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Hepatocellular Carcinoma: A Comparison Between Two Staging Systems for Respectable Tumors

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1. Abstract

1.1. Background: Hepatocellular carcinoma is one of the most common causes of cancer death. Prognosis of resected hepatocellular carcinoma has been a matter of debate with various staging system; the Japanese system and the system of Vauthey et al are two commonly used staging systems. We sought to validate these two systems using survival data from the Surveillance Epidemiology and End Results data (SEER).

1.2. Methods: The SEER database was searched for patients diagnosed with hepatocellular carcinoma (HCC) between 2004-4014. Data extracted included age, race, lesion size, number of lesions, vascular invasion, duration of follow up, overall survival, liver fibrosis and levels of alpha-fetoprotein. Validation of the two staging systems was conducted using discrimination and calibration of the survival data. We propose a new system based on points for lesion size, number and vascular invasion.

1.3. Results: There were 7710 patients who had resection for HCC; in validation of the present staging systems, the Vauthey system performed better than the Japanese staging system. The proposed system performed better than both and it is more user friendly.

1.4. Conclusion: The staging system of resected HCC based on point system for size, number and vascular invasion performed well for prediction of overall survival after resection of HCC.

2. Introduction

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer death. It ranks fifth amongst all cancers and fourth in cancers of the gastrointestinal tract [1]. Majority of cases occur in Asia, in patients with cirrhosis caused by the Hepatitis B virus. In Western countries, alcoholic liver disease and Hepatitis C in drug users are the most common risk factors, followed by non-alcoholic steatohepatitis (NASH/NAFLD) [2]. Surgical resection and liver transplant are the only potentially curative treatment options. Other treatment modalities are often palliative, with the ablation of smaller lesions being an exception. Majority of HCC patients are suitable for palliative treatment only. This is due to both tumor extent and/or underlying liver disease at the time of diagnosis. Patients with HCC are a heterogeneous group. They may present asymptomatically or with clinical features from tumor effect and/or decompensated liver disease [3]. They may present with variable stages of liver decompensation, cardiopulmonary and renal comorbidities, alcohol dependence, and hepatitis virology state [4]. Accurate staging of HCC is important for: estimation of long-term survival, stratifying patients according to pre-treatment survival probability, selecting the most appropriate treatment modality, and for objective comparison of patient outcomes among different treatment centers [5]. The stage at the diagnosis is the most important independent prognostic factor. There are more than 15 HCC staging systems, each developed in different study populations and based on various clinical, radiological, and biochemical parameters [6]. This makes it difficult to select the most appropriate system for treatment decisions. Hence, it is imperative to find a staging system that provides a 'common language' for treating doctors and other health professionals. The four most commonly used systems are: the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) system, the Barcelona Clinic Liver Cancer (BCLC) system, the Okuda system, and the Cancer of the Liver Italian Program (CLIP) score. Generally, there are two types features included in staging systems: pathological and clinical [6]. Sys-

tems that include clinical features attempt to assess underlying liver function. Generally, it has been shown that pathological systems such as the AJCC TNM are better at predicting prognosis in candidates for resection, as most of these patients have adequate liver function (Childs-Pugh A) [6]. In contrast, clinical systems including the BCLC, Okuda, and CLIP systems, are better at predicting prognosis in patients with advanced disease (generally those with poor underlying liver function), who are suitable for palliative therapies only.

The CLIP system incorporates the stage of liver cirrhosis, tumor morphology, alpha-fetoprotein level, and presence of vascular invasion. The Okuda system includes tumor size and measures of cirrhosis [7]. The Okuda and CLIP systems have been said to be more suitable for predicting prognosis in patients with non-respectable lesions [8]. The BCLC system is widely used and stratifies patients into stages according to tumor extent, performance status, Okuda stage, and Childs-Pugh score. The BCLC system includes an algorithm to select a treatment modality based on BCLC stage [9]. Studies evaluating the predictive performance of the BCLC system show conflicting performance [10]. Also, the system is limited in prognosticating for patients who have a single lesion larger than 5 cm, and those with marginally decompensated liver disease who usually fall under group B of this system [11]. For these reasons the system is often not used in clinical decision making [11]. The American Joint Committee on Cancer (AJCC) classification is based on the universally accepted TNM classification scheme. It is validated in patients treated with hepatic resection or transplant [10, 12]. In 2002, Vauthey, Lauwers [12] developed a 'simplified' system by combining prognostic groups from the previous AJCC TNM system which had similar prognosis. The system is based on tumor size, number of the lesions, and vascular invasion. This was adopted as the 6th edition of the AJCC TNM system in 2002 (simplified staging system; SSS). The 7th edition of system subdivided stage III into 2 groups: stage IIIA included only multiple tumors or any tumor larger than 5 centimeters (T3a); stage IIIB included only tumors of any size involving a major portal vein or hepatic vein (T3b) [13]. However, validation studies showed conflicting results on the prognostic performance of this edition. Only some demonstrated the ability of the system to stratify stage III into sub-stages. The 8th edition subdivided tumors according to size (less then or greater than 2 cm). This update was based on data that showed there was good survival in patients with tumors less than 2 cm in size [14]. A recent evaluation of the AJCC 8th edition suggested that future revisions should consider distinguishing solitary tumors >2 cm with vascular invasion, from multifocal tumors that are 5 cm or less, as these groups had differences in survival but are grouped together in the current system [15]. Further, it was suggested to consider the prognostic impact of vascular invasion for multifocal tumors that are less than 5 cm, as those with vascular invasion had worse survival [15]. Recently, a large validation study of the AJCC 8th edition, found that the system failed to show a difference in outcome for patients with IB and II tumors [16].

In 2007, a Japanese TNM staging system was developed [17]. Like the AJCC TNM system, the Japanese TNM system was developed in HCC patients undergoing hepatic resection [17]. The Japanese TNM system stages patients based on tumor size, number, and vascular invasion in a simple and predictable manner. In the initial development study, the system performed better than the AJCC TNM system for predicting prognosis in HCC patients undergoing resection with curative intent [17]. Predicting prognosis for patients with lymph node involvement is a limitation of both the AJCC and Japanese TNM systems. Both systems were developed with only a small proportion of patients with lymph node data [12, 17]. This is because lymph node dissection is not commonly performed during hepatic resection, and only some patients undergo portal node dissection. Therefore, accurate N staging does not often occur. In both systems, patients with lymph node involvement are combined into another prognostic group [18]. From the literature it is clear that some staging systems are more appropriate for certain subsets of HCC patients. This retrospective study is an attempt to compare and validate the AJCC and Japanese TNM systems in a population of patients who underwent surgical resection for HCC. We used data extracted from the Surveillance, Epidemiology and End Results (SEER) group database.

3. Methods

3.1. Study cohort

Prospectively collected data from the Surveillance Epidemiology and End Results (SEER) database (US National Cancer Institute) was searched for patients who were diagnosed with HCC from 2004-2014 [19]. The SEER group collects data on all cancer reported from 20 geographical areas of the United States. This represents approximately 28% of the US population. The database was searched for HCC site codes C22 using the site and histology codes according to the International Classification of Disease 3rd edition (ICD-0-3) [20]. We used the histological codes to identify patients with HCC that was resected and confirmed histologically (codes: 8170-8175). Unusual histological variants and vague histology codes (8000-8003), as well as undetermined histology/"carcinoma NOS" codes (8010-8013) and undifferentiated carcinoma codes (8120-8122) were not included in the final analyses. Adult patients (18 years or more) who underwent surgical resection for HCC that was histologically confirmed, with no evidence of distant metastasis, were identified for the time period from 2004 to 2014. We excluded from the analyses: patients under the age of 18, patients who did not undergo liver resection, patients who had a liver transplant, patients who had some form of ablative or palliative procedure(s), and patients who did not have histologically confirmed HCC. Data collected included: age, gender, ethnicity, marital status, size, number of lesions, presence of vascular invasion, type of surgery, number of harvested lymph nodes and positive nodes in portal lymph nodes dissection (if nodal dissection was completed), Japanese TNM stage, AJCC TNM stage (6-8th editions), presence of liver fibrosis, tumor grade, long-term survival.

Data on the presence of liver fibrosis, lymph node dissection, and levels of Alpha-fetoprotein (AFP) are sparsely reported and emerged more in recent years.

3.2. Statistics

Descriptive statistics were reported as mean and standard deviation (s.d), or median and inter-quantile range (IQR). The Chi-squared (χ^2) test was used for comparing categorical variables. The Mann-Whitney U test was used to compare continuous variables (not normally distributed). Calculation of 95% confidence intervals (CI) was based on the Wald method. Overall survival was estimated using Kaplan-Meier survival curves and compared using the log-rank-Mantle-Cox methods. A Cox proportional hazards model was used to estimate overall survival using known prognostic factors in the literature (lesion size, lesion number, and vascular invasion). Hazard ratios were calculated based on Wald test and 95% CIs were calculated from the Cox model.

A Cox proportional hazards model was designed to compare prognostic factors and assess the effect of each factor on the outcome (overall 5-year survival). The results were reported as medians with 95% CI for survival times. The hazard ratio and Beta coefficient for each prognostic factor was calculated [21]. The discrimination and calibration performance of both the Vauthey SSS and Japanese TNM systems were evaluated by binary logistic regression, with calculation of Harrel's C index and Somers' D. Based on the Japanese TNM and the Vauthey SSS staging systems, we classified patients by a modified system which we developed, which assigned a point to each known prognostic factor. Points were assigned for lesion size, multiple lesions, and vascular invasion (see below). This stratified patient with resected HCC into three stages, where patients with a HCC less than 5 cm with no vascular invasion were categorized as T1. All other patients staged according to the number of points they received (see below). This scale assumes that patients with multiple lesions, with one larger than 5 cm with vascular invasion (4 points) is non-respectable according to the BCLC system [9]. We chose 5 cm as the cutoff for tumor size as this has been shown to be most appropriate previously [12]. Further, Cho, Gonen [22] developed a prognostic nomogram for resected HCC which showed that tumors more than 5 cm in size, were an adverse prognostic factor. They divided tumor size into 2 categories; those 5 cm or less, and those more than 5 cm [22]. Based on these findings we classified tumor size into these two categories.

Box 1. Our proposed model.

Size: less than 5 cm = 1 point; more than 5 cm = 2 points
Vascular invasion 1 point
Multiple lesions 1 point
1. T1: single lesion less than 5 cm with no vascular invasion (1 Point)
2. T2: single lesion less than 5 cm with vascular invasion;
or single lesion greater than 5 cm with no vascular invasion; or multiple
lesions with vascular invasion no more than 5 cm (2 points)
3. T3: Single HCC more than 5 cm with vascular invasion; or multiple lesions any of them greater than 5 cm with no vascular invasion
(3 Points)

To validate the models, we divided patients randomly into two groups: a test and validation group. Boot strapping was used in both samples for internal validation. The discriminative performance of each staging system was assessed using Harrel's C index derived from the Cox proportional hazards model. Also, an ROC curve was developed from binary logistic regression which included time-to-event data for 5-year survival. The standard error of the C index was computed empirically based on 1000 bootstrap samples. A C index of 0.5 indicates that the discrimination of the model is no better than random prediction (chance), whereas a C index of 1 indicates perfect discrimination. We compared the prognostic performance of the Japanese TNM, Vauthey SSS, and proposed system using measures of discrimination and calibration. The discrimination power of the new prognostic index was evaluated by calculation of the C index and Sommers' D statistic. The calibration accuracy of each prognostic index was compared using the Hosmer-Lemeshow χ^2 goodness of fit test based on binary logistic regression [23-25]. A separate Cox proportional hazards model was used to assess the effect of other variables on the prognostic index such as: age, gender, AFP levels, and level of liver fibrosis. Data analysis was performed with SPSS Inc. (Chicago, Illinois, version 23).

3.4. Results

This study included a cohort of 7710 patients with data retrieved from the SEER database for the time period of 2002 to 2014. These patients were diagnosed with HCC and underwent liver resection for curative intent. There was a steadily rising number of reported cases of HCC throughout the study period. Median age was 61 years of age. 74.5% of patients were men. Majority of patients were Caucasian (64%) or Asian (27%). The remainder (9%) were of another ethnic background. The demographics are shown in (Table 1). Variables that are reported include: gender, age, AJCC TNM stage (7th and 8th editions), SSS stage (AJCC 6th edition), Japanese TNM stage, lymph node status, number of lesions, presence of vascular invasion, survival outcome, AFP level, and presence of liver fibrosis (Table 1). As mentioned previously, only a proportion of patients had information regarding AFP level and liver fibrosis. Only 1156 patients (15%) were reported to have undergone lymph nodes dissection, of whom 131 patients had proven lymph node metastases. The number of lymph nodes harvested ranged from 1 to 6, with a median of three lymph nodes harvested.

Table 1: Demographic feature of patients who had curative surgery (7710 patients)

	Number	Percentage
Gender		
Males	5860	76.0%
Females	1850	24.0%
Tumor size		
</= 2 cm	1548	20.0%
>2 cm and <5 cm	3740	48.6%
>/=5 cm	2422	31.4%
Number		
Single	5660	73.4%
Multiple	2050	26.6%
Vascular Invasion		
Present	1386	18.0%
Absent	6324	82.0%
T stage (AJCC 8th edition)	902	
T1a	3223	11.7%
T1b	2452	41.8%
T2	925	31.8%
T3	208	12.0%
T4		2.7%
Nodal dissection		
Performed	1156	15.0%
Positive nodes	131 of total	1.7% of total
Not reported	6554	85.0%
Fibrosis		
0	843	10.9%
1	1563	20.3%
Not reported	5304	68.8%
Alpha-fetoprotein (AFP) level		
10 (elevated)	3189	41.4%
20 (normal)	1866	24.2%
30 (borderline)	8	0.1%
Not reported	2647	34.3%
Outcome		
Alive	4680	60.7%
Died	3030	39.3%
Staging SSS (Vauthey)		
1	4549	59.0%
2	2313	30.0%
3	848	11.0%
Japanese TNM system		
1	925	12.0%
2	4087	53.0%
3	2544	33.0%
4	154	2.0%
Prognostic index (Proposed score)		
1	3161	41.0%
2	3238	42.0%
3	1311	17.0%
AJCC TNM 7th Edition		
IA	878	11.4%
IB	3215	41.7%
II	2422	31.4%
IIIA	863	11.2%
IIIB	201	2.6%
IVA	131	1.7%

3.5. Survival analyses by size, vascular invasion, and number of lesions

The difference in survival between patients with single or multiple tumors was estimated using Kaplan-Meier curves, and then compared with the log-rank test. Median survival was 79 months for patients with single tumors (95% CI 72-85 months), compared with 77 months in patients with multiple tumors (95% CI 65-88 months; p=0.016). As expected tumor size had a significant effect on overall survival, and patients with larger tumors had poorer survival. Patients with tumors equal to or less than 2 cm, had a median survival of 93 months (95% CI 90-96 months). Patients with tumors greater than 2 cm but less than or equal to 5 cm, had a median survival of 81 months (95% CI 79-83 months). Patients with tumors larger than 5 cm had a mean survival of 59 months (95% CI 56-61 months; p<0.0001). Vascular invasion had a significant impact on survival. Patients with vascular invasion had a median survival of 46 months (95% CI 40-51 months). Comparatively, those with no vascular invasion had a median survival of 87 months (95% CI 80-93 months; p<0.0001) (Figure 1).

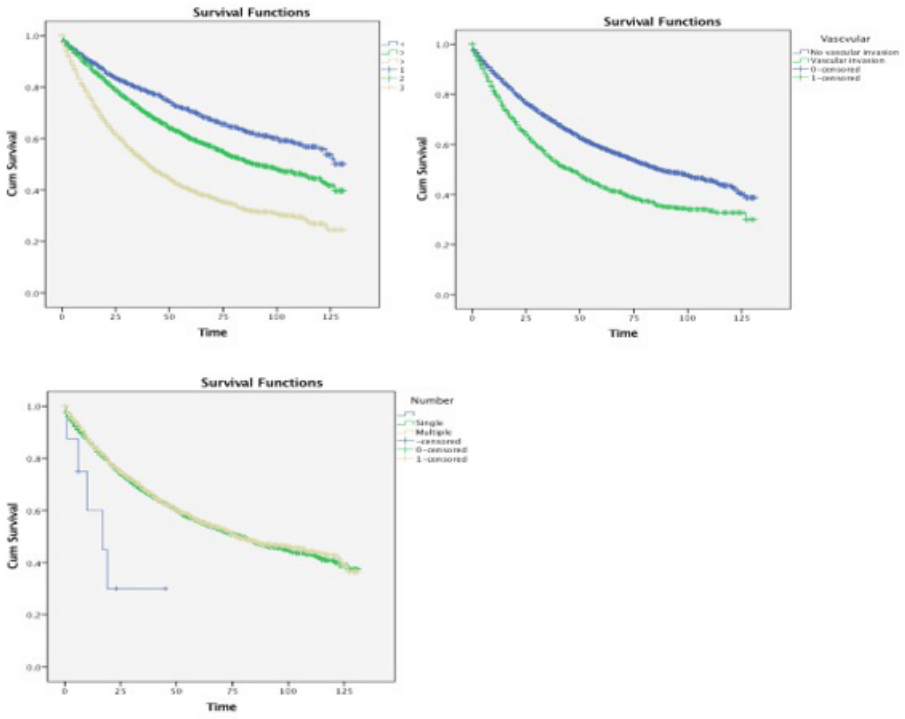

Figure 1: Kaplan-Meier estimated survival curves by tumor size (a), vascular invasion (b), and number of lesions (c)

3.6. Multivariate analysis

The significant and known predictors of survival were entered into a Cox proportional hazards model. The results of this multivariate analysis is shown in (Table 2). The significant prognostic factors identified by multivariate analysis included: size (P=0.003), age (P=0.001), presence of vascular invasion (P<0.0001), and AFP level (P=0.001). The hazard ratio and associated standard errors for each variable are included. Presence of vascular invasion had the greatest impact on survival (hazard ratio 0.594), followed by AFP level, then age. Although lesion number did not reach significance in our model, we included this predictor in our proposed scheme as it has been shown to be a significant predictor in the literature [12, 17].

Table 2: Multivariate Analysis by Cox Proportional Hazards Model

Variable	P value	Hazard Ratio	95% CI	
Size	0.003	1.001	1.001	1.002
Number	0.792	0.980	0.844	1.138
Vascular	<0.0001	0.594	0.505	0.700
Gender	0.867	0.987	0.839	1.161
Age	0.001	1.023	1.016	1.031
Fibrosis	0.165	1.345	0.967	1.297
AFP	0.001	1.121	1.165	1.563

3.7. Proposed classification system

Based on these results and known predictors from the literature we stratified patients into 3 groups based on: lesion size, presence of multiple lesions, and presence of vascular invasion. The proposed tool was similar to the system (SSS; AJCC 6th edition) developed by Vauthey et al [7]. As described above, our tool stratified patients into three T groups. Patients with a single lesion less than 5 cm and without vascular invasion are designated T1. Patients with a single lesion less than 5 cm and with vascular invasion; or with a single lesion greater than 5 cm and without vascular invasion; or with multiple lesions and with vascular invasion and no more than 5 cm in size are designated T2. Patients with a single lesion greater than 5 cm and with vascular invasion, or with multiple lesions any of which are greater than 5 cm are designated T3 (see Box 1). Kaplan-Meier survival curves for the different staging systems are shown in (Figure 2,3). Median and 5-year survival by the different staging systems are shown in (Table 3). The survival curves in the proposed scoring system for these 3 groups were clearly separate (Figure 2c). The differences in survival were also significant (P<0.0001).

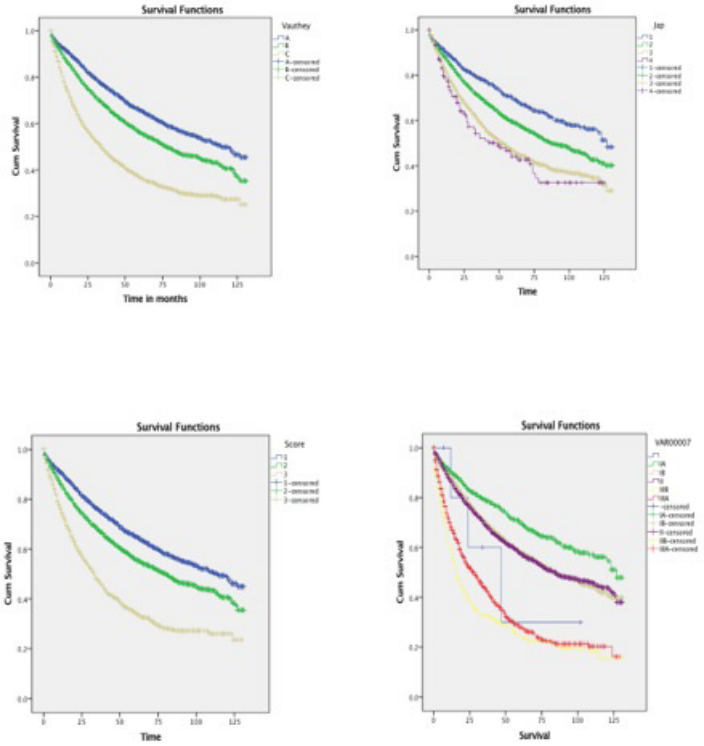

Figure 2: Kaplan-Meier estimated survival curves according to the Vauthey (a), Japanese (b), and proposed system (c), AJCC TNM 8th edition (d).

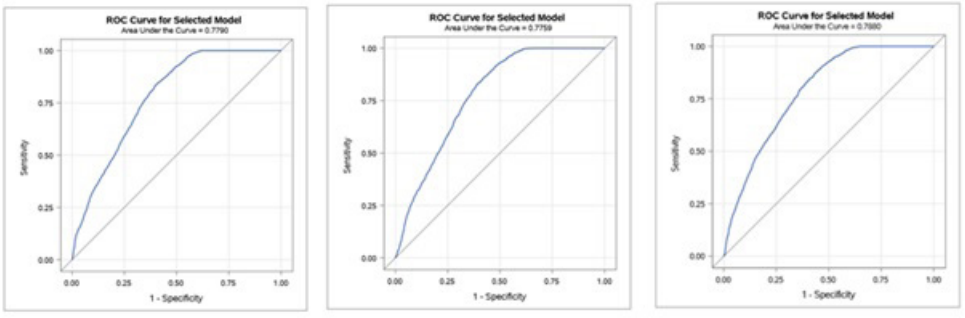

Figure 3: ROC curve for the Vauthey (a), Japanese (b), and proposed systems (c) with AUC calculation

Table 3: Kaplan-Meier estimated survival curves by classification using proposed model

System	Median survival	95% Confidence interval		P Value	5 Years Survival
Vauthey (SSS)		113	125		28%
A	119			0.0001	
B					
C	78				
	34	69	86		29.8%
		30	37		15.7%
Japanese TNM					
1	127	112	138	0.0001	35%
2	87	79	94		26.5%
3	53	48	57		24%
4	49	28	69		24%
Proposed Score					
1	114	103	125	0.0001	30%
2	80	72	87		28%
3	34	30	37		25%

3.8. Discrimination and calibration of the different staging systems

In addition to bootstrapping that was performed initially for internal validation of the proposed tool, a total of 7710 patients in the study were randomly assigned to a training or validation sample (50% of patients in each group). We evaluated the performance of the new model in terms of discrimination and calibration. Discrimination was assessed. This is the ability of the model to correctly classify patients according to their risk. Discrimination was informally appraised by assessing the separation of the KM curves for each classification of the new score. As described above there was good separation between each of the 3 classifications (Figure 2). In addition to this we developed a ROC curve for the proposed model and calculated the AUC and c index (Figure 3). The c index (and AUC) value of 0.79 shows that the proposed model has a high discriminative ability. In other words, for a randomly selected pair of patients from this data, the patient who lived longer was predicted to do so by the staging system. Next we assessed calibration of the proposed model using binary logistic regression and the Hosmer and Lemeshow goodness of fit test. This is the agreement between observed and predicted risk. In addition to this we also produced a calibration plot. This was done by comparing observed proportion of events against predicted probabilities based on 10ths of risk groups, for specific time points. The Hosmer-Lemeshow χ^2 test was used to determine the goodness of fit between observed events and predicted probabilities. The χ^2 value for the proposed model was 148.9188 ($p<0.0001$). The null hypothesis for this test is good fit between observed proportions and predicted probabilities. Therefore, the significance of this value indicates there is poor fit, and that the model lacks calibration. However, the Hosmer-Lemeshow χ^2 test has been shown to be overly sensitive with very large samples which may explain the significance of this test [26].

3.9. External validation of the Vauthey and Japanese systems

For external validation of the Vauthey and Japanese systems, we again evaluated the performance of these models in terms of discrimination and calibration. Firstly, the survival curves using the Vauthey model were clearly separate (Figure 1). The differences in survival were also significant ($P<0.0001$). The median survival (95% CI) and 5-year survival rate of patients in the groups were as follows: 115 (113-125) months for A. 78 (69-86) months and for B. 34 (30-37) months and for C (Table 3). The Japanese model also had separate survival curves. However, this was less evident for later survival times for the T3 and T4 stages. The difference in survival was significant ($P<0.0001$). The median survival (95% CI) and 5-year survival rate of patients in the groups were as follows: 127 (112-138) months and for T1; 87 (79-94) months and for T2. 53 (48-57) months and for T3; 49 (28-69) months for T4 (Table 3).

A ROC curve was created for both systems, and the associated AUC and c-index was calculated (Table 4). The Vauthey model had better discriminative ability as indicated by a higher AUC compared with the Japanese model (0.7790 vs 0.7759). Next, we assessed calibration of both models. We conducted the Hosmer-Lemeshow χ^2 test on each model based on binary logistic regression. For the Japanese model the χ^2 value was 173.3418 ($p<0.0001$). The χ^2 value for the Vauthey model was higher at 226.8870 ($p<0.0001$). A lower score indicates less observed difference between observed proportions and predicted probabilities, and thus the Japanese model showed better calibration for this population. Nevertheless, both χ^2 values were significant (null hypothesis is rejected), indicating that observed pro-

portions and predicted probabilities were significantly different. This may be explained by the limitations of the Hosmer-Lemeshow χ^2 test as described above.

3.10. The impact of Alpha-fetoprotein on survival

Only a proportion (65.7%) of patients in this population had Alpha-fetoprotein level reported. Nevertheless, patients who had normal levels (code 20) had better survival compared with patients with elevated levels (code 10). Median survival was 90 months (CI 79-100 months) for patients with normal levels, compared with 63 months (CI 57-68 months) for those with elevate levels ($p < 0.0001$; (Figure 5).

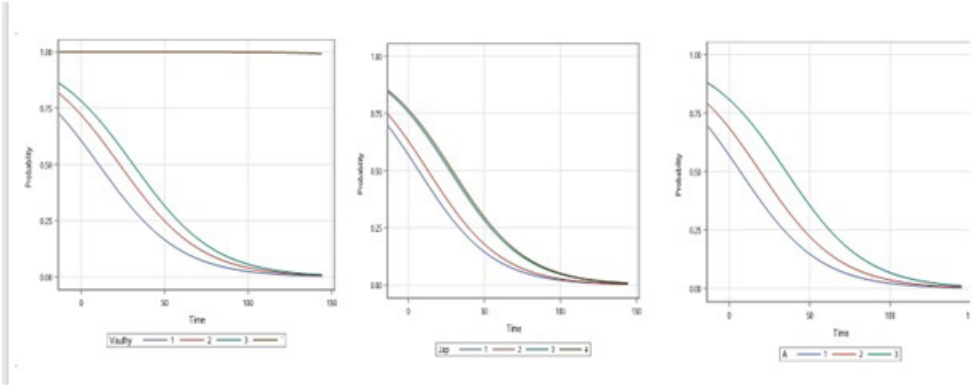

Figure 4: Survival by different staging systems

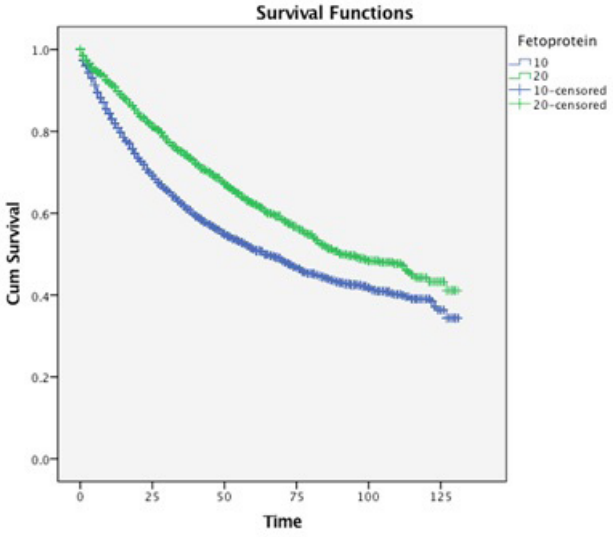

Figure 5: Survival by alpha-fetoprotein level (10 elevated, 20 normal)

Table 4: Discrimination of predictive statistics for different systems

	Vauthey SSS	Japanese TNM	Proposed Score
Concordant pairs	77.7%	77.4%	78.4%
Discordant pairs	21.9%	22.2%	21.2%
Ties	0.5%	0.4%	0.4%
Sommer's D	0.558	0.552	0.572
C statistic	0.779	0.776	0.786
AUC	0.78	0.77	0.79

4. Discussion

Resection of HCC is the only chance for cure in patients suitable for surgical intervention (Childs-Pugh stage A). Surgery is a radical and meaningful treatment with good overall survival [27]. This is particularly applicable for T1 and T2 tumors (small HCC) [27, 28]. Even in patients with tumors that are large, multi-nodular, or with macrovascular invasion, surgery has been shown to have acceptable overall survival benefit [28]. Based on the results from the SEER database, surgery is still under-utilized in patients with potentially respectable HCC due to variety of reasons such as: patient age, tumor factors, associated liver disease, and hospital factors [29]. Nevertheless, advancement in liver surgery has increased the indication for hepatic resection, with more patients being suitable for surgical treatment with reasonable survival outcome [30]. Further, improvements in surgical techniques and postoperative management has reduced hospital mortality [31]. In patients that are unsuitable for traditional

resection due to insufficient disease-free liver remnant, portal vein embolization is a proven strategy to increase liver functional reserve and provides a bridge to curative resection, with comparable survival outcome in these patients [32]. Sequential trans-arterial chemo-embolization (TACE) and portal vein embolization prior to surgery, is another strategy that could expand rates of surgical resection and potentially increase overall and recurrence free survival results, compared with only portal vein embolization prior to resection [33, 34].

This study was a comparison and validation of the Japanese TNM and the Vauthey SSS systems [7]. Our studies focus was to compare staging systems for prognosticating surgical candidates i.e. Childs-Pugh A patients with good functional liver reserve. Other systems such as the BCLC, are more suitable for patients with poor liver function (Childs-Pugh B and C). These patients are candidates for palliative therapies only (loco-regional or systemic therapy). It is clear from the literature that there is no 'one size fits all' staging system for HCC. Pathological staging systems such as the AJCC and Japanese TNM systems have been shown to be more suitable for predicting prognosis for HCC patients that are candidates for resection [17]. From our analysis it seems that the Vauthey model had better discriminative ability, while the Japanese model had better calibration.

Recently it seems that prognostic models for patients with HCC are becoming increasingly complex [13, 35]. Our group is of the view that a simpler staging tool that is practical is more likely to be universally accepted. We suggest a simple prognostic index for resected HCC by minor adjustment/reclassification the scoring system suggested by Vauthey et al [7]. This could be easily implemented in clinical practice. The proposed scoring system had very good discriminative ability with c-statistic of 0.79, higher than both the Japanese TNM and SSS systems. Our system is considered to have powerful discrimination [36]. Accuracy of the proposed scoring system was described by the measure of calibration (whether predicted probabilities agree with observed proportions) [37]. The Hosmer-Lemeshow χ^2 test was significant for all 3 models (indicating poor calibration). However, this test has been shown to be limited in studies with larger power. Although a crude measure, the χ^2 values alone are a better indication of calibration in this setting, with smaller values indicating better agreement between predicted probabilities and observed proportions. As our score had the lowest χ^2 value (148.9188), it showed better calibration than the other two models.

We also evaluated the current 8th edition of the AJCC system (Figure 2d). There was poor separation between the groups of this system. Specifically, there was similar survival between the IB and II groups, as well as the subgroups of group III. However, our focus was on a simpler system for prognostication, so we decided not to directly compare this iteration of the AJCC system with our proposed model. Rather, it was more appropriate to compare our model with the 6th edition (SSS), as this system was the basis of development for our proposed model.

The prognosis of patients who undergo radical surgical treatment for HCC depends on disease stage as estimated by known prognostic factors such as size, presence of multiple lesions, and vascular invasion [7, 38]. These factors are included in most staging systems including AJCC, CLIP, Barcelona clinic and the Japanese TNM staging system. The incidence of vascular invasion seems to increase with tumor size. 69% of HCC lesions measuring more than 10 cm have evidence of vascular invasion [39]. Previous studies have shown an association between size and vascular invasion. It is suggested that this may explain why tumor size has less effect on survival, when studies control for vascular invasion [28, 40]. Interestingly, lesion number was not a significant prognostic factor in our Cox model. This may be due to an association between lesion number and one of the other two variables in our proposed prognostic model. In any case, we chose to include lesion number in our model as it is a known predictor in the literature [38].

One limitation of our study is the assignment of equal weighting to all 3 prognostic factors. However, as simplicity was a priority, we chose to neglect the relative weights of each factor in our system. Although we could have included additional prognostic factors in our system, we included only three, as this makes our system simple for clinicians to use, while conferring good prognostic performance. Further, more complex systems tend to give more overoptimistic predictions, which is not ideal in HCC staging [41].

Microvascular invasion in HCC is a known prognostic factor but the difference between that and macrovascular invasion is not clear [42]. The extent of vascular invasion and number of vessels invaded is variable and might influence the outcome [43]. Patients who had resection of multinodular HCC tend to have more microvascular invasion that seems proportional to the number of lesions [43, 44]. Invasion of a muscular layer of a blood vessel, particularly if it is more than 1 cm away from the lesion was shown to reduce overall survival and associated with early recurrence. The risk was found to be proportional to the number of involved blood vessels [43, 45].

There are other prognostic factors that are discussed in the literature. Alpha-fetoprotein level is a prognostic factor that is known to have significant impact on survival. Particularly in patients with HCC more than 10 cm in size and with a degree of liver fibrosis [39]. Alpha-fetoprotein is incorporated in the prognosis of CLIP staging system for HCC [46, 47]. Age had a significant impact on overall survival in the current study. However, it is not incorporated in any staging system have shown that the MELD score can estimate survival after HCC resection. Three-year survival was 66% when the MELD score was less than or equal to 9, and 32% when MELD score was greater than 9 [48]. The MELD score accounts for liver disease, which has a significant effect on overall survival. Liver fibrosis is another factor that affects long term survival but is difficult to reliably assess [39]. Serum albumin, resection margins, and estimated intraoperative blood loss has been also suggested to have an impact on overall survival [49, 50]. With increasing advancement in diagnostics, future models could incorporate other factors in the prognostic staging system for resected

HCC that could potentially include Alpha-fetoprotein levels, patient age, MELD score, liver fibrosis and possibly portal hypertension.

The study is limited by the complex statistics that relies on traditional validation procedures (discrimination and calibration). These procedures are not standardized in the current literature. We used the traditional and popular methodology of the C statistic for discrimination, and the Hosmer- Lemeshow goodness of fit for calibration. These measures are criticized as a crude assessment methods [25]. Our model should be externally validated in another population to determine whether it can be generalizable to other patients.

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