatic venous invasion, or (2) >5 cm, ≤3 tumour nodules and no intrahepatic venous invasion, which are considered as Stage B in the BCLC staging system.[8,21] While the HKLC staging system considers patients with intermediate tumours for potentially curative treatments such as resection, ablation or transplantation, the BCLC staging system offers palliative chemoembolization. Although the HKLC staging system offers a more aggressive treatment approach that may lead to a better outcome in some patients, the inclusion of patients with intermediate tumours as Stage 2 in the HKLC staging system largely explains the significantly shorter overall survival compared with Stage A in the BCLC staging system. Moreover, treatment options were largely guided by the BCLC staging system during the study period.

One of the limitations of our study is that we could not look into the treatment choice based on the two different staging systems and the effect on the overall survival. As aforementioned, treatment options were largely guided by the BCLC staging system during the study period. Moreover, the choice of treatment also depended on the availability of local expertise and resources. Ideally, the performance of the two staging systems in guiding the treatment of HCC should be compared in a randomized study, but this may not be feasible due to the complexity of the disease (both the tumour and underlying liver disease), individual patient factors and expertise of the attending multi-disciplinary team. Second, the study was retrospective and there were missing data that

would not allow us to properly stage some of the patients. Another limitation is that this is a single centre study and may not be generalized to the entire Malaysian population. Nevertheless, we believe our report provides some insight into the demography, aetiology, clinical features and classifications of this disease in Malaysia.

CONCLUSION

In conclusion, while chronic hepatitis B infection is still the leading aetiology for HCC in a multi-ethnic population in Malaysia, a marked increase in cryptogenic and NASH-related HCC has been observed. Both the BCLC and HKLC staging systems were able to stratify patients according to overall survival but the two staging systems only had moderate agreement with marked differences in overall survival observed especially between BCLC Stage A and HKLC Stage 2. Further studies are needed to determine which staging system would perform better in guiding treatment option for HCC patients.

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ETHICAL APPROVAL

This study was approved by the University of Malaya Medical Centre Medical Research Ethics Committee (MRECID No.: 201688-4126, Approval Date: 21 September 2016). Written informed consent was obtained from each participating subject.

CONFLICTS OF INTEREST DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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