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Validation of the Hong Kong Liver Cancer Staging System in Determining Prognosis of the North American Patients Following Intra-arterial Therapy

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Abstract

Background & Aims—There is debate over the best way to stage hepatocellular carcinoma (HCC). We attempted to validate the prognostic and clinical utility of the recently developed Hong

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Kong Liver Cancer (HKLC) staging system, a hepatitis B-based model, and compared data with that from the Barcelona Clinic Liver Cancer (BCLC) staging system in a North American population who underwent intra-arterial therapy (IAT).

Methods—We performed a retrospective analysis of data from 1009 patients with HCC who underwent intra-arterial therapy from 2000 through 2014. Most patients had hepatitis C or unresectable tumors; all patients underwent IAT, with or without resection, transplantation, and/or systemic chemotherapy. We calculated HCC stage for each patient using 5-stage HKLC (HKLC-5) and 9-stage HKLC (HKLC-9) system classifications, as well as the BCLC system. Survival information was collected up until end of 2014 at which point living or unconfirmed patients were censored. We compared performance of the BCLC, HKLC-5, and HKLC-9 systems in predicting patient outcomes using Kaplan-Meier estimates, calibration plots, c-statistic, Akaike information criterion, and the likelihood ratio test.

Results—Median overall survival time, calculated from first IAT until date of death or censorship, for the entire cohort (all stages) was 9.8 months. The BCLC and HKLC staging systems predicted patient survival times with significance (P<.001). HKLC-5 and HKLC-9 each demonstrated good calibration. The HKLC-5 system outperformed the BCLC system in predicting patient survival times (HKLC c=0.71, Akaike information criterion=6242; BCLC c=0.64, Akaike information criterion=6320), reducing error in predicting survival time (HKLC reduced error by 14%, BCLC reduced error by 12%), and homogeneity (HKLC $\chi 2$=201; P<.001; BCLC $\chi 2$=119; P<.001) and monotonicity (HKLC linear trend $\chi 2$=193; P<.001; BCLC linear trend $\chi 2$=111; P<.001). Small proportions of patients with HCC of stages IV or V, according to the HKLC system, survived for 6 months and 4 months, respectively.

Conclusion—In a retrospective analysis of patients who underwent IAT for unresectable HCC, we found the HKLC-5 staging system to have the best combination of performances in survival separation, calibration, and discrimination; it consistently outperformed the BCLC system in predicting survival times of patients. The HKLC system identified patients with HCC of stages IV and V who are unlikely to benefit from IAT.

Keywords

liver cancer; risk factors; prognosis; predicted outcome

BACKGROUND & AIMS

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related mortality in the world[1]. It has been increasing worldwide and has nearly tripled in the last decades in the Unites States [2, 3]. Etiologic and clinical heterogeneity in HCC populations has hampered efforts in establishing a universally adopted treatment scheme to improve patient care. An ideal staging system would be able to provide accurate prognosis, stratify patients into distinct prognostic groups, and suggest up-to-date therapeutic strategies [4].

The uniquely challenging aspect of staging HCC is the interplay of two diseases, liver cirrhosis and cancer [5, 6]. Liver cirrhosis ultimately results in both reduced liver function and can lead to cancer. Cancer in turn worsens liver function by mass effect and parenchymal

invasion. Staging is further complicated by patient's social history and co-morbidities often relevant in this patient population. There has been at least eight proposed HCC staging systems, including the Barcelona Clinic Liver Cancer (BCLC) staging system[7].

The BCLC staging system is currently the most widely used system in Europe and the Unites States given its comprehensive algorithm tied to treatment recommendations. It has been externally validated and provides a common framework to enable comparison between patient cohorts and institutions[7, 9–11]. However, BCLC staging often draws criticism because of conservative treatment recommendations in patients for whom aggressive treatment approaches have become commonplace due to technical safety and effectiveness[12–16]. Although widely quoted in the scientific literature, efforts have been underway to modify and update the BCLC staging.

The recently developed Hong Kong Liver Cancer (HKLC) staging system has garnered international attention because of its comprehensive nature, based on the largest patient cohort to date for HCC staging, and tied to treatment recommendations that addresses the aforementioned limitations of the BCLC system [17]. Compared to BCLC, HKLC staging system provided superior survival discrimination in their internal validation cohort. However, the 3958 patients in the HKLC study were mainly Asians with hepatitis B virus (HBV). Hence, the authors called for external validation outside of Asia, where there are more heterogeneous etiologies of HCC [17]. The purpose of our study is to assess the external prognostic validity and clinical utility of the recently developed HKLC staging system in a North American population with unresectable HCC and compare the performance with the BCLC system.

METHODS

Patient population

This Institutional Review Board-approved and Health Insurance Portability and Accountability Act compliant study was performed at a single tertiary referral hospital in North America (Johns Hopkins Hospital, Baltimore, MD, USA). 1009 consecutive HCC patients derived from an ongoing database tracking HCC patients from 2000 – 2014 and who underwent at least one IATs (Lipiodol, drug-eluting beads, or radio-embolization) +/− systemic chemotherapy, liver transplantation, resection, and/or ablation were included [18]. 131 patients (representing 13.0% of total) had missing lab or radiologic data that prevented calculation of either HKLC or BCLC stages. A complete-case analysis was performed. A comprehensive review of medical charts, imaging and outcomes were included in the database.

Treatment Criteria & Modality

The diagnosis of HCC was made by imaging appearance and/or by biopsy as defined by guidelines [8, 10, 19, 20]. Patients with newly diagnosed HCC referred to our center were discussed at weekly multidisciplinary conference for treatment decision. Patients eligible for immediately curative treatments were routed to the corresponding specialties. The remaining patients ineligible for immediate curative therapy were considered for IAT +/− sorafenib,

transplantation, and/or delayed resection/ablation as part of individualization of patient care; these were often outside of BCLC treatment guidelines. The cohort consisted of mainly unresectable HCC that included liver transplantation candidates undergoing bridging using IAT, questionably resectable candidates undergoing down-staging with IAT, and select BCLC D patients.

A majority of patients underwent TACE in this cohort. For conventional TACE (cTACE), a mixture of ethiodized oil, doxorubicin (Adriamycin; Pharmacia & Upjohn, Kalamazoo, Mich), mitomycin-C (Bedford Laboratories, Bedford, Ohio), and cisplatin (Bristol-Myers Squibb, Princeton, NJ) was injected in the hepatic arterial vasculature through a microcatheter. This was followed by injection of up to 4 mL of 100–300-μm microsphere particles (Embosphere; Biosphere Medical, Boston, Mass). For TACE with drug-eluting beads (DEB-TACE), patients received 2 mL of 100–300-μm-diameter microsphere particles (LC Beads; BioCompatibles, Surrey, England) loaded with 50 mg of doxorubicin hydrochloride (25 mg/mL) and mixed with nonionic contrast material (300 mg of iodine per milliliter, Oxilan; Guerbet, Bloomington, Ind)[21].

Study Design & Data Analysis

The TRIPOD checklist was adopted to ensure accuracy and comprehensiveness of the external validity assessment [22]. The HKLC staging scheme is shown in Figure 1 [17]. HKLC staging with both five major classifications (stages I, II, III, IV, V; here referred as HKLC-5) and the full nine sub-classifications (stages I, IIa, IIb, IIIa, IIIb, IVa, IVb, Va and Vb; here referred as HKLC-9) were considered. All laboratory values were taken from the time immediately before the first IAT session at our institution. Treatment information was gathered from structured data as well as freestyle clinician notes in the institutional electronic medical record (EMR).

The outcome of interest, overall survival (OS), was computed from the date of first IAT at our institution to death or last known clinic follow-up. OS was ascertained by two methods. First, the institutional EMR was checked to confirm patient's vital status and death date if available. Second, all patients with unknown vital status were queried once on the United States Office of Vital Records registry in late 2014. All patients who were alive or had unknown vital status were censored on the last known clinical follow-up date. Kaplan-Meier survival curves were plotted and the log-rank test was used to assess the significance of the survival curve separation [23, 24]. A difference with a two-tailed *P*-value of $< .05$ was considered statistically significant.

Model calibration, discrimination, reduction in error, monotonicity of gradient, and homogeneity were reported as important measures of staging system performance [25–28]. Measurement of discrepancy between observed and predicted overall survival time was made through calibration plots of validation cohort versus original HKLC predictions [29] The ability of the staging system to assign distinct stages to patient groups with different survival was measured using Harrell's c-statistic, a rank-order statistic that relates to the area under the ROC curve [30]. Akaike information criterion (AIC) from the Cox proportional hazards model was used to further confirm survival discrimination [31]. Each staging system's ability to reduce error in predicting survival time was calculated as previously reported in literature

[32]. Cox model with likelihood ratio (LHR) chi-square test was used to measure homogeneity and monotonicity of gradients [33]. Monotonicity of gradient was calculated to measure the consistency of worsening patient survival with worsening stages [25]. Homogeneity was used to measure similarity in patient survival within a given stage [25]. Greater C-statistic, reduction in error, and LHR chi-square values corresponded to better staging system performance while the opposite was the case for AIC.

Analysis was performed in the full cohort as well as some in sub-cohorts with HBV carriers and hepatitis C virus (HCV) carriers to assess any clinically relevant trends in different subgroups. Pre-2008 and Post-2008 subgroup analysis was performed to assess for temporal validity. Further subgroup analysis of only confirmed dead patients on pre and post-2008 sub-cohorts was done to explore the effect of censoring. The full validation cohort was primarily analyzed for comparison with the original HKLC cohort while both HBV and HCV sub-cohorts were primarily analyzed for comparison with the full validation cohort. All statistical analysis and plotting were done in R: Statistical Programming Language Version 3.8.11 (Vienna, Austria) and Microsoft Excel 2010.

RESULTS

Validation Cohort & Survival Information

A total of 881 patients were included in the full validation cohort. Detailed baseline clinico-pathologic characteristics are summarized in Table 1. Notable distinguishing characteristics of this validation cohort from the original development cohort was the predominance of Caucasian (n=520, 59.0%) male (n=698, 79.2%) patients with HCV (n=427, 48.5%) and alcohol (n=269, 30.5%) as major HCC etiologies. Other major characteristics of this cohort included Eastern Cooperative Oncology Group (ECOG) performance score 0 (n=426, 48.4%) and Child-Pugh Class A (n=534, 60.6%) (Table 1). All patients received cTACE (n=534, 60.6%), DEB-TACE (n=326, 37.0%), or radioembolization with yttrium-90 (n=21, 2.4%). One-third of the patients received treatment using liver transplantation, resection, or sorafenib at some point in the treatment course.

The full validation cohort on average had slightly more advanced disease compared to the original HKLC cohort [17], with smaller proportions of Child-Pugh A (60.6% vs. 72.6%, validation cohort vs. the original HKLC cohort, respectively), ECOG performance score 0 (48.4% vs. 56.9%, respectively), patients with tumor size < 2cm (7.0% vs. 9.3%, respectively), and patients with a solitary nodule (30.6% vs. 47.3% respectively) (Table 1). There was larger presence in our study of BCLC C patients (60.8% vs. 39.1% for the original HKLC cohort) (Table 2).

Median OS, as calculated from first IAT date at our institution to date of death or censorship, for the entire cohort across all stages was 9.8 months. Detailed median OS information and the number of patients corresponding to each stage for BCLC, HKLC-5, and HKLC-9 are reported in Table 2. Three most represented groups in cross-tabulations were HKLC III / BCLC C patients (n=193, 21.9%), HKLC IV / BCLC C (n=162, 18.3%), and HKLC II / BCLC C (n=145, 16.5%) (Supplemental Table 1).

Prognostic Validation

HKLC and BCLC staging systems predicted survival with significance ($P<0.001$). Specifically, BCLC and HKLC-5 staging achieved separation of the survival curves (Figure 2A and 2B), whereas the survival curves for HKLC-9 had overlaps in survival for stages IIIa, IIIb, IVa, and Va, all of which had median OS of approximately 11 months (Figure 2C).

Both calibration curves for HKLC-5 and HKLC-9 demonstrated matching of OS between the validation cohort and the original cohort (Figure 3). Both plots result in R^2 values > 0.9 signifying goodness of fit, with HKLC-5 ($R^2 = 0.95$) being slightly better than HKLC-9 ($R^2 = 0.90$).

HKLC-5 and HKLC-9 demonstrated stronger survival discrimination than BCLC as illustrated by both Harrell's c-statistic and AIC (Table 3). Greater homogeneity was observed with HKLC compared to BCLC (Table 3), suggesting similar overall survival within each given stage. The sum of errors in survival prediction for the entire cohort when using median OS as the sole survival predictor was 782 days. Compared to using the median OS alone, when using the BCLC staging as the survival predictor, 12% overall error reduction was observed whereas greater error reductions of 14% and 16% were measured using HKLC-5 and HKLC-9, respectively, (Table 3).

Sub-cohort Analysis: HBV vs HCV and pre-2008 vs post-2008

The predominant population in the HBV sub-cohort was an Asian (n = 49, 37.1%), male (n=111, 85.1%) patient with ECOG performance score 0 (n=66, 50.0%), and Child-Pugh Class A (n=90, 68.2%) (Table 1). Predominant patient characteristics in the HCV sub-cohort was Caucasian (n=232, 54.3%), male (n=349, 81.7%), ECOG performance score 0 (n=217, 50.8%), and Child-Pugh Class A (n=240, 56.2%) (Table 1). Overall, the survival curves demonstrate similar qualitative degree of separation among HBV and HCV cohorts, though with some more overlaps, possibly due to smaller sample size in each stage in this subcohort compared to the full validation cohort (Table 2, Supplemental figure 1).

Pre-2008 (n = 554) and Post-2008 (n=327) subgroup Kaplan-Meier curves (supplemental figure 2) demonstrated excellent survival curve separation in both subgroups. The most represented patients in pre-2008 were White (n = 313, 56%), male (n = 427, 77%) patients with ECOG performance score 0 (n = 240, 43%), and Child-Pugh Class A (n = 342, 62%). Similarly, the most represented patients in post-2008 were White (n = 207, 63%), male (n = 270, 83%) patients with ECOG performance score 1 (n = 167, 51%), and Child-Pugh Class A (n = 327, 59%). Most notable difference in pre and post-2008 groups was improvements in survival of HKLC stage I and BCLC stage A patients. Of note, censorship proportions for pre-2008 and post-2008 groups were 19% (n = 63) and 47% (n = 258), respectively. Sub-analysis of only confirmed dead patients for pre and post 2008 sub-cohorts (supplemental figure 3) demonstrated similar trends of overall survival changes with worsening stages, except in HKLC stage I in post-2008 sub-cohort where most patients were censored. Overall, HKLC demonstrated excellent survival discrimination and error reduction in various sub-cohorts. The sub-cohorts demonstrated consistent worsening of survival with

worsening stages, similar to the full validation cohort, as expected of a staging system (Table 3).

DISCUSSION

The present study showed prognostic external validity of the HKLC staging system in a North American HCC cohort whose main treatment modality was TACE and primary HCC etiology was HCV and/or EtOH. Specifically, the HKLC-5 staging demonstrated significantly improved performance over BCLC based on calibration, discrimination, monotonicity/homogeneity, and survival curve separation. Furthermore, HKLC-5 identified stages IV and V patients who had very poor survival despite IAT. In light of the superior predictive power and more practically relevant treatment decision support, the HKLC staging system may have a significant impact on HCC patient stratification for research design, clinical decision recommendation, and patient care.

External prognostic validation is an important step in staging system establishment because prediction models almost always perform better on the development cohort [34]. Furthermore, validation process allows assessment of model robustness in a new patient cohort where underlying assumptions, such as patient demographics, treatment strategy, and disease etiology are violated by measurable amounts.

Asian and North American HCC cohorts have key differences in treatment strategies, etiologic factors, and socioeconomic background. Measurable differences included disease etiology and baseline patient characteristics. Unmeasured differences include patient social history and medical comorbidity that could have influence on prognosis but difficult to quantify in a research study. Hence, the value of staging system validation in an independent cohort cannot be overstated.

The treatment course for HCC patients is often driven by availability of local expertise, which is mainly TACE at our institution (>70% of HCC patients). Compared to the original HKLC cohort, our validation cohort had fewer small-sized (< 2cm) single HCC patients, especially those classified as Child-Pugh Class A. This is because a large number of very early stage patients proceeded to ablation or resection without requiring IAT. Furthermore, it explains why our validation cohort had percent-wise higher proportion of BCLC C patients and slightly lower median OS compared to the development cohort. Similar to the development cohort however, the validation cohort consisted of a wide variety of patients ranging from BCLC A to D and HKLC I to V. A large number of patients in our validation cohort as well as those who received IATs in the original HKLC cohort were BCLC C patients for whom systemic chemotherapy was recommended per BCLC scheme.

An important secondary finding from this study is the HKLC system’s identification of patient groups who did not appear to benefit from current treatment strategy. HKLC stages IV and V had uniformly poor survival at 6 months and 4 months, respectively. A large percentage of patients in this cohort were treated with TACE, hence very poor survival in these two stages implicate TACE should not be used in this particular group. Consequently, an important benefit of the HKLC system may be the identification of exclusion criteria for

IAT. The 9.8 months mOS for the full validation cohort appeared particularly poor compared to other studies, but explained by difference in mOS calculation methodology (i.e. start from first IAT date instead of first imaging/pathology diagnosis).

Furthermore, temporal validity of BCLC and HKLC as shown in supplemental figure 1 raises two important questions. First, despite active ongoing research and clinical trials, HCC patients in “intermediate or advanced” stages continue to survive poorly. The sorafenib era from 2008 – 2014 did not appear to change the poor survival outcome seen in this cohort. Second, BCLC A and HKLC I patients have shown substantial improvement in mOS over time. Patients in these stages were often receiving IAT to bridge for transplantation or to downstage prior to resection.

There were several limitations to our study. First, all patients in this validation cohort underwent IAT at some point in the treatment course. This underrepresented resectable HCC cases as well as primary advanced/metastatic cases that were determined ineligible for IAT and treated with systemic chemotherapy only. However, >70% of HCC patients received IAT at some point in their treatment course at our institution, in conjunction with resection, transplantation, and systemic chemotherapy. Furthermore, accurate staging would arguably be of greatest relevance in unresectable HCC cases. Second, this is a single-institution study at a tertiary center subject to referral bias. Further study in community setting would be beneficial. Third, the study had high proportion of censored patients (36.4%), including those with incomplete survival data, which resulted in increased variance and potential bias.

Despite the stated limitations, HKLC staging system’s demonstrated external prognostic validity has important implications. As in this North American study, in three patient cohorts of more than 5000 patients from Europe and Asia, HKLC outperformed BCLC as a survival classification system in two of the three cohorts and similarly performed to BCLC in one cohort [17, 35, 36]. The HKLC might become the first HCC staging system accepted across the West and the East, for the purposes of patient stratification for research studies, accurate prediction of patient prognosis, and clinical decision support.

CONCLUSION

HKLC-5 demonstrated the best combination of performances in survival separation, calibration, and discrimination, while consistently outperforming BCLC staging as a prognostic classification system in this cohort. Furthermore, HKLC identified stages IV and V patients who are unlikely to benefit from IAT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AFP	alpha-fetoprotein
BCLC	Barcelona Clinic Liver Cancer
ECOG	Eastern Cooperative Oncology Group
EVM	extravascular metastasis
IAT	intra-arterial therapy
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HKLC	Hong Kong Liver Cancer
NASH	non-alcoholic steatohepatitis
TACE	transarterial chemoembolization
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis

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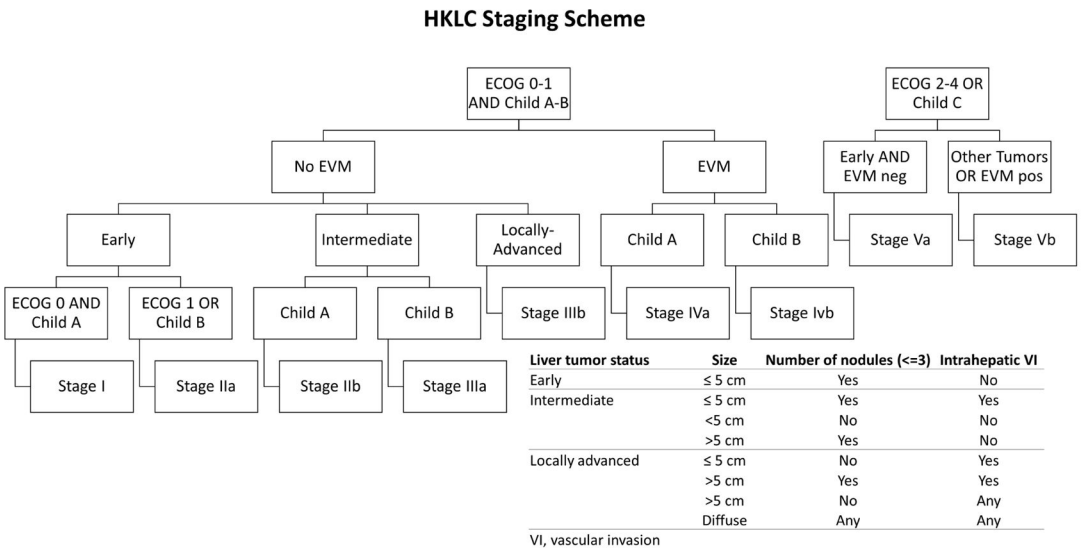

Figure 1. Hong Kong Liver Cancer staging

The Hong Kong Liver Cancer staging scheme as proposed by Yau et al (2014).

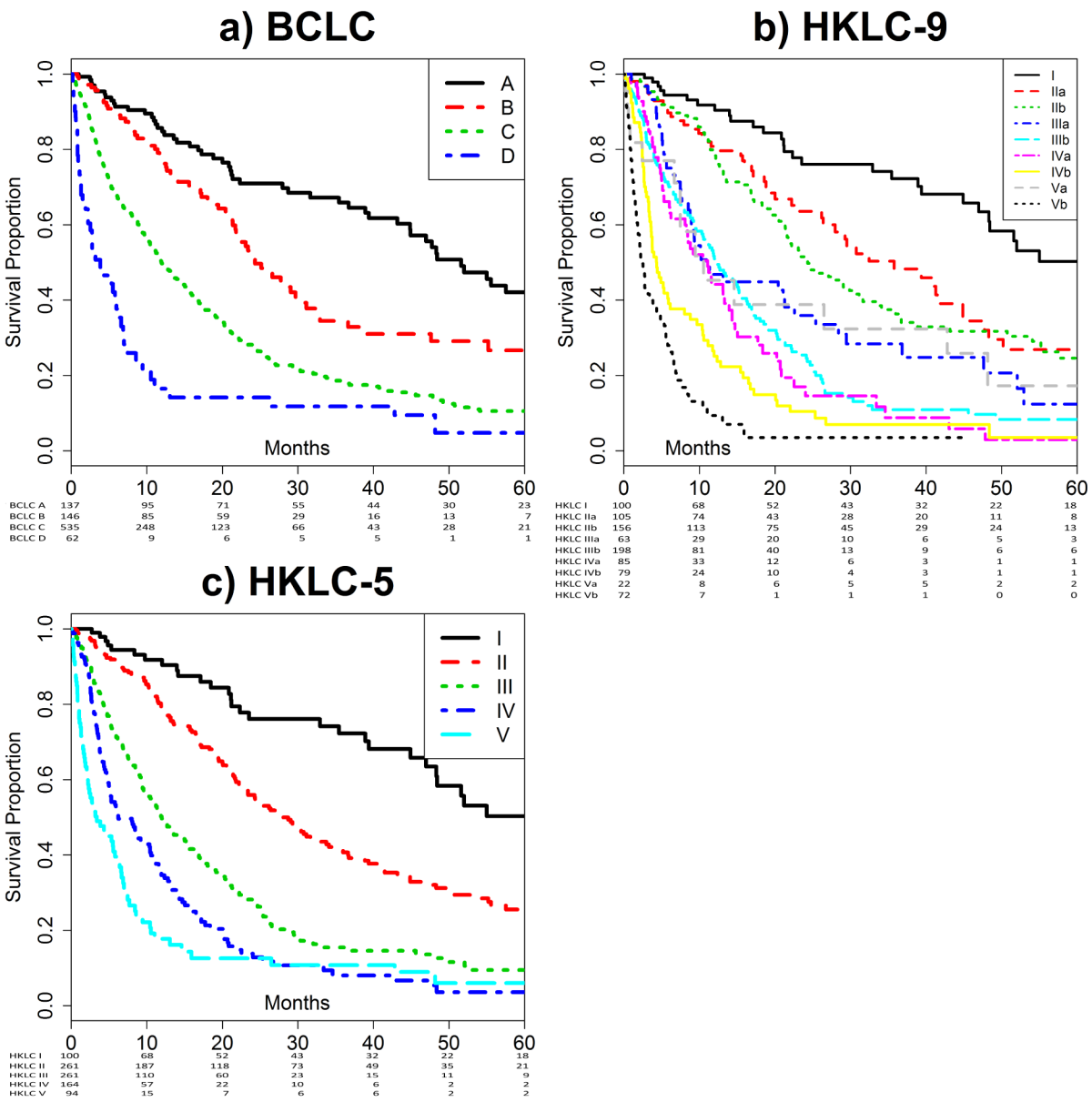

Figure 2. Kaplan-Meier Curves

Stratification by BCLC staging (A), HKLC-5 staging (B) and HKLC-9 staging (C). All three staging systems demonstrate separation of survival curves. The HKLC-9 staging has several overlaps, notably in stages IIIa, IIIb, IVa, and Va. Number at risk tables are attached below each subfigure.

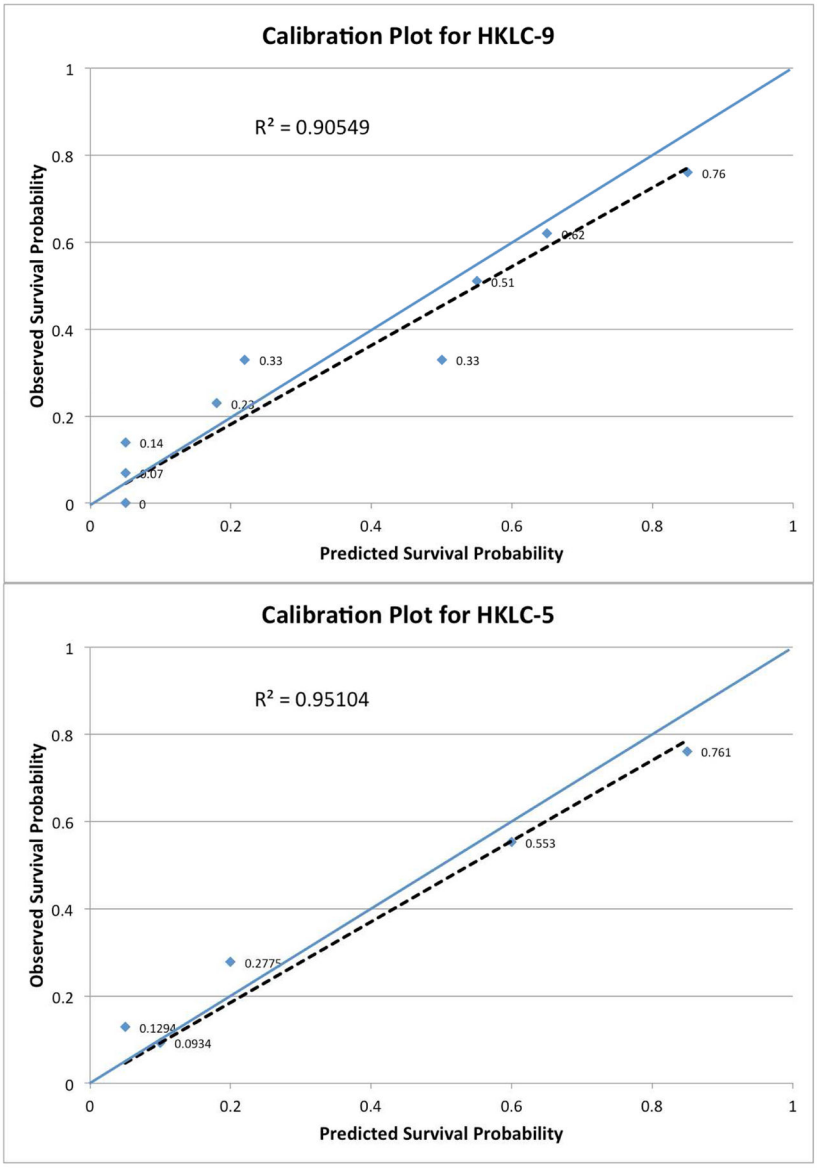

Figure 3. Calibration plots for HKLC-5 and HKLC-9

Calibration plots for HKLC-9 (A) and for HKLC-5 (B). They plot the validation cohort patients' actual survival time (y-axis) versus the HKLC staging system's predicted survival (x-axis). The closer points are to the reference line (blue), the better the calibration. The dotted line represents the least-squares trendline. Both HKLC-9 and HKLC-5 demonstrate moderate to good calibration with R2 = 0.9055 and R2 = 0.9510, respectively.

Table 1

Characteristics of the Validation Cohort

	Full cohort (N=881)		HBV group (N=132)		HCV group (N=427)	
Median age in y (IQR)	62	(56–71)	58	(51–69)	59	(55–65)
Sex						
Male	698	79.2%	111	(84.1%)	349	(81.7%)
Female	183	20.8%	21	(15.9%)	78	(18.3%)
Ethnicity						
White	520	59.0%	36	(27.3%)	232	(54.3%)
Black	200	22.7%	24	(18.2%)	152	(35.6%)
Asians	69	7.8%	49	(37.1%)	8	(1.9%)
Others	92	10.4%	23	(17.4%)	35	(8.2%)
Etiologies of HCC**						
HCV	427	48.5%	-	-	427	(100%)
HBV	132	15.0%	132	(100%)	-	-
Alcoholism	269	30.5%	-	-	-	-
NASH	60	6.8%	-	-	-	-
Cryptogenic	48	5.4%	-	-	-	-
Clinico-pathologic Factors						
ECOG PS						
0	426	48.4%	66	(50.0%)	217	(50.8%)
1	407	46.2%	60	(45.5%)	188	(44.0%)
2	38	4.3%	6	(4.5%)	17	(4.0%)
3	10	1.1%	0	(0%)	5	(1.2%)
4	0	0.0%	0	(0%)	0	(0%)
Child-Pugh grade						
A	534	60.6%	90	(68.2%)	240	(56.2%)
B	292	33.1%	35	(26.5%)	157	(36.8%)
C	55	6.2%	7	(5.3%)	30	(7.0%)
AFP level, ng/mL						

	Full cohort (N=881)		HBV group (N=132)		HCV group (N=427)	
Median (IQR)	64	(9–1131)	96	(18–4604)	102	(14–923)
Liver tumor factors						
Size						
≤ 2cm	62	7.0%	5	(3.8%)	39	(9.1%)
> 2cm to ≤ 5cm	327	37.1%	41	(31.1%)	194	(45.4%)
> 5cm	480	54.5%	83	(62.9%)	191	(44.7%)
Diffuse	12	1.4%	3	(2.3%)	3	(0.7%)
No. of nodules						
Solitary (1)	270	30.6%	43	(32.6%)	122	(28.5%)
Oligonodular (2–3)	237	26.9%	31	(23.5%)	125	(29.3%)
Multinodular (> 3)	374	42.5%	58	(44.0%)	180	(42.2%)
Intrahepatic VI	227	25.8%	37	(28.0%)	105	(24.6%)
EVM	195	22.1%	35	(26.5%)	84	(19.7%)
Extrahepatic VI	124	14.1%	27	(20.5%)	53	(12.4%)
Extrahepatic metastasis	92	10.4%	11	(8.3%)	41	(9.6%)
Treatment Received						
Intra-arterial Therapy						
cTACE	534	60.6%	85	(64.4%)	245	(57.4%)
DEB-TACE	326	37.0%	39	(29.5%)	176	(41.2%)
Y-90	21	2.4%	8	(6.1%)	6	(1.4%)
Other Treatments***						
Sorafenib	176	20.0%	32	(24.2%)	83	(19.4%)
Resection	19	2.2%	5	(3.8%)	2	(0.5%)
Liver Transplantation	94	10.7%	13	(9.8%)	66	(15.5%)
Follow-up summary						
Enrollment Pre-2008	327	37.1%	*	*	*	*
Vital Status						
Dead, confirmed	560	63.6%	83	(62.9%)	242	(56.7%)
Alive or censored	321	36.4%	49	(37.1%)	185	(43.3%)
Overall Survival, mo						

	Full cohort (N=881)		HBV group (N=132)		HCV group (N=427)	
Median (IQR)	9.8	(3.4–22.2)	11.3	(3.5–29.6)	9.2	(3.4–21.3)

Abbreviations: ECOG PS, Eastern Coooperative Oncology Group performance status; HBV, Hepatitis B Virus;

** Numbers do not add up to N due to one person potentially carrying multiple etiologies

*** These represent treatments *in addition* to IAT

Table 2

Median Overall Survival by Stage

Full Cohort				HBV Cohort		HCV Cohort	
	Stage	**mOS [95% CI]***	**N**	**mOS [95% CI]***	**N**	**mOS [95% CI]***	**N**
BCLC							
	A	52 [45,71]	137	63 [45,NA]	22	52 [39,92]	79
	B	24 [21,31]	146	27 [18, NA]	21	27 [20, NA]	78
	C	12 [11,14]	536	13 [9,25]	83	11 [9,15]	235
	D	4 [3,7]	62	1 [1,NA]	6	6 [3,9]	35
HKLC-5							
	I	63 [48, 92]	100	63 [52, NA]	14	55 [47, NA]	67
	II	29 [23, 34]	261	32 [18, 45]	42	29 [23, 45]	114
	III	12 [10, 16]	262	25 [11, 27]	34	12 [9,20]	129
	IV	6 [5, 11]	164	6 [3, 18]	31	6 [4, 9]	69
	V	3 [2, 6]	94	2 [1, NA]	11	6 [3, 7]	48
HKLC-9							
	I	63 [48, 92]	100	63 [52, NA]	14	55 [47, NA]	67
	IIa	36 [26, 48]	105	32 [16, NA]	14	30 [23, NA]	63
	IIb	24 [21, 31]	156	31 [18, NA]	28	28 [21, NA]	51
	IIIa	11 [9, 25]	63	28 [25, NA]	5	21 [9, NA]	36
	IIIb	12 [10, 15]	199	15 [10, 27]	29	12 [9, 16]	93
	IVa	11 [8, 14]	85	13 [6, NA]	22	8 [5, 15]	30
	IVb	4 [3, 8]	79	3 [2, NA]	9	4 [3, 12]	39
	Va	11 [7, N/A]	22	26 [2, N/A]	3	15 [7, NA]	13
	Vb	2 [1, 5]	72	1 [1, NA]	8	5 [3, 7]	35

*mOS is in months; Abbreviations: mOS, median overall survival

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Table 3

Summary of Staging System Performance Measures

	BCLC	HKLC-5	HKLC-9
Full			
Harrell's c-statistic	0.643 ± 0.012	0.707 ± 0.013	0.717 ± 0.014
AIC *	6321	6241	6200
Likelihood Ratio $\chi 2$	119	201	250
Error Reduction (%)	12%	14%	16%
HBV			
Harrell's c-statistic	0.677 ± 0.032	0.747 ± 0.035	0.759 ± 0.036
AIC *	642	629	612
Likelihood Ratio $\chi 2$	29	45	69
Error Reduction (%)	13%	16%	18%
HCV			
Harrell's c-statistic	0.668 ± 0.019	0.715 ± 0.020	0.732 ± 0.021
AIC *	2426	2399	2387
Likelihood Ratio $\chi 2$	63	92	113
Error Reduction (%)	13%	14%	16%

* smaller the better

Abbreviation: AIC, Akaike's Information Criterion; LHR, lik elihood ratio;