Supplementary

Table S1 Baseline characteristics of the patients in the validation cohorts

Characteristics	Validation cohort 1 (n=84)	Validation cohort 2 (n=14)	Validation cohort 3 (n=234)
Follow-up duration, years	5.7 (5.0–6.5)	0.8 (0.6–2.2)	3.8 (3.4–4.2)
Diabetes	9 (11%)	2 (14%)	25 (11%)
Cholelithiasis	16 (19%)	1 (7%)	18 (8%)
Albumin <35 g/L	16 (19%)	1 (7%)	12 (5%)
Platelet count, $\times 10^9$/L			
<100	8 (10%)	1 (7%)	18 (8%)
100–300	67 (80%)	12 (86%)	202 (86%)
>300	9 (11%)	1 (7%)	14 (6%)
HBV infection	33 (39%)	7 (50%)	28 (12%)
AFP >50 ng/mL	25 (30%)	3 (21%)	17 (7%)
CA19-9 >37 kU/L	48 (57%)	9 (64%)	110 (47%)
CEA, ng/mL			
<2.5	35 (42%)	7 (50%)	118 (50%)
2.5–5.0	21 (25%)	4 (29%)	53 (23%)
>5·0	28 (33%)	3 (21%)	63 (27%)
Tumor size			
≤2.0	10 (12%)	2 (14%)	19 (8%)
2.0–3.0	16 (19%)	1 (7%)	31 (13%)
3.1–5.0	19 (23%)	3 (21%)	69 (30%)
>5	39 (46%)	8 (57%)	115 (49%)
Tumor number			
1	61 (73%)	13 (93%)	188 (80%)
2	9 (11%)	1 (7%)	7 (3%)
≥3	14 (17%)	0	39 (17%)
Resection type			
Minor resection	60 (71%)	6 (43%)	134 (57%)
Hemihepatectomy	13 (16%)	6 (43%)	94 (40%)
Extended hepatectomy	11 (13%)	2 (14%)	6 (3%)
Lymph node metastasis	31 (37%)	6 (43%)	60 (26%)

Data are median (IQR) or n (%). Percentages may not add up to 100% due to rounding. The results obtained from the training cohort were validated in three independent cohorts drawn from School of Medicine, Shanghai Jiao Tong University (Renji Hospital; validation cohort 1), Fujian Medical University (Mengchao Hepatobiliary Hospital; validation cohort 2), and Fudan University (Zhongshan Hospital; validation cohort 3). IQR, interquartile range; HBV, hepatitis B virus; AFP, alpha fetoprotein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

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Table S2 Multivariate analyses of Cox and logistic models

Variable	SE[a]	HR (95% CI)[a]	P[a]	SE[b]	Coef[b]	P[b]
Diabetes	0.10	1.47 (1.22–1.78)	<0.001	0.37	2.12	<0.001
Cholelithiasis	0.11	1.01 (0.82–1.25)	0.914	0.67	2.58	<0.001
Albumin <35 g/L	0.09	1.38 (1.17–1.63)	<0.001	0.41	1.70	<0.001
Platelet count, $\times 10^9$/L	0.06	1.27 (1.12–1.44)	<0.001	0.17	0.55	0.002
HBV infection	0.07	0.78 (0.69–0.90)	<0.001	0.17	−0.24	0.165
AFP >50 ng/mL	0.10	1.61 (1.32–1.97)	<0.001	0.39	1.44	<0.001
CA19-9 >37 kU/L	0.08	2.79 (2.38–3.27)	<0.001	0.23	2.41	<0.001
CEA, ng/mL	0.04	1.16 (1.07–1.27)	<0.001	0.11	0.28	0.012
Tumor size, cm	0.05	1.44 (1.31–1.59)	<0.001	0.10	0.65	<0.001
Tumor number	0.06	1.23 (1.11–1.37)	<0.001	0.21	0.73	0.001
Resection type	0.06	0.95 (0.84–1.06)	0.363	0.20	0.40	0.041
Lymph node metastasis	0.08	1.51 (1.29–1.76)	<0.001	0.34	2.11	<0.001

[a], calculated using Cox regression; [b], calculated using logistic regression. SE, standard error; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; AFP, alpha fetoprotein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

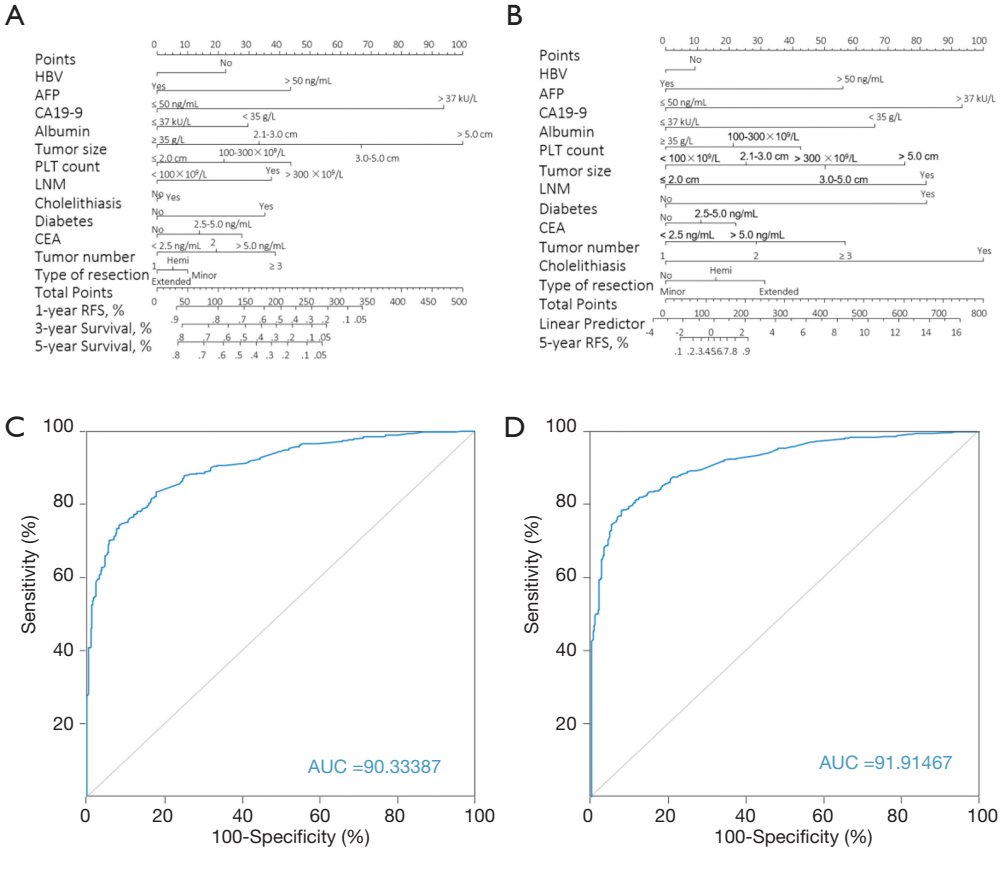

Figure S1 Development and evaluation of nomograms for prediction of recurrence of intrahepatic cholangiocarcinoma after resection using significant covariates from univariate analyses. To calculate predicted survival, all significant factors from the univariate analyses were located on the left row and a straight line is drawn up to the points to determine the corresponding points. Total points were matched to "1-year Survival, %", "3-year Survival, %", and "5-year Survival, %" or "Linear Predictor" with "Predicted Value, %" to determine the individualized predicted survival probability. (A) Cox regression model. (B) Logistic regression model. (C) ROC curve for Cox univariate regression model. (D) ROC curve for logistic univariate regression model. AUC, area under curve; ROC, receiver operating characteristic.

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Table S3 Calibration and discrimination of Cox and logistic regression models

Variable	R^2	g	gr	Brier	C	Dxy
Cox univariate model	0.428	1.168	3.215	0.168	0.9033	0.490
Cox multivariate model	0.428	1.164	3.204	0.151	0.9041	0.490
Logistic univariate model	0.622	3.684	39.814	0.107	0.9191	0.838
Logistic multivariate model	0.621	3.672	39.327	0.130	0.9186	0.837

Gr, g-index on the odds ratio scale.

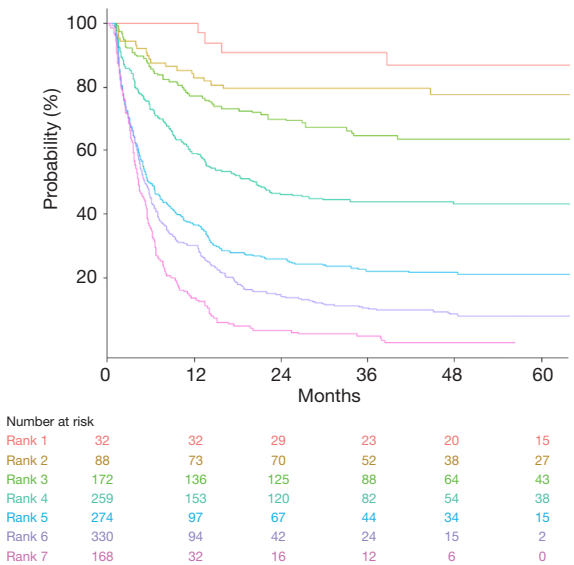

Figure S2 Kaplan-Meier estimation for recurrence-free survival of the training cohort according to ranks stratified by the CCLRS. CCLRS, combined Cox & logistic ranking system.

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Table S4 Common circumstances and the corresponding ranks and risks according to the CCLRS

Tumor size (cm)	CA19-9 (kU/L)	Albumin (g/L)	Platelet (10^9/L)	HBV	Lymph node metastasis	Cholelithiasis	Diabetes	CEA (ng/mL)	AFP (ng/mL)	Resection type	Tumor number	Rank	Risk
≤2.0	≤37	≥35	Any	Any	Absent	Absent	Absent	≤5.0	≤50	Minor	1	1	Low
2.1–3.0	≤37	≥35	≤300	Present	Absent	Absent	Absent	≤5.0	≤50	Minor	2	1	Low
≤2.0	≤37	≥35	≤300	Any	Absent	Absent	Absent	≤5.0	>50	Minor	1	2	Low
2.1–3.0	≤37	≥35	>300	Any	Absent	Absent	Absent	<2.5	≤50	Hemi	1	2	Low
3.1–5.0	≤37	≥35	≤300	Any	Absent	Absent	Absent	<2.5	≤50	Minor	1	2	Low
2.1–3.0	≤37	≥35	≤300	Any	Present	Absent	Absent	>5.0	≤50	Minor	1	3	Moderate
3.1–5.0	≤37	≥35	≤300	Absent	Absent	Absent	Absent	>5.0	≤50	Hemi	1	3	Moderate
2.1–3.0	≤37	≥35	≤300	Any	Absent	Absent	Present	≤5.0	≤50	Hemi	2	4	Moderate
3.1–5.0	≤37	<35	≤300	Absent	Absent	Absent	Absent	≤5.0	≤50	Any	1	4	Moderate
2.1–3.0	>37	≥35	≤300	Any	Absent	Absent	Absent	>5.0	≤50	Hemi	1	5	Moderate
3.1–5.0	>37	≥35	≤300	Absent	Absent	Absent	Absent	≤5.0	≤50	Minor	1	5	Moderate
>5.0	≤37	≥35	<100	Any	Absent	Present	Absent	≤5.0	≤50	Minor	1	5	Moderate
2.1–3.0	>37	≥35	≤300	Absent	Present	Absent	Absent	<2.5	≤50	Minor	1	6	High
3.1–5.0	≤37	≥35	>300	Absent	Present	Absent	Absent	>5.0	≤50	Hemi	1	6	High
>5.0	≤37	≥35	≤300	Absent	Absent	Absent	Absent	<2.5	≤50	Extended	≥3	6	High
3.1–5.0	>37	<35	>300	Absent	Present	Present	Absent	≤5.0	≤50	Minor	1	7	High
>5.0	>37	<35	>300	Absent	Present	Present	Present	≤5.0	>50	Extended	≥3	7	High

CCLRS, combined Cox & logistic ranking system; CA19-9, carbohydrate antigen 19-9; HBV, hepatitis B virus; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein.

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Table S5 Characteristics of the validation cohorts according to the CCLRS ranks

Characteristics	Rank 1 (n=36)	Rank 2 (n=40)	Rank 3 (n=19)	Rank 4 (n=40)	Rank 5 (n=22)	Rank 6 (n=117)	Rank 7 (n=58)	P
Validation cohort 1	8 (22%)	4 (10%)	2 (11%)	12 (29%)	7 (32%)	33 (28%)	18 (31%)	
Validation cohort 2	0	3 (8%)	0	2 (5%)	3 (14%)	2 (2%)	4 (7%)	
Validation cohort 3	28 (78%)	33 (83%)	17 (89%)	27 (66%)	12 (55%)	81 (69%)	36 (62%)	
Diabetes	0	1 (3%)	1 (5%)	3 (7%)	5 (23%)	15 (13%)	11 (19%)	0.013
Cholelithiasis	0	1 (3%)	0	1 (2%)	5 (23%)	14 (12%)	14 (24%)	<0.001
Albumin <35 g/L	0	0	0	2 (5%)	1 (5%)	10 (9%)	15 (26%)	<0.001
Platelet count, $\times10^9$/L								0.001
<100	10 (28%)	2 (5%)	1 (5%)	4 (10%)	3 (14%)	6 (5%)	1 (2%)	
100–300	24 (67%)	37 (93%)	18 (95%)	36 (88%)	18 (82%)	99 (85%)	49 (84%)	
>300	2 (6%)	1 (3%)	0	1 (2%)	1 (5%)	11 (9%)	8 (14%)	
HBV infection	12 (33%)	8 (20%)	1 (5%)	12 (29%)	7 (32%)	19 (16%)	9 (16%)	0.059
AFP >50 ng/mL	2 (6%)	1 (3%)	0	5 (12%)	3 (14%)	17 (15%)	17 (29%)	0.001
CA19-9 >37 kU/L	0	3 (8%)	0	11 (27%)	4 (18%)	92 (79%)	58 (100%)	<0.001
CEA, ng/mL								<0.001
<2.5	28 (78%)	23 (58%)	19 (100%)	20 (49%)	12 (55%)	49 (42%)	9 (16%)	
2.5–5.0	6 (17%)	15 (38%)	0	15 (37%)	7 (32%)	29 (25%)	6 (10%)	
>5.0	2 (6%)	2 (5%)	0	6 (15%)	3 (14%)	38 (32%)	43 (74%)	
Tumor size								
≤2.0	17 (47%)	3 (8%)	2 (11%)	3 (7%)	3 (14%)	3 (3%)	0	<0.001
2.0–3.0	16 (44%)	4 (10%)	0	11 (27%)	3 (14%)	14 (12%)	0	
3.1–5.0	3 (8%)	17 (43%)	17 (89%)	8 (20%)	6 (27%)	34 (29%)	6 (10%)	
>5	0	16 (40%)	0	19 (46%)	10 (45%)	65 (56%)	52 (90%)	
Tumor number								<0.001
1	36 (100%)	39 (98%)	19 (100%)	33 (80%)	17 (77%)	89 (76%)	29 (50%)	
2	0	0	0	2 (5%)	2 (9%)	7 (6%)	6 (10%)	
≥1	0	1 (3%)	0	6 (15%)	3 (14%)	20 (17%)	23 (40%)	
Resection type								0.001
Minor	31 (86%)	27 (68%)	17 (89%)	23 (56%)	10 (45%)	66 (56%)	26 (45%)	
Hemi	5 (14%)	12 (30%)	1 (5%)	16 (39%)	8 (36%)	44 (38%)	27 (47%)	
Extended	0	1 (3%)	1 (5%)	2 (5%)	4 (18%)	6 (5%)	5 (9%)	
Lymph node metastasis	0	1 (3%)	1 (5%)	2 (5%)	9 (41%)	41 (35%)	43 (74%)	<0.001

Data are n (%). The validation cohort 1 was drawn from Renji Hospital (School of Medicine, Shanghai Jiao Tong University), validation cohort 2 from Mengchao Hepatobiliary Hospital (Fujian Medical University), and validation cohort 3 from Zhongshan Hospital (Fudan University). Characteristics were compared using the Pearson's chi-square test. CCLRS, combined Cox & logistic ranking system; HBV, hepatitis B virus; AFP, alpha fetoprotein; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

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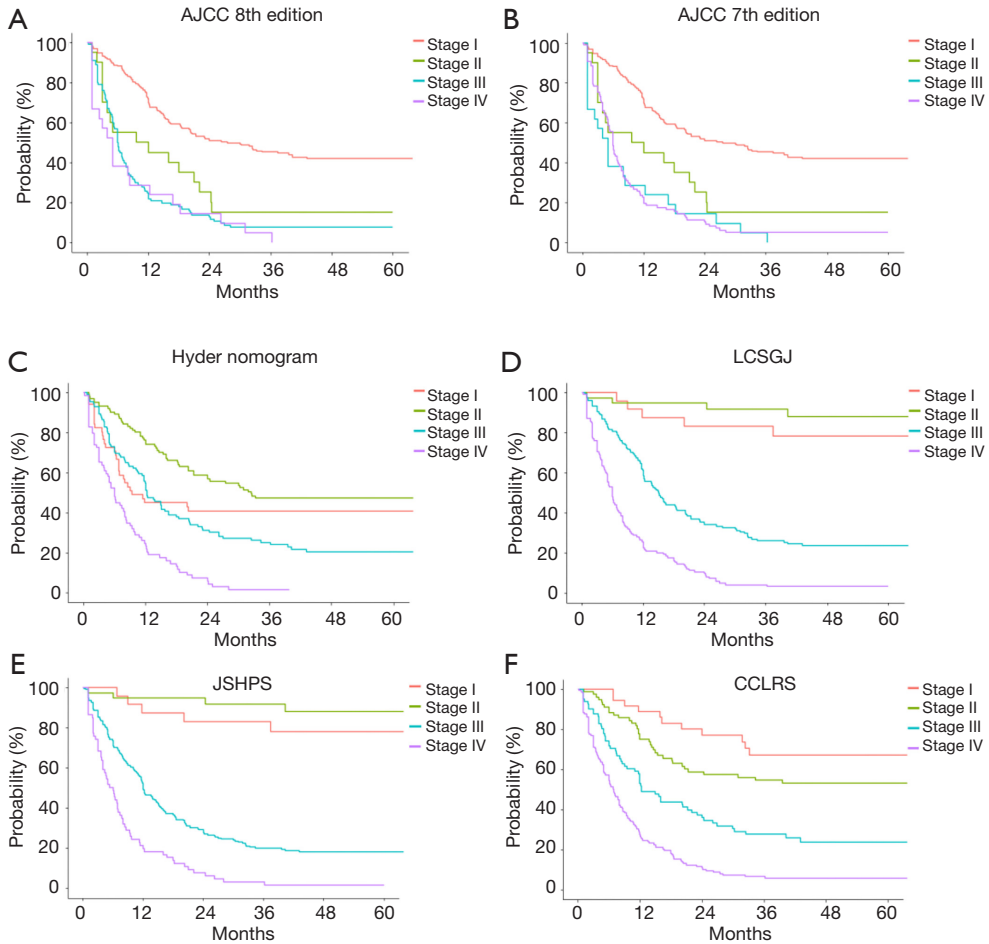

Figure S3 Kaplan-Meier estimations comparing the CCLRS and preexisting ICC staging systems. (A) American Joint Committee on Cancer (AJCC) eighth edition. (B) AJCC seventh edition. (C) Hyder nomogram. (D) Liver Cancer Study Group of Japan (LCSGJ). (E) Japanese Society of Hepato-Biliary Pancreatic Surgery (JSHBPS). (F) CCLRS. To compare with other preexisting systems with 4 stages, the patients in validation cohorts were divided into 4 groups according to the interquartile of risk probability (stage I, 0 to Q1; stage II, Q1 to Q2; stage III, Q2 to Q3; stage IV, Q3 to 1). CCLRS, combined Cox & logistic ranking system; ICC, intrahepatic cholangiocarcinoma.

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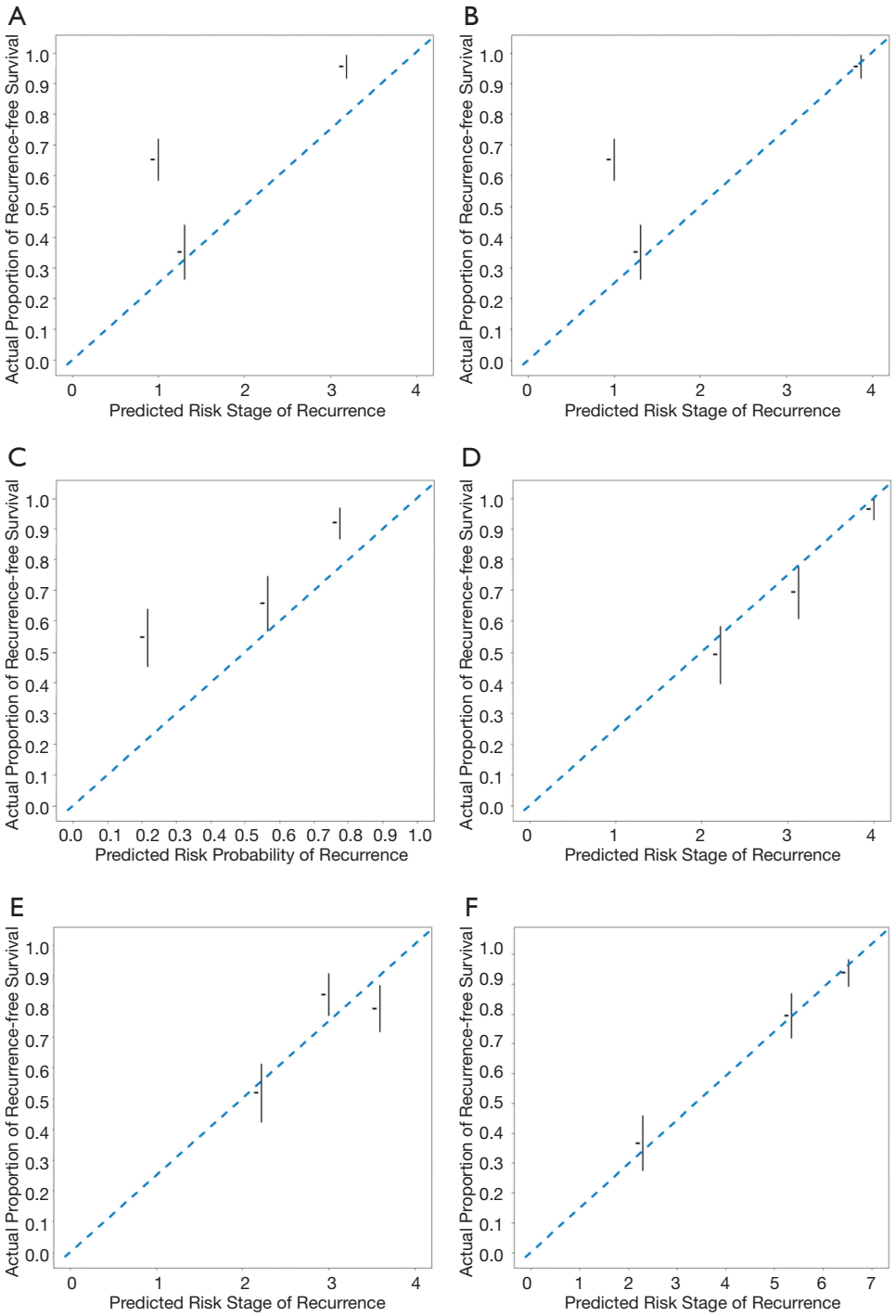

Figure S4 Calibration plots for CCLRS and other ICC prognostic prediction models. (A) American Joint Committee on Cancer (AJCC) eighth edition. (B) AJCC seventh edition. (C) Hyder nomogram. (D) Liver Cancer Study Group of Japan (LCSGJ). (E) Japanese Society of Hepato-Biliary Pancreatic Surgery (JSHBPS). (F) CCLRS. CCLRS, combined Cox & logistic ranking system.

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