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Original Article

Preoperative Prediction Model for Early Recurrence of Intrahepatic Cholangiocarcinoma after Surgical Resection: Development and External Validation Study

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Purpose We aimed to develop a preoperative risk scoring system to predict early recurrence (ER) of intrahepatic cholangiocarcinoma (ICCA) after resection, utilizing clinical and computed tomography (CT) features.

Materials and Methods This multicenter study included 365 patients who underwent curative-intent surgical resection for ICCA at six institutions between 2009 and 2016. Of these, 264 patients from one institution constituted the development cohort, while 101 patients from the other institutions constituted the external validation cohort. Logistic regression models were constructed to predict ER based on preoperative variables and were subsequently translated into a risk scoring system. The discrimination performance of the risk scoring system was validated using external data and compared to the American Joint Committee on Cancer (AJCC) TNM staging system.

Results Among the 365 patients (mean age, 62±10 years), 153 had ER. A preoperative risk scoring system that incorporated both clinical and CT features demonstrated superior discriminatory performance compared to the postoperative AJCC TNM staging system in both the development (area under the curve [AUC], 0.78 vs. 0.68; p=0.002) and validation cohorts (AUC, 0.69 vs. 0.66; p=0.641). The preoperative risk scoring system effectively stratified patients based on their risk for ER: the 1-year recurrence-free survival rates for the low, intermediate, and high-risk groups were 85.5%, 56.6%, and 15.6%, respectively (p < 0.001) in the development cohort, and 87.5%, 58.5%, and 25.0%, respectively (p < 0.001) in the validation cohort.

Conclusion A preoperative risk scoring system that incorporates clinical and CT imaging features was valuable in identifying high-risk patients with ICCA for ER following resection.

Key words Liver, Cholangiocarcinoma, Multidetector computed tomography, Recurrence

Introduction

Intrahepatic cholangiocarcinoma (ICCA) is the second most common type of primary liver cancer, and its incidence and mortality rates have been rising globally in recent decades [1-3]. While complete surgical resection is regarded as the only curative treatment option for ICCA, only 20%-30% of patients present with resectable diseases [4,5]. However, the cumulative tumor recurrence rates and patient survival rates following curative surgical resection are approximately 70% and 30% at 5 years, respectively, indicating a persistently poor prognosis [6-8]. Notably, 50%-70% of patients who undergo surgery experience recurrence, with the majority occurring in the early postoperative period [6,9].

Early recurrence (ER) of ICCA following surgical resection is clinically significant, as patients who experience ER tend to have a poorer prognosis compared to those with late recurrence (LR) [10,11]. Moreover, the predictors for ER differ from those for LR; specifically, tumor size and multifocality are significantly associated with ER but not with LR; therefore, identifying patients who are at risk for ER and understanding the predictors of ER is crucial for developing personalized treatment strategies and management plans.

Given the limited number of patients who benefit from surgery alone, there is a growing interest in the adoption of neoadjuvant chemotherapy for patients with ICCA [5].

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Neoadjuvant chemotherapy may be recommended for ICCA patients with resectable disease who are at high risk of ER [5]. This recommendation is based on recent studies indicating that, among patients with stage I-III ICCA, neoadjuvant therapy is associated with longer overall survival (OS) compared to upfront surgical resection [12-14]. However, the predictive factors associated with a high risk of ER have not been well established. Previous studies have identified several predictors and risk models for ER in ICCA following surgical resection, but these studies were limited by small sample size, single-center design, or a lack of external validation [11,15-18]. Additionally, most of these studies focused on postoperative pathological features, which are not available preoperatively or when determining the implementation of neoadjuvant chemotherapy. In particular, considering that imaging features are available preoperatively and can independently contribute to the prognostication of ICCA, we hypothesized that a preoperative risk model utilizing clinical and computed tomography (CT) imaging features could effectively predict ER in ICCA after surgical resection.

Therefore, we aimed to develop and validate a preoperative risk scoring system to predict the ER of ICCA patients following surgical resection by using clinical and CT imaging features.

Materials and Methods

1. Study design and population

This multicenter, retrospective study was approved by the institutional review boards of all participating centers, which waived the requirements for informed consent. The study included consecutive patients who underwent curative-intent hepatic resection for ICCA at one of six institutions between January 2009 and December 2016. Patients were included if they (1) were 18 years of age or older and (2) underwent multiphasic CT prior to surgery. Patients were excluded if they met any of the following criteria: (1) a history of other malignancies, (2) synchronous hepatocellular carcinoma (HCC), (3) any prior treatment for ICCA, (4) no contrast-enhanced CT within 3 months before surgery, (5) other types of ICCA (e.g., intraductal papillary neoplasm of the bile duct [IPNB]), (6) palliative hepatic resection, or (7) death or loss to follow-up without any evidence of recurrence within 1 year after resection. Data from Asan Medical Center were used to develop the scoring system, while data from the other five institutions (Severance Hospital, Gangnam Severance Hospital, Seoul National University Bundang Hospital, Korea University Ansan Hospital, and National Health Insurance Service Ilsan Hospital) were utilized for external validation (Fig. 1). Of the 365 patients finally enrolled in this study, 314 had been previously reported [19]. While the prior study developed a prognostic model using magnetic resonance imaging (MRI) features to predict OS in patients with ICCA after resection, this study aimed to develop a risk scoring system based on CT and clinical features to predict ER of ICCA.

2. Clinical data

Clinical and pathological data, including demographics, serum tumor markers (carbohydrate antigen 19-9 [CA19-9] and carcinoembryonic antigen [CEA]), viral markers (hepatitis B surface antigen [HBsAg] and hepatitis C antibody), tumor differentiation, the extent of hepatectomy, adjuvant treatment status, and postoperative outcomes, were retrospectively collected from the electronic medical records of each institution. Major hepatectomy was defined as the resection of three or more Couinaud segments, while minor hepatectomy was defined as the resection of two or fewer segments or a wedge resection. Chronic biliary disease was defined as a clinical history of any chronic biliary condition, such as intrahepatic bile duct stones, liver fluke infection, primary sclerosing cholangitis, or primary biliary cirrhosis.

3. CT acquisition and analysis

CT examinations were performed using 16-, 64-, 128-, or 256-slice CT scanners from various vendors (GE HealthCare, Philips Healthcare, and Siemens Healthineers) (Supplementary Methods). CT images were acquired both before and after the intravenous injection of 120-150 mL of non-ionic iodinated contrast at a rate of 3-4 mL/sec, followed by a 20 mL saline flush administered via an automatic power injector. Arterial-phase (AP) images were obtained using a bolus-tracking technique, with a delay of 10-25 seconds after reaching a peak abdominal aortic enhancement of 100 Hounsfield units. Portal venous phase and delayed-phase images were captured at 70-80 seconds and 3 minutes after contrast injection, respectively. The scanning parameters were 70-130 kVp, 120-240 mAs utilizing automatic exposure control, and a slice thickness of 2-5 mm with no gap. Coronal reformatted images for the portal venous phase were available for all patients.

Three board-certified abdominal radiologists, each with over 13 years of experience in hepatic imaging, independently reviewed the CT images from both the development and validation cohorts. To minimize the inter-reader variability across the institutions, prior to the independent review, the three reviewers discussed and defined each imaging finding using 50 representative ICCA cases that were not included in this study. The reviewers were blinded to clinical, pathological, and prognostic information during the image analysis. All images were provided as anonymized Digital Imaging and Communications in Medicine (DICOM) files and were

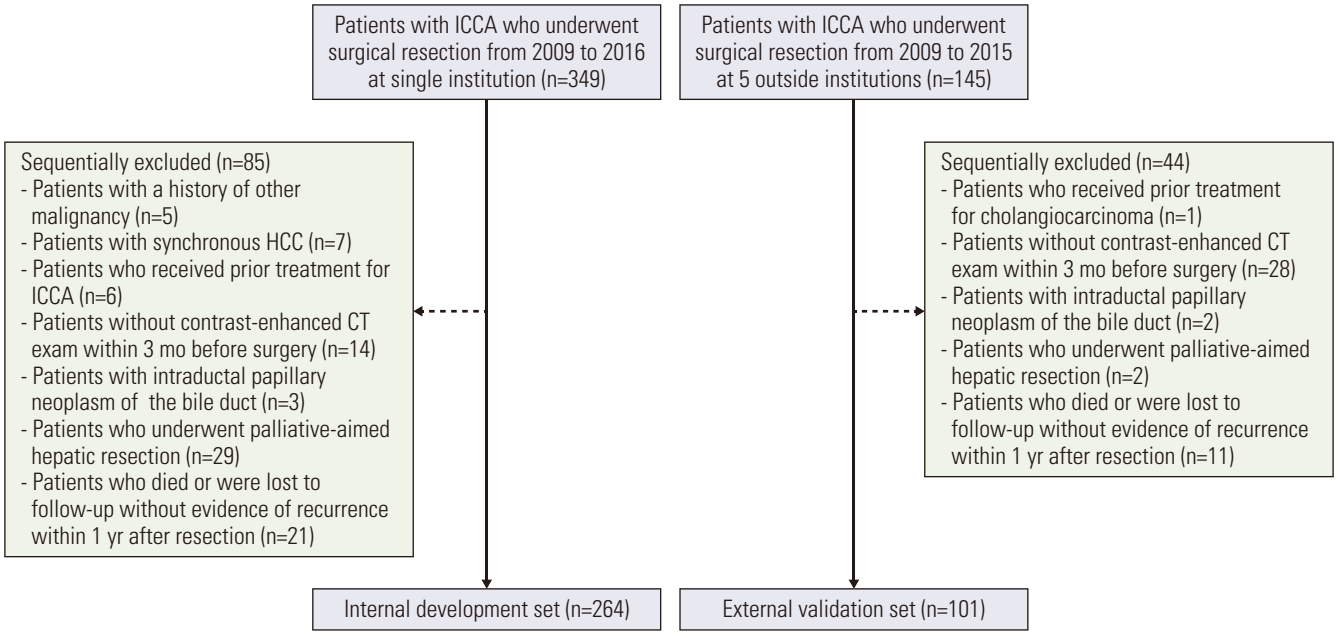

Fig. 1. Flow diagram of the study population. CT, computed tomography; HCC, hepatocellular carcinoma; ICCA, intrahepatic cholangiocarcinoma.

analyzed using a commercial DICOM viewer (RadiAnt DICOM Viewer, Medixant). The CT findings assessed included tumor size, tumor contour, tumor location, AP enhancement pattern, AP peritumoral enhancement, delayed central enhancement, tumor multiplicity, vascular invasion, tumor-in-vein, extrahepatic organ invasion, suspicious lymph node metastasis, and bile duct invasion. The definitions of each CT feature are detailed in S1 Table. In cases where discrepancies arose among the reviewers' interpretations, they re-evaluated the images collaboratively to reach a consensus.

4. Pathologic analysis and determination of American Joint Committee on Cancer TNM stage

ICCA was pathologically diagnosed using the surgical specimen, in accordance with the 2019 World Health Organization classification. Tumor size, number, microvascular or macrovascular invasion, visceral peritoneal invasion, and extrahepatic organ invasion were evaluated, and the pathologic T category was determined according to the eighth edition of the American Joint Committee on Cancer (AJCC) system (S2 Table) [20]. The presence of lymph node metastasis was also assessed (pN0 or pN1 category). In patients who did not undergo lymphadenectomy (Nx category), the following composite reference standards were used to determine the N category: the development of suspicious regional lymph nodes on follow-up imaging tests, such as CT, MRI, or positron emission tomography (PET), within 3 months after surgery was classified as N1; conversely, the absence of suspicious regional lymph nodes on follow-up imaging tests for at least 1 year after surgery was classified as N0.

5. Follow-up

After surgical resection, patients were regularly monitored through serum tumor markers and imaging studies, including contrast-enhanced CT or MRI, at intervals of 3 to 6 months, in accordance with each institution's protocol. For patients with rising tumor marker levels and inconclusive imaging findings, additional PET-CT was performed. Recurrence was defined as any sign of recurrent ICCA, either pathologically-proven or suspected on CT/MRI (documented progression on serial imaging or confirmed hypermetabolism on additional PET/CT) with or without elevated CA 19-9 [21].

The primary endpoint of our study was the incidence of ER, defined as the occurrence of recurrence within 1 year after resection. While the definition of ER varied across studies, the majority of studies used 12 months as the cutoff for ER [15,16,22,23], and we adopted this definition of ER. Very early recurrence (VER) was defined as the occurrence of recurrence within 6 months after resection. Recurrence-free survival (RFS) was defined as the interval between surgical resection and either tumor recurrence or all-cause death, while OS was defined as the interval between resection and all-cause death.

6. Statistical analysis

Categorical variables were compared using chi-squared or Fisher's exact tests and are summarized as counts with percentages. Continuous variables were compared using two-sample t-tests or Wilcoxon rank-sum tests and are expressed as means with standard deviations or medians with interquartile ranges (IQRs). Inter-reader agreements for imaging characteristics were evaluated using Fleiss' κ statistics for categorical variables and the intraclass correlation coefficient for tumor size. A κ statistic of 0.8-1.0, 0.6-0.79, 0.40-0.59, 0.2-0.39, and 0-0.19 was considered to indicate excellent, good, moderate, fair, and poor agreement, respectively.

In the development cohort, univariable and multivariable logistic regression analyses were performed to identify preoperative factors independently associated with ER following surgical resection. For continuous variables, the optimal cutoff points were determined using the maximum Youden index from the receiver operating characteristic (ROC) curve for ER. Variables with a p-value < 0.05 in the univariable analysis were retained for the multivariable analysis. To assess the additional value of imaging features in predicting ER, we tested two models: Model 1, which utilized only preoperative clinical features, and Model 2, which incorporated both preoperative clinical and CT features. These risk models were developed based on the final step of the multivariable logistic regression analysis. Specifically, the β coefficients of the risk factors for ER identified in the final step of the respective multivariable logistic regression models were employed. The discrimination performance of the two models was quantified using the area under the ROC curve (AUC) and compared through DeLong's test. Among the two risk models (model 1 vs. model 2), the preoperative model demonstrating superior predictive performance was selected, and the risk score was calculated by dividing each β by the smallest β. The performance of the preoperative risk scoring system was compared with that of the AJCC TNM staging system, which was based on postoperative pathological results. The calibration abilities were evaluated using a calibration plot of the predicted probabilities against the observed outcomes. Additionally, the optimal cutoffs for the preoperative risk scoring system were determined to stratify patients into low, intermediate, or high-risk categories for ER, utilizing the X-tile program [24]. Differences in RFS among these three patient groups were assessed using the Kaplan-Meier method with the log-rank test. In the external validation cohort, we compared the predictive performance of the preoperative risk scoring system with the AJCC TNM staging system, and we assessed the differences in RFS among the three risk groups: low, intermediate, and high risk. Additionally, the performance of preoperative risk scoring system for predicting VER was evaluated in both the development and validation cohorts.

Statistical analyses were performed using SPSS ver. 29.0 (IBM Corp.) or R ver. 4.3.2 (R Foundation for Statistical Computing), with $p < 0.05$ indicating statistical significance.

Results

1. Patient characteristics

Of the 494 eligible patients, 129 were excluded for the following reasons: five with a history of other malignancies, seven with synchronous HCC, seven who had received prior ICCA treatment, 42 without preoperative contrast-enhanced CT, five with IPNB, 31 who underwent palliative resection, and 32 who either died or were lost to follow-up within a year without recurrence (Fig. 1). Consequently, the study included 365 patients (mean age, 62±10 years, 264 in the development cohort and 101 in the validation cohort). Clinical, pathological, and CT imaging characteristics of the development and validation cohorts are summarized in Table 1 and S3 Table. Compared to the validation cohort, the development cohort exhibited a higher proportion of patients who were positive for HBsAg (23.5% vs. 9.7%, p=0.010) and a lower proportion of those with centrally located tumors (22.0% vs. 32.7%, p=0.034). Also, there were significant differences in microvascular invasion (MVI; $p < 0.001$), lymph node metastasis (p=0.045), visceral peritoneum perforation (p=0.008), and TNM stage (p=0.015) between the development and validation cohorts. No significant differences were observed in other clinical, pathological, or CT imaging characteristics between the two cohorts.

During a median follow-up of 36.8 months, 365 patients received follow-up CT (median exam number, 13; IQR, 7 to 24) and 118 received MRI (median exam number, 2; IQR, 1 to 4). Among the 365 patients, 240 experience recurrence: 96 (40.0%) were diagnosed with recurrence by confirming hypermetabolism at the suspected recurrence site on PET/CT in addition to CT/MRI examinations, 45 (18.8%) by pathological diagnosis, and 99 (41.2%) by confirming progression on serial imaging with or without elevated CA 19-9. Of the 240 patients with recurrence, 153 patients experienced ER, and 102 experienced VER. Among the 153 patients with ER, 44 (28.8%) had intrahepatic recurrence only, 68 (44.4%) had extrahepatic recurrence only, and 41 (26.8%) had both intrahepatic and extrahepatic recurrences. Patients without ER demonstrated significantly longer OS compared to those with ER (median OS, 63.0 vs. 15.7 months; $p < 0.001$) (S4 Fig.).

2. Development of a preoperative risk scoring system to predict ER

According to the maximum Youden index, the optimal

Table 1. Clinical and imaging characteristics of the developmental and validation cohorts

	Development cohort (n=264)	Validation cohort (n=101)	p-value
Clinical feature			
Age (yr)	61.6±10.3	62.6±9.1	0.415
Sex			
Men	167 (63.3)	62 (61.4)	0.741
Women	97 (36.7)	39 (38.6)	
HBsAg (+)	62 (23.5)	7 (9.7)	0.010
Anti-HCV (+)	7 (2.7)	4 (5.6)	0.228
Serum CA 19-9 (U/mL)	37.8 (12.0-250.4)	39.5 (11.5-282.3)	0.830
≥ 37 U/mL	137 (51.9)	60 (59.4)	0.198
≥ 330 U/mL	60 (22.7)	21 (20.8)	0.691
Serum CEA (ng/mL)	2.7 (1.7-4.9)	2.3 (1.6-4.1)	0.140
Chronic biliary disease[a]	36 (13.6)	15 (14.9)	0.765
Cirrhosis	41 (15.5)	8 (7.9)	0.056
Tumor differentiation[b]			
Well or moderately differentiated	192 (75.0)	80 (82.5)	0.137
Poorly differentiated	64 (25.0)	17 (17.5)	
Resection procedure			0.131
Major hepatectomy	155 (58.7)	68 (67.3)	
Minor hepatectomy	109 (41.3)	33 (32.7)	
Adjuvant treatment	118 (44.7)	46 (45.5)	0.884
CT imaging feature			
Tumor size (cm)	5.0±2.5	4.6±2.3	0.285
≥ 5 cm	107 (40.5)	36 (35.6)	0.392
Tumor contour			
Round/Lobulated	235 (89.0)	91 (90.1)	0.764
Infiltrative	29 (11.0)	10 (9.9)	
Tumor location			
Central	58 (22.0)	33 (32.7)	0.034
Peripheral	208 (78.0)	68 (67.3)	
AP enhancement pattern			
Hypo/rim enhancement	230 (87.1)	89 (88.1)	0.797
Non-rim enhancement	34 (12.9)	12 (11.9)	
AP peritumoral enhancement	89 (33.7)	41 (40.6)	0.219
Delayed central enhancement	105 (39.8)	41 (40.6)	0.886
Tumor multiplicity (≥ 2)	55 (20.8)	16 (15.8)	0.281
Vascular invasion	116 (43.9)	48 (47.5)	0.538
Tumor-in-vein	11 (4.2)	3 (3.0)	0.765
Extrahepatic organ invasion	15 (5.7)	5 (5.0)	0.784
Suspicious lymph node metastasis	70 (26.5)	28 (27.7)	0.816
Bile duct invasion	125 (47.3)	46 (45.5)	0.757

Values are presented as mean±SD, number (%), or median (IQR). AP, arterial-phase; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CT, computed tomography; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; IQR, interquartile range; SD, standard deviation. [a]Defined as the clinical history of any kind of chronic biliary condition, such as intrahepatic bile duct stone, liver fluke infection, primary sclerosing cholangitis, or primary biliary cirrhosis, [b]Data for 12 patients are unavailable.

cutoff values for serum CA 19-9 and CEA were 330 U/mL and 7.5 ng/mL, respectively. In the multivariable analysis using only clinical features (model 1), CA 19-9 (≥ 330 U/mL; odds ratio [OR], 3.44; 95% confidence interval [CI], 1.74 to 6.78; $p < 0.001$) and tumor differentiation (poorly differentiated; OR, 2.31; 95% CI, 1.26 to 4.21; p=0.006) were identified as independent predictors of ER after surgery (Table 2). In the multivariable analysis incorporating both clinical and

Table 2. Univariable and multivariable analyses of predictors of early recurrence of ICCA in the development cohort

Variable	Univariable analysis		Multivariable analysis for model 1[a]			Multivariable analysis for model 2[b]		
	OR (95% CI)	p-value	OR (95% CI)	p-value	Regression coefficient	OR (95% CI)	p-value	Regression coefficient
Clinical factor								
Age (< 65 yr)	1.25 (0.76-2.04)	0.379						
Sex (female)	1.23 (0.74-2.04)	0.423						
HBsAg (+)	1.02 (0.57-1.81)	0.947						
Serum CA 19-9 (≥ 330 U/mL)	4.28 (2.30-7.97)	< 0.001	3.44 (1.74-6.78)	< 0.001	1.235	2.88 (1.41-5.87)	0.004	1.058
Serum CEA (≥ 7.5 ng/mL)	3.60 (1.77-7.30)	< 0.001						
Chronic biliary disease (+)	2.32 (1.13-4.77)	0.022						
Cirrhosis (+)	0.56 (0.28-1.14)	0.110						
Tumor differentiation (poorly differentiated)	2.01 (1.14-3.56)	0.016	2.31 (1.26-4.21)	0.006	0.836	2.42 (1.26-4.64)	0.008	0.884
Imaging factor								
Tumor size (per cm)	1.20 (1.08-1.33)	0.001						
Tumor contour (infiltrative)	2.02 (0.92-4.41)	0.079						
Tumor location (central)	2.68 (1.47-4.89)	0.001				2.26 (1.12-4.53)	0.022	0.814
AP enhancement pattern (hypo/rim)	3.35 (1.40-8.02)	0.006						
AP peritumoral enhancement	2.56 (1.52-4.32)	< 0.001				2.28 (1.26-4.12)	0.007	0.882
Delayed central enhancement	0.71 (0.43-1.17)	0.176						
Tumor multiplicity	6.15 (3.10-12.19)	< 0.001				5.52 (2.62-11.65)	< 0.001	1.708
Vascular invasion	2.58 (1.56-4.25)	< 0.001						
Tumor-in-vein	1.61 (0.48-5.42)	0.441						
Extrahepatic organ invasion	5.76 (1.59-20.95)	0.008				5.13 (1.21-21.74)	0.026	1.635
Suspicious lymph node metastasis	3.55 (2.00-6.31)	< 0.001						
Bile duct invasion	2.41 (1.47-3.97)	0.001						

AP, arterial-phase; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, confidence interval; HBsAg, hepatitis B surface antigen; ICCA, intrahepatic cholangiocarcinoma; OR, odds ratio. [a]Model using only clinical features that are preoperatively available, [b]Model using imaging features in addition to preoperatively available clinical features.

Table 3. Final preoperative risk scoring system for early recurrence of ICCA

Factor	Risk score
Serum CA 19-9 (≥ 330 U/mL)	2
Poorly differentiated ICCA	1.5
Central tumor location	1.5
AP peritumoral enhancement	1.5
Tumor multiplicity	3
Extrahepatic organ invasion	3

AP, arterial-phase; CA, carbohydrate antigen; ICCA, intrahepatic cholangiocarcinoma.

CT features (model 2), CA 19-9 (OR, 2.88; 95% CI, 1.41 to 5.87; p=0.004), tumor differentiation (OR, 2.42; 95% CI, 1.26 to 4.64; p=0.008), central location (OR, 2.26; 95% CI, 1.12 to 4.53; p=0.022), AP peritumoral enhancement (OR, 2.28; 95% CI, 1.26 to 4.12; p=0.007), tumor multiplicity (OR, 5.52; 95% CI, 2.62 to 11.65; p < 0.001), and extrahepatic organ invasion (OR, 5.13; 95% CI, 1.21 to 21.74; p=0.026) were identified as independent predictors of ER.

The inter-reader agreement for the four significant CT imaging features among the three reviewers ranged from fair to good (S5 Table). Among these features, the agreement for tumor location (κ=0.78), AP peritumoral enhancement (κ=0.63), and tumor multiplicity (κ=0.59) were moderate to good, whereas the agreement for extrahepatic organ invasion (κ=0.39) was fair. The overall percentage of agreement ranged from 74.2% to 87.5%.

Because Model 2 demonstrated significantly higher discrimination performance than Model 1 (AUC, 0.79 [95% CI, 0.73 to 0.84] vs. 0.68 [95% CI, 0.62 to 0.74]; p < 0.001), Model 2 was selected as the final predictive model and was subsequently translated into a risk scoring system. The risk score was calculated as follows: score sum=2 (CA 19-9 ≥ 330 U/mL)+1.5 (poorly differentiated)+1.5 (central location)+1.5 (AP peritumoral enhancement)+3 (tumor multiplicity)+3 (extrahepatic organ invasion) (Table 3).

3. Performance of the preoperative risk scoring system to predict ER

In the development cohort, the risk scoring system showed good discriminatory performance with an AUC of 0.78 (95% CI, 0.73 to 0.84), which was significantly higher than that of the TNM staging system (AUC, 0.68 [95% CI, 0.63 to 0.74]) (p=0.002). Calibration plots indicated that the predicted risk was well-aligned with the observed risk (S6 Fig.). Table 4 shows the predicted and observed risks for ER stratified by risk groups. Based on the risk score, patients were categorized into low-risk (risk score < 1.5), intermediate-risk (risk score 1.5-5), or high-risk (risk score ≥ 5) groups. The 1-year RFS rates in the low-, intermediate-, and high-risk groups were 85.5%, 56.6%, and 15.6%, respectively (p < 0.001) (Fig. 2A).

In the validation cohort, the AUC was 0.69 (95% CI, 0.58 to 0.79), which was slightly higher than that of the TNM staging system (AUC, 0.66 [95% CI, 0.59 to 0.73]) (p=0.641). The 1-year RFS rates in the low-, intermediate-, and high-risk groups were 87.5%, 58.5%, and 25.0%, respectively (p < 0.001) (Fig. 2B).

For predicting VER, the AUC of the risk scoring system was 0.77 (95% CI, 0.70 to 0.83) in the development cohort and 0.74 (95% CI, 0.61 to 0.86) in the validation cohort.

Discussion

In this study, we found that ER of ICCA following surgical resection was significantly associated with high levels of CA 19-9 (≥ 330 U/mL; OR, 2.88; p=0.004), poorly differentiated ICCA (OR, 2.42; p=0.008), central tumor location (OR, 2.26; p=0.022), AP peritumoral enhancement (OR, 2.28; p=0.007), tumor multiplicity (OR, 5.52; p < 0.001), and extrahepatic organ invasion (OR, 5.13; p=0.026) (Fig. 3). Using these clinical and CT imaging features, we developed a preoperative risk scoring system to predict the ER of ICCA. This system demonstrated superior predictive performance for ER compared to the postoperative AJCC TNM staging system in both the development cohort (AUC, 0.78 vs. 0.68; p=0.002) and the validation cohort (AUC, 0.69 vs. 0.66; p=0.641).

Table 4. Predicted and observed risks for early recurrence of ICCA based on the risk scores

Sum of risk scores	Development set		Validation set	
	Predicted risk	Observed risk (95% CI)	Predicted risk	Observed risk (95% CI)
< 1.5 (low risk)	0.17	0.15 (0.08-0.24)	0.22	0.13 (0.03-0.32)
≥ 1.5, < 5 (intermediate risk)	0.44	0.46 (0.37-0.54)	0.39	0.42 (0.29-0.54)
≥ 5 (high risk)	0.85	0.84 (0.71-0.94)	0.70	0.75 (0.43-0.95)

CI, confidence interval; ICCA, intrahepatic cholangiocarcinoma.

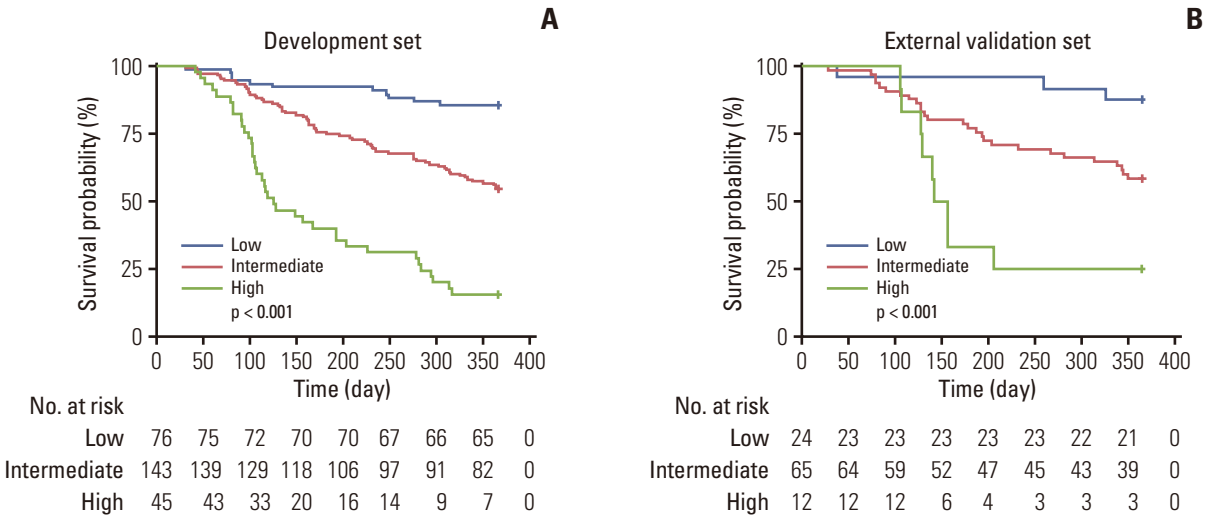

Fig. 2. Kaplan-Meier curves of 1-year recurrence-free survival across risk groups stratified based on the preoperative risk scoring system in the development (A) and external validation (B) cohorts.

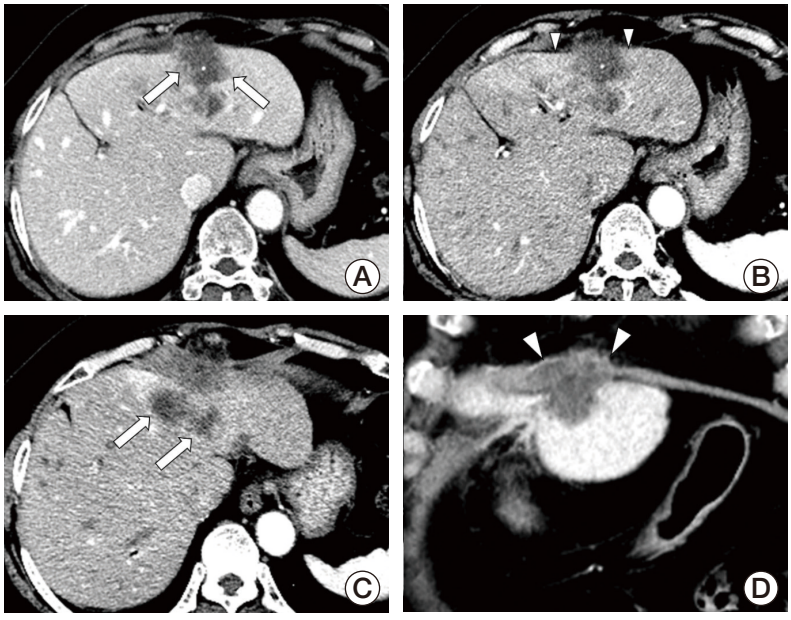

Fig. 3. Dynamic computed tomography (CT) images of a 77-year-old female patient with intrahepatic cholangiocarcinoma. (A) The axial portal venous phase image showed a 4-cm hypoenhancing mass with exophytic growth anteriorly in segment III (arrows). (B) The axial arterial-phase image showed peritumoral enhancement with broad contact to the tumor border (arrowheads). (C) The arterial-phase image shows two satellite metastatic lesions in the same segment (arrows), also accompanied by peritumoral enhancement. (D) The coronal portal venous phase image displays the main tumor directly invading the adjacent diaphragm (arrowheads). The preoperative serum carbohydrate antigen 19-9 level was 6,613 U/mL, and the tumor was classified as poorly differentiated. The total risk score was 11, categorizing the patient as high-risk for early recurrence. The patient underwent left hemihepatectomy and diaphragm resection, achieving a margin-negative resection. However, tumor recurrence was detected on follow-up CT 5 months after surgery, presenting with intrahepatic and peritoneal metastasis (not shown).

The risk model that incorporates both clinical and CT features significantly outperformed the prediction of ER of ICCA compared to the model using clinical features alone (AUC, 0.79 vs. 0.68; $p < 0.001$). While elevated CA 19-9 levels, which indicate a higher tumor burden, and poor differentiation, reflecting aggressive tumor biology, are well-established prognostic markers for ICCA [6,25], CT imaging features play a crucial role in estimating the risk of ER. CT scans provide accurate information regarding the extent of the tumor, including the presence of multiplicity and extrahepatic organ invasion, and these features are widely utilized in various postoperative prognostic models [20,26,27]. Additionally, tumor location (central vs. peripheral) assessed by CT has prognostic significance. Centrally located ICCAs are known to have a poor prognosis, likely due to the high incidence of margin-positive resections associated with technical challenges in the surgical field. Furthermore, AP peritumoral enhancement was significantly related to the ER of ICCA. Considering that AP peritumoral enhancement is a well-known imaging feature associated with MVI in both HCC and combined hepatocellular-cholangiocarcinoma [28,29], and pathological MVI in ICCA is associated with high post-surgical recurrence rate [11], AP peritumoral enhancement may serve as a significant predictor for ER of ICCA.

Our preoperative risk scoring system demonstrated good discriminatory performance in both the development and external validation cohorts and outperformed the postoperative AJCC TNM staging system. By leveraging a large multicenter cohort and focusing exclusively on preoperative variables, our risk scoring system represents a significant advancement, providing a practical tool that can be utilized prior to surgical intervention. Specifically, this system can guide clinical decisions regarding neoadjuvant therapy. Although the role of neoadjuvant chemotherapy in ICCAs remains a topic of debate, growing evidence suggests its potential to achieve longer OS [12,13]. Because neoadjuvant therapy may help reduce the risk of ER or disease progression by eliminating micrometastatic disease, our preoperative risk scoring system may enhance patient selection by identifying those who are likely to benefit from neoadjuvant chemotherapy, particularly patients with early progression. For example, neoadjuvant therapy may offer substantial advantages in ICCA patients classified as high-risk using our scoring system (risk score ≥ 5). In contrast, upfront surgery appears to be more suitable for those classified as low-risk (risk score < 1.5). However, further clinical trials are necessary to validate whether neoadjuvant therapy in high-risk patients indeed improves postoperative survival and cost-effectiveness.

Our risk scoring system effectively predicted the ER of ICCA and outperformed the postoperative AJCC TNM system in the developmental cohort. However, the discriminatory performance slightly decreased in the external validation cohort. The differences between the development and validation cohorts can primarily be attributed to significant variations in pathological tumor characteristics. Compared to the development cohort, the validation cohort exhibited more aggressive pathological features, including a higher incidence of MVI, lymph node metastasis, and advanced tumor stages (S3 Table). Additionally, the frequency of HBsAg and cirrhosis was higher in the development cohort, suggesting that small-duct type ICCA was more prevalent in this group than in the validation cohort. Given that small-duct type ICCA has a better prognosis than large-duct type ICCA [30], we can infer that there was substantial heterogeneity in prognosis as well as in tumor characteristics between the two cohorts. These results may indicate the robustness of the prediction model, demonstrating that our risk scoring system can perform satisfactorily even in cohorts with significantly different baseline characteristics. Therefore, the scoring system we proposed is generalizable across various clinical settings, providing a reliable tool for preoperative risk stratification.

This study has several limitations. First, its retrospective design may introduce selection bias, potentially limiting the generalizability of our findings. To mitigate this limitation, we included eligible patients from multi-institutional cohorts. Second, while the multi-institutional nature of the study cohort enhances methodological rigor and generalizability, it may have led to heterogeneity in surgical indications and techniques among the participating institutions. In addition, inter-reader variability and bias for assessing CT imaging features may be substantial in the multicenter study. In our study, the overall percentage of agreement of significant CT imaging features was over 74%. Given the moderate agreement, our results should be carefully interpreted. Third, we utilized multiphasic CT as the imaging modality instead of MRI. Although MRI may provide more detailed diagnostic and prognostic information, it has several disadvantages, including limited accessibility, longer scan times, higher costs, and susceptibility to motion artifacts. Given the greater generalizability of CT compared to MRI, we chose CT to develop a preoperative risk scoring system. Fourth, while current guidelines advocate for a 6-month regimen of adjuvant chemotherapy after curative resection of ICCA [5,31,32], only 44.9% of patients in our cohort underwent adjuvant therapy, which may have influenced survival outcomes. This is primarily because the study included patients treated between 2009 and 2016, a time when robust evidence from randomized clinical trials supporting adjuvant chemotherapy was not yet available. Nevertheless, this percentage exceeds the rates of adjuvant chemotherapy reported in

more recent studies on ICCA (18.9%-36.3%) [10,11,23,33].

In conclusion, we developed and validated a preoperative risk scoring system to predict ER in patients with ICCA following curative-intent resection, utilizing clinical and CT imaging features. Our risk scoring system exhibited superior performance in predicting ER of ICCA compared to the postoperative AJCC TNM staging system. This may offer valuable insights for identifying high-risk patients with ICCA who could benefit from neoadjuvant chemotherapy.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The institutional review boards of all participating institutions approved this study and the requirement for informed consent was waived due to the retrospective nature of the study.

Author Contributions

Conceived and designed the analysis: Kim DH, Choi SH.
Collected the data: Choi SH, Rhee H, Cho ES, Yeom SK, Park S, Lee SS, Park MS.
Contributed data or analysis tools: Kim DH, Choi SH, Kim S.
Performed the analysis: Kim DH, Choi SH, Kim S.
Wrote the paper: Kim DH, Choi SH, Kim S, Lee SS.
Visualization: Kim DH, Choi SH.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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