ORIGINAL RESEARCH

Selecting an Optimal Staging System for Intermediate-Stage Hepatocellular Carcinoma: Comparison of 9 Currently Used Prognostic Models

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Purpose: It remains unknown which staging system is best in predicting the survival of patients with intermediate stage hepatocellular carcinoma (HCC). We aimed to investigate the performance of nine currently used HCC staging systems.

Patients and Methods: Between 2005 and 2014, a large cohort of 880 consecutive patients with intermediate stage HCC and sufficient data for utilization in all staging systems were enrolled. The prognostic performance of each staging system was compared. Independent prognostic variables were also identified.

Results: Multivariate analysis revealed that alkaline phosphatase (ALP), aspartate aminotransferase (AST), etiology, alpha-fetoprotein (AFP), Child-Pugh stage, tumor size, and tumor number were independent prognostic factors for survival. In the entire cohort, the Hong Kong Liver Cancer (HKLC) staging system was associated with the highest Harrell's c-index and lowest Akaike information criterion value in comparison with other systems. In subgroup analysis according to treatment strategy, the HKLC staging system remained the best prognostic model in patients undergoing hepatic resection (n=222) or transarterial chemoembolization (n=658). Additional prognostic factors of AST, ALP, etiology, and AFP improved the discriminatory ability of HKLC.

Conclusion: The HKLC staging system is stable and consistently the best prognostic model in all patients with intermediate-stage HCC and in patients subjected to different treatment strategies. Selecting an optimal staging system is helpful in improving the design of future clinical trials in intermediate stage HCC.

Keywords: hepatocellular carcinoma, intermediate-stage, staging system, prognosis, overall survival, hepatic resection, transarterial chemoembolization

Introduction

The purposes of cancer staging are to accurately predict the patient's prognosis and to determine the appropriate intervention. Hepatocellular carcinoma (HCC) is somewhat unique in that it usually affects patients with underlying liver disease, and both the tumor burden and liver function must be carefully evaluated at the time of the prognostic prediction and treatment recommendation. Over the past several decades, many organizations have proposed staging systems for HCC (Table 1) based on tumor burdens and liver reserve to guide accurate treatment programs with a good prognostic value. Among these systems, the Barcelona Clinic Liver Cancer (BCLC) staging

system[1] has been validated by several groups in the United States and Europe and provides the best stage classification system and guidance for HCC treatment assignments.[2,3] However, intermediate-stage (BCLC-B) HCC includes a heterogeneous group of patients with different tumor burdens, liver functions and other associated factors.[4]

Transarterial chemoembolization (TACE) is recommended by the BCLC guideline as the first-line treatment for intermediate-stage HCC. TACE results in varying clinical benefit in the BCLC-B group.[5–7] Recently, the role of hepatic resection (HR) was reviewed[8,9] and the question "What treatment yields the best outcome for patients with BCLC stage B HCC?" has been under intense debate.[10–17] Thus, a staging system is needed to help predict survival outcomes and also help to determine the optimal medical care, especially in this era of controversy regarding choices for the treatment of intermediate-stage HCC. Additionally, there is a pressing need to properly interpret data from clinical trials of patients with intermediate-stage HCC. Whether any of the

staging systems have more information in patients with intermediate-stage HCC, and whether other variables not included in these systems have prognostic significance is unknown.

Moreover, when evaluating the performance of a staging system, we believe that the type of treatment and its efficacy should be considered. For this reason, we evaluated the prognostic power of each staging system in a specific cohort of patients after TACE and HR treatments. We also explored whether the staging systems identified as the best for the population of intermediate-stage HCC could be improved by the inclusion of additional prognostic factors identified in a multivariate analysis.

Patients and Methods
Eligibility

We retrospectively identified patients with HCC who were evaluated by clinical oncologists in the Department of Hepatobiliary Oncology of Sun Yat-sen University Cancer Center between February 2005 and August 2014.

Table 1 The Variables Included in Nine Staging Systems for Intermediate Stage HCC

Staging System	Performance Status	Liver Function	Tumor Status	Alpha-Fetoprotein	Staging Category
TNM	×	×	Number of nodules, tumor size, portal vein thrombosis, and metastasis	×	II, III
CLIP	×	CTP class	Tumor extent greater or less than 50% area of liver, and portal vein thrombosis	<400 or ≥400 ng/mL	Score 1 to 4
Okuda	×	Albumin, bilirubin, and ascites	Tumor extent greater or less than 50% area of liver	×	I, II, III
CUPI	Presence of symptoms	Bilirubin, alkaline phosphatase, and ascites	TNM	<500 or ≥500 ng/mL	Low, intermediate, high risk
GRETCH	Karnofsky index	Bilirubin, alkaline phosphatase	Portal vein thrombosis	<35 or ≥35 µg/L	Low, intermediate, high risk
JIS	×	CTP class	TNM	×	Score 1 to 3
Tokyo	×	Albumin, bilirubin	Number of nodules, tumor size <2 or >5 cm or between 2 cm and 5 cm	×	Score 1 to 8
BCLC B Sub-Stage	ECOG score	CTP score	Up to seven	×	B1, B2, B3, B4
HKLC	ECOG score	CTP class	Nodules ≤3 or >3, tumor size ≤5 or >5 cm, portal vein thrombosis, metastasis	×	I, IIa/b, IIIa/b

Abbreviations: TNM, tumor node metastasis; CTP, Child-Turcotte-Pugh; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; JIS, Japan Integrated Staging; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HKLC, Hong Kong Liver Cancer.

Patients were included if they were initially diagnosed with intermediate-stage HCC and received TACE or HR as the first-line treatment for HCC at our institute after diagnosis. HCC was diagnosed by histology or radiologic criteria of two imaging studies (eg, ultrasound, computed tomography [CT], or magnetic resonance imaging [MRI]) according to the European Association for the Study of the Liver diagnostic criteria.[18] Intermediate-stage (BCLC-B) HCC was defined on the basis of BCLC classification as follows: 2–3 tumors, of which at least 1 was >3 cm in diameter; more than 3 tumors of any diameter; and absence of extrahepatic metastasis and absence of tumor invasion into the portal or hepatic veins and performance status 0.[19]

Patients were excluded if data were missing for the classification of patients in any of the nine staging systems or if there was no follow-up data. Patients with other concurrent malignancies were also excluded.

This study was approved by the Institutional Review Board and complied with the standards of Declaration of Helsinki and current ethical guidelines.

Staging

All data needed to fulfill these nine staging systems were collected for classification according to the recently proposed BCLC B sub-classification,[4] Tumor Nodes Metastasis (TNM) seventh edition,[20] Cancer of the Liver Italian Program (CLIP),[21] Okuda,[22] Japan Integrated Scoring Score (JIS score),[23] the Chinese University Prognostic Index (CUPI),[24] Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire Prognostic classification (GRETCH),[25] Tokyo score,[26] and Hong Kong Liver Cancer staging system (HKLC).[27] An overview of the variables used in the nine staging systems for HCC is presented in Table 1.

Treatment

At our center, HR was offered to patients with resectable disease if functional reserve was sufficient.[28,29] Resectable disease was defined as the possibility of completely removing all tumors with an expected remnant liver volume of no less than 250 mL/m².[30] HR was performed using the technique that we have previously described.[29,31] TACE was offered to patients with unresectable HCC, or resectable HCC with low predicted remnant liver volume, and patients unwilling to undergo surgery. For TACE, the Seldinger's technique of arterial embolization was administered as the standard TACE procedure to achieve complete flow

stagnation in tumor(s), as we have previously reported.[32] In addition, all patients with HBV-related HCC who were prepared for treatment for their HCC in our hospital were counseled by a hepatologist for antiviral therapy regardless of the serum HBV DNA result.

Statistical Analysis

Overall survival (OS) of patients was the single end point used to assess the performance of the different scoring systems. OS was calculated from the date of initial diagnosis with intermediate-stage HCC until death or the end of the follow-up period. Survival time was estimated by the Kaplan–Meier method, and the survival difference among prognostic strata was assessed by the Log rank test. The median of survival was calculated with its 95% confidence interval (CI). The Cox regression model was used to identify independent predictors of survival.

The prognostic performance of each scoring system was statistically assessed following Ueno et al,[33] evaluating homogeneity within the classification groups, discriminatory ability, and monotonicity of the gradients in the association between stages and survival rates. The Cox regression model was then used to calculate the likelihood ratio (LR) x^2 to determine homogeneity. The linear trend x^2 was then used to measure the discriminatory ability of each staging system. Both the linear trend x^2 and LR x^2 were also used to measure the monotonicity of survival gradients, and the degree of freedom was 1, so two prognostic systems with different stages could be compared. In addition, the consequences of the Cox model were expressed with the Akaike information criterion (AIC), which showed how the explanatory variable (staging systems) affected the dependent variable (survival of HCC).[34] In addition, Harrell's c-index, which requires no assumption in the model, was calculated to verify the discriminatory ability of each staging system. To reduce the confounding effect of treatment on survival response variables, we also performed a separate analysis for subgroups of patients who received HR or TACE.

Finally, for the best staging system, the additional independent prognostic variables that were previously identified were added to it. A new c-index was calculated to quantify the improvement. The c-index of the resulting model was internally validated using bootstrap to quantify the improvement.[35] The statistical analysis was performed using IBM SPSS v.19.0 (SPSS, Armonk, NY, USA) and R 2.13.2 (http://www.r-project.org/). All statistical tests were 2-tailed, and a p value less than 0.05 was considered significant.

Results

Patient Characteristics

Between February 2005 and August 2014, 1027 patients with intermediate-stage HCC were seen by medical oncologists at the Sun Yat-sen University Cancer Center; among these patients, 147 patients either did not fulfill the inclusion or had one or more of the exclusion criteria. Eventually, 880 patients were staged according to each of the nine different HCC staging systems discussed in the Methods section (Table 1). A total of 222 (25%) patients had HR, and 658 (75%) patients underwent TACE. In addition, 129/658 patients undergoing TACE combined with local treatment (radiofrequency ablation (RFA), n=86; microwave ablation (MWA), n=43).

All patients with demographic, clinical, and tumor information are shown in Table 2.

Survival

When the data were censored, 580 (66%) patients had died, with a median follow-up time of 25.0 months. The 1-, 3-, and 5-year OS rates for all patients were 68.7%, 34.3.0%, and 22.6%, respectively (Figure 1A). The 1-, 3- and 5-year OS rates were 76.3%, 44.0%, and 33.3% for patients who underwent HR, 86.0%, 56.6%, and 26.8% for patients who underwent TACE+RFA/MWA, and 60.9%, 23.4%, and 15.8% for patients who underwent TACE, respectively (Supplementary Figure 1).

Prognostic Factors

Univariate analysis showed that etiology, alanine transaminase (ALT), aspartate aminotransferase (AST), albumin (ALB), alkaline phosphatase (ALP), Child-Pugh stage, serum-fetoprotein (AFP), tumor extension, tumor size, and tumor number were significant baseline predictors of survival in patients with intermediate HCC (Supplementary Table 1). The independent prognostic factors identified by multivariate analysis are reported in Table 3. The most significant of these prognostic factors that are often used as part of the different staging system are tumor size, Child-Pugh stage, and tumor number. Identified other prognostic factors included elevated ALP, AST, AFP levels, and etiology.

Evaluation of Staging Systems

Because the study focused on patients with intermediate stage HCC, no patients with early cases, such as TNM stage I, CLIP score 0, JIS score 0, and Tokyo score 0, were

Table 2 Baseline Demographic and Clinical Characteristics of Patients with Intermediate Stage HCC

Characteristics	Patients (n=880)
Age, years	52.4±12.3
Sex, %	
Male	804 (91)
Female	76 (9)
Etiology, %	
HBV	776 (88)
HCV	26 (3)
Other	78 (9)
Liver cirrhosis (Yes), %	620 (70)
Ascites (Yes), %	59 (7)
Portal hypertension (Yes)*, %	126 (14)
Laboratory values	
PLT, 10^9/L	186.3±86.4
PT, s	12.5±1.4
ALT, U/L	55.5±41.4
AST, U/L	62.2±50.4
TBIL, μmol/L	16.2±11.0
ALB, g/L	40.6±4.1
ALP, U/L	127.6±107.9
Creatinine, μmol/L	76.3±17.8
AFP, ng/mL	14,521.9±33,419.2
MELD score	5.0±3.0
Liver function by Child-Pugh stage, %	
A	838 (95)
B	42 (5)
Tumor size (cm)	7.4±3.5
Tumor extension, %	
≤50	859 (98)
>50	21 (2)
Tumor number	
≤3	370 (42)
>3	510 (58)
Treatment offered, %	
Hepatica resection	222 (25)
TACE	658 (75)

Notes: Variables are expressed as the mean ± SD or no. (%), unless otherwise indicated. *Portal hypertension was defined as the presence of esophageal varices or a platelet count of less than 100 ×10⁹/L in association with splenomegaly.
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet; PT, prothrombin time; ALT, alanine transaminase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; ALP, alkaline phosphatase; AFP, alpha fetoprotein; MELD, model for end-stage liver disease; TACE, transarterial chemoembolization.

included. None of the patients were classified as end-stage disease, such as TNM stage IV, CLIP score ≥4, JIS score ≥4, and HKLC stage IV/V (Table 1). The patient

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distribution among the stage groups is presented in Supplementary Table 2. Interestingly, patients with different HKLC stages were more evenly distributed in compared with other staging systems, with 12.4%, 43.9%, and 43.7% of patients having an HKLC stage of I, II, or III, respectively.

When Kaplan-Meier survival analysis (n = 880) was used to analyze nine prognostic staging systems, the survival probability of each staging system was significantly different across the different stages (log-rank P<0.001 in all cases, Figure 1B–J). Figure 1F, G and I show that the GRETCH (stages low, intermediate and high), Tokyo (scores 2 and 3), and BCLC B sub-classification (stages B3 and B4) systems had poor survival stratification for the

intermediate stages HCC, while the HKLC, TNM, CLIP, CUPI, JIS, and Okuda systems had better survival stratification across all stages.

In all patient cohorts, the HKLC system had the highest homogeneity (LRχ2=87.3), indicating the survival of patients in the same stage was less differences (Table 4).

Compared with other systems, the HKLC classification also had the highest discriminatory score (linear trendχ2=84.0). The HKLC system had the best monotonicity of gradient based on the linear trendχ2 and LRχ2. The AIC of the HKLC system was lowest, indicating that the model containing the HKLC system was the most informative when explaining the survival of patients with intermediate-stage HCC (Table 4). Further evidence showed
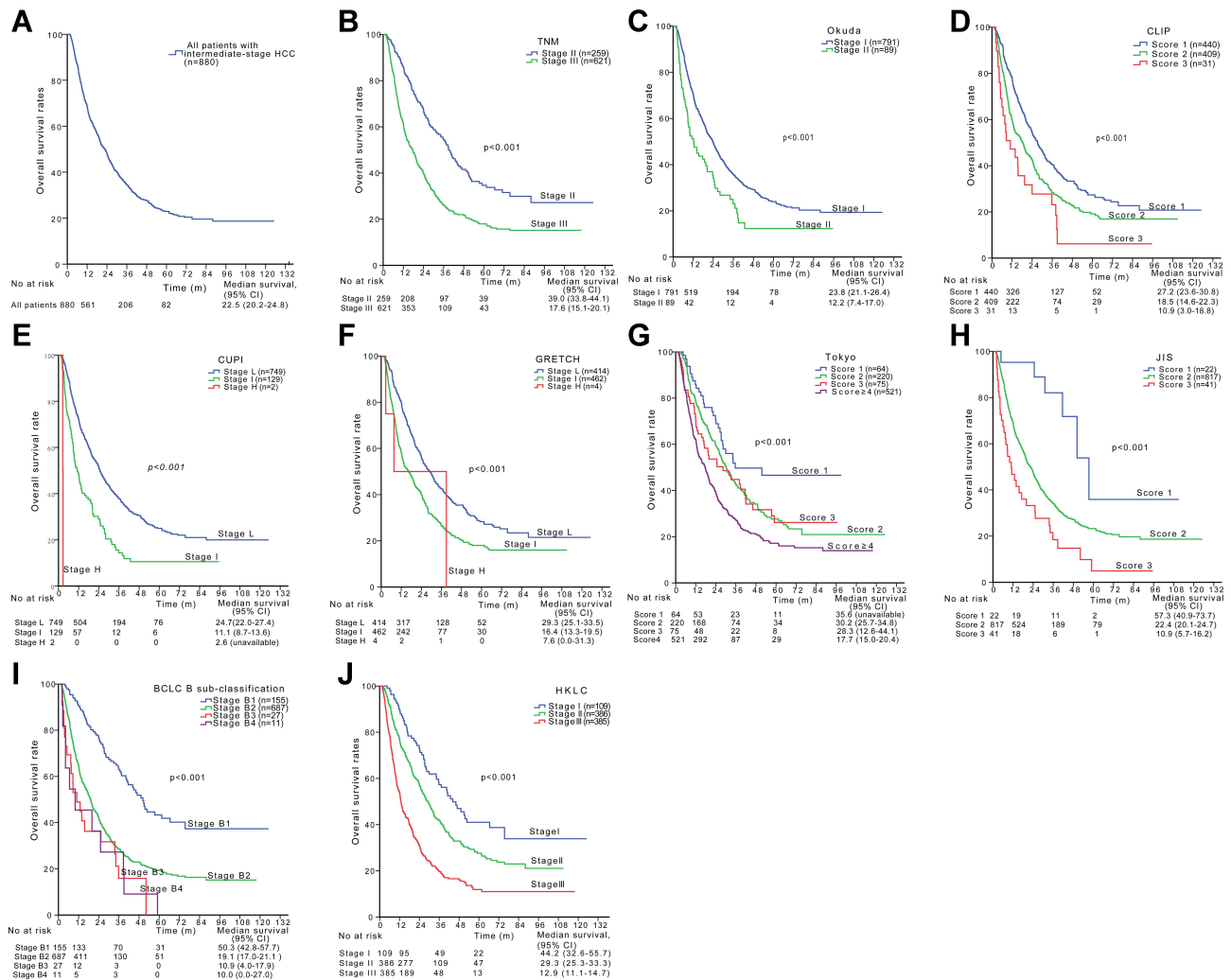

Figure 1 Survival curves for all patients with intermediate-stage hepatocellular carcinoma (**A**) and by different staging systems: TNM 7th edition (**B**), Okuda (**C**), Cancer of the liver Italian program (**D**), Chinese university prognostic index (**E**), Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (**F**), Tokyo score (**G**), Japan integrated staging score (**H**), Barcelona Clinic liver cancer sub-classification (**I**) and Hong Kong liver cancer (**J**).

Table 3 Independent Prognostic Factors for Overall Survival in Patients with Intermediate Stage HCC According to Multivariate Analysis

Variable	Hazard Ratio	95% CI	P
Tumor size (>5 cm)	1.752	1.436–2.138	<0.001
Child-Pugh stage (B)	1.668	1.182–2.354	0.004
ALP (>200 U/L)	1.588	1.219–2.068	0.001
AST (>45 U/L)	1.479	1.243–1.760	<0.001
Etiology (Others)	1.469	1.117–1.932	0.006
Tumor number (>3)	1.444	1.217–1.715	<0.001
AFP (>400 ng/mL)	1.224	1.038–1.444	0.016

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; AFP, alpha fetoprotein; CI, confidence interval.

that the HKLC system provided the best prediction of survival in our cohort with the highest c-index. When patients were stratified according to treatment strategy, the HKLC system remained the most accurate system in patients receiving either HR or TACE treatments (Table 4).

Improvement of HKLC Staging Systems

The addition of ALP, AST, etiology, and AFP improved the discriminatory ability of HKLC with a higher c-index of 0.727 (95% CI: 0.688–0.766) compared with 0.620 (bootstrap validated).

Discussion

Treatment strategies for intermediate-stage HCC are currently a controversial topic in the HCC field.[10–12,14,36] To resolve this controversy, identifying patients who are suitable for TACE or HR is essential. In addition, the interpretation of clinical trials in intermediate HCC may also depend on the staging system used. We identified and then compared nine commonly used staging systems in terms of their prognostic abilities using AIC, discriminatory ability (c-index), homogeneity within classification, and monotonicity of the gradient. This study is the first to compare prognostic scores on a specific population of intermediate-stage HCC, and the results indicated that the HKLC is the best prognostic model among the nine currently used staging systems. More importantly, our results were consistent in the subgroup analysis among patients undergoing HR and TACE treatments, indicating that its predictive accuracy is highly stable and independent of the treatment strategy.

The newly developed HKLC classification system introduced substantial amendments that have been verified in a large cohort of almost 4000 consecutively diagnosed and treated patients.[27] It incorporates performance status, liver synthetic function, and tumor stage and also provides treatment recommendations. Recently, a study from Singapore showed that HKLC system and BCLC system have the same prognostic value, but HKLC system can better guide treatment.[37] Moreover, the HKLC system introduces a multilayered stratification of tumor status using the triad of tumor size (5 cm as the new cut-off diameter), number of tumors, and vascular invasion in various combinations to more precisely characterize the status of the cancer. Therefore, the benefits of the HKLC system are clearly apparent when dealing with patients who have intermediate-stage disease with a performance status score of 0.[38] In addition, the HKLC system is a more fluent staging system, with a less demarcated border between curative and palliative treatment arms, enabling aggressive treatment pathways to be pursued in subgroups of patients with an otherwise truly dismal prognosis. Therefore, the HKLC system may be regarded as a more fluent model with better predictive ability of intermediate-advanced stage disease compared with the BCLC system.[38–40]

In our study, important predictors of prognosis for intermediate-stage HCC were identified. Multivariate analysis showed that independent predictors of survival were mostly related to the tumor burden (ie, tumor size, tumor number, and AFP) and liver function (ie, Child-Pugh stage, elevated AST, and high ALP level). The intermediate-stage HCC patient's general health status was strictly defined by BCLC classification with a score of zero. Thus, incorporating more information on tumor burden and liver function may result in better predictive abilities in intermediate stage HCC. This inclusion may explain why HKLC was the best predictive model of survival in our cohort of intermediate-stage HCC patients. We also confirmed that the addition of the prognostic variables of ALP, AST, etiology, and AFP improved the discriminatory ability of HKLC.

Until now, the optimal treatment of intermediate-stage HCC patients still remains controversial. BCLC guidelines recommend patients with intermediate-stage HCC to receive TACE treatment for first-line therapy. However, in fact surgical resection remains the primary curative modality in the management of intermediate-stage HCC. Furthermore, a recent meta-analysis data provided

Table 4 Comparison of Prognostic Stratification of Nine HCC Staging Systems

Variables	Discriminatory Ability Linear Trend ($\chi2$)	Homogeneity LR Test ($\chi2$)	AIC	c-Index
All patients (n=880)				
HKLC	84.0	87.3	6979.6	0.620 (0.599–0.641)
Tokyo	64.0	63.5	6988.0	0.618 (0.594–0.641)
BCLC B Sub-Stage	59.7	57.0	6998.6	0.582 (0.564–0.599)
TNM	51.2	54.8	7008.5	0.585 (0.567–0.604)
GRETCH	30.8	30.3	7034.5	0.575 (0.554–0.596)
CLIP	24.1	23.3	7042.0	0.564 (0.542–0.587)
CUPI	42.7	35.3	7023.5	0.551 (0.534–0.568)
JIS	20.9	20.4	7042.2	0.529 (0.516–0.541)
Okuda	14.4	12.5	7050.9	0.528 (0.513–0.543)
Patients receiving TACE (n=658)				
HKLC	56.4	59.0	4944.6	0.620 (0.596–0.643)
TNM	48.8	51.7	4950.4	0.599 (0.577–0.620)
BCLCB Sub-Stage	37.8	35.4	4957.7	0.583 (0.557–0.593)
Tokyo	33.3	33.8	4956.2	0.615 (0.587–0.642)
GRETCH	27.3	26.8	4976.1	0.580 (0.556–0.605)
CLIP	21.1	20.3	4983.4	0.569 (0.543–0.595)
CUPI	35.5	29.5	4968.5	0.555 (0.535–0.575)
JIS	20.3	20.1	4979.2	0.536 (0.519–0.552)
Okuda	10.4	9.0	4993.2	0.526 (0.509–0.543)
Patients receiving resection (n=222)				
HKLC	20.2	20.5	1386.69	0.609 (0.565–0.653)
BCLC B Sub-Stage	19.7	22.0	1387.15	0.580 (0.545–0.615)
Tokyo	18.2	17.0	1392.52	0.599 (0.552–0.647)
TNM	10.7	11.8	1393.53	0.564 (0.527–0.600)
Okuda	6.1	5.1	1400.15	0.537 (0.506–0.567)
CUPI	4.8	4.1	1401.20	0.532 (0.503–0.562)
CLIP	4.3	4.1	1402.90	0.555 (0.513–0.597)
GRETCH	3.8	3.8	1401.52	0.555 (0.512–0.598)
JIS	0.9	0.9	1404.51	0.508 (0.492–0.523)

Abbreviations: TNM, tumor nodes metastasis; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; JIS, Japan Integrated Staging; BCLC, Barcelona Clinic Liver Cancer; HKLC, Hong Kong Liver Cancer; AIC, Akaike Information Criterion.

evidence that TACE+RFA as a combination therapy provides outcomes comparable to surgical resection.[41] Our results also confirmed the above findings. Therefore, we suggest that in future studies, TACE+RFA should be included in the Hong Kong guiding treatment system and help to determine the optimal medical care for intermediate-stage HCC.

There were a few potential limitations in this study. First, our effort was limited by the single-institution experience and the retrospective nature of the study. Second, with approximately 90% of the patients having evidence of HBV infection, our data require validation

from other study groups in which HCV infection or alcohol is the prevailing etiology of chronic liver disease. In addition, this study only included patients with intermediate-stage HCC undergoing resection or TACE. When patients with different disease stages receive different treatments, future multicenter prospective studies are necessary to validate our findings.

Conclusion

For intermediate-stage HCC, our results indicate that the HKLC is the best predictor among the 9 currently used staging systems. The performance of the HKLC is reliable

for long-term prognostic prediction and is independent of the treatment strategy. This finding is crucial because selecting an optimal staging system is helpful in improving the design of future clinical trials for intermediate-stage HCC.

Disclosure

The authors declare no conflicts of interest.

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