Original Article

Predictive model for very early recurrence of patients with perihilar cholangiocarcinoma: a machine learning approach

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Background: Although offering the best chance of potential cure for patients with localized perihilar cholangiocarcinoma (pCCA), resection has been associated with high morbidity and sometimes poor long-term outcomes due to recurrence. We sought to develop a predictive model to identify individuals at high risk for very early recurrence (VER) after curative-intent surgery for pCCA.

Methods: Patients who underwent curative-intent surgery for pCCA between 2000–2023 were identified from a multi-institutional database. An eXtreme Gradient Boosting (XGBoost) model was developed to estimate the risk of VER, defined as recurrence within 6 months after resection. The relative importance of clinicopathologic factors was determined using SHapley Additive exPlanations (SHAP) values.

Results: Among 434 patients undergoing curative-intent resection for pCCA, 65 (15.0%) patients developed VER. Median overall survival (OS) among patients with and without VER was 8.4 [interquartile range (IQR) 6.6–11.3] versus 38.5 (IQR 31.9–45.7) months (P<0.001). An XGBoost model was able to stratify patients relative to the risk of VER [low-risk: 6-month recurrence-free survival (RFS) 94.6% *vs.* intermediate-risk: 6-month RFS 88.3% *vs.* high-risk: 6-month RFS 40.0%; P<0.001]. Similarly, 3-year OS incrementally worsened based on VER risk (low-risk: 75.3% *vs.* intermediate-risk: 19.5% *vs.* high-risk: 4.6%; P<0.001). The SHAP algorithm identified age, preoperative carbohydrate antigen 19-9 (CA19-9) levels, tumor size and differentiation/grade, as well as lymph node metastasis as the five most important predictors of VER. The predictive accuracy of the model was good in the training [c-index: 0.74, 95% confidence interval (CI): 0.67–0.81] and internal validation (c-index: 0.77, 95% CI: 0.71–0.83) cohorts. An easy-to-use risk calculator for VER was developed and made available online at: https://junkawashima.shinyapps.io/VER_hilar/.

Conclusions: A novel, machine learning based model was able to predict accurately the chance of VER after curative-intent resection of pCCA. In turn, the tool may help surgeons in the selection of patients likely

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to benefit the most from resection, as well as counsel individuals about the anticipated risk of recurrence in the early post-operative period.

Keywords: Perihilar cholangiocarcinoma (pCCA); very early recurrence (VER); predictive model; online calculator; machine learning (ML)

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Introduction

Perihilar cholangiocarcinoma (pCCA) is the most common primary bile duct malignancy with an increasing incidence over the last several decades (1,2). Unfortunately, surgical treatment, which is the only potentially curative treatment for patients with localized pCCA, has been associated with high mortality and sometimes poor oncological outcomes (3). Of note, 44.0% to 83.2% of patients with pCCA will have a recurrence after curative-intent resection (3-5). Additionally, postoperative adjuvant chemotherapy has only modest benefits among patients following resection of pCCA (6). Accurate identification of patients who are at high risk of developing recurrence may help select individuals who benefit the most from surgical resection. In particular, a subset of patients may experience early recurrence within the first year of surgery (3-5,7-9). Patients with early versus late recurrence of pCCA generally have a worse prognosis following resection (3). In turn, patients who have an early recurrence often experience decisional regret, depression, and worse quality-of-life (10-12).

Early recurrence for pCCA, as well as other hepatobiliary cancers, has been defined as a recurrence occurring within 12 to 30 months after surgical resection (3,13-15). Notably, a previous study from our own group reported that approximately one-quarter of patients with intrahepatic cholangiocarcinoma (ICC) had very early recurrence (VER) (i.e., recurrence within 6 months after initial resection) (16,17). Patients with ICC who experienced VER had a very poor overall survival (OS) that was similar to patients with advanced cholangiocarcinoma who received systemic therapy only, indicating that patients at risk for VER may derive little benefit from resection (16,17). Prediction of VER may also help frame individualized surveillance strategies following resection, as well as inform adjunct treatment including perioperative systemic chemotherapy (3). To date, there are no tools to predict VER among pCCA patients following curative-intent resection for pCCA. Most predictive models have utilized conventional statistical techniques and have not employed novel machine learning (ML) methods (18). As such, the objective of the current study was to develop a predictive model to identify individuals at risk of VER after curative-intent surgery for pCCA. We developed and validated an ML model [i.e., eXtreme gradient boosting (XGBoost) algorithm] to predict VER using a large international multi-institutional database. Furthermore, to facilitate the clinical applicability of the model, an easy-to-use online calculator to predict the risk of VER among individuals undergoing curative-intent surgery for pCCA was provided. This article is presented in accordance with the TRIPOD reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-385/rc).

Highlight box

Key findings

- In this multi-institutional cohort study, 15.0% of patients developed very early recurrence (VER) following resection for perihilar cholangiocarcinoma (pCCA) with a detrimental association with overall survival (OS) (3-year OS, 9.2%). Predictive models and an easy-to-use risk calculator were developed to identify high-risk patients for VER with good predictive accuracy in the training as well as the internal validation data sets.

What is known and what is new?

- While surgical treatment is the only potentially curative option for patients with localized pCCA, it is associated with high mortality rates and sometimes poor oncological outcomes.
- The frequency, prognosis, and risk factors of VER in patients who underwent curative-intent surgery for pCCA have been identified.

What is the implication, and what should change now?

- These data emphasize that VER is associated with poor prognosis after pCCA resection and highlight the need for individualize management of perioperative treatment and surveillance according to the risk of recurrence in the early postoperative period.

Methods

Study population and data collection

Patients who underwent curative-intent resection for pCCA between 2000 and 2023 were identified from an international multi-institutional database from eight major hepatobiliary institutions across the globe. VER of pCCA was defined as recurrence within 6 months after resection, consistent with the definition used in previous studies (16,19-22). Patients who had extrahepatic metastasis, R2 resection margins, or who died within 30 days following surgery were excluded. Additionally, individuals who had palliative surgery or who had missing data on key clinicodemographic characteristics were also not included. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of The Ohio State University Wexner Medical System (IRB#2108C0025). All participating institutions (Yokohama City University, University of Verona, Curry Cabral Hospital, Emory University, Erasmus University Medical Centre, University of Sydney, Cleveland Clinic, and The Ohio State University Wexner Medical System) were informed and agreed the study. Obtaining informed consent from all individual participants was not required as the study relied on secondary data analysis of de-identified patient data.

Variables and outcomes of interest

Patient demographic and clinicopathologic variables included age, sex, year of surgery (i.e., 2000–2010 or 2011–2023), region (i.e., western or eastern), receipt of preoperative systemic chemotherapy, preoperative jaundice, portal vein embolization (PVE), preoperative carbohydrate antigen 19-9 (CA19-9), type of surgery (i.e., extrahepatic bile duct resection only, right hepatectomy, left hepatectomy, extended right hepatectomy, extended left hepatectomy, right trisectionectomy, left trisectionectomy, central hepatectomy, or other), combined vascular resection, lymphadenectomy, intraoperative blood loss, operation time, intraoperative frozen section analysis of margin status, number of harvested lymph node (LN) (i.e., <6 or ≥6), T-category (i.e., T1/T2 versus T3/T4), LN metastasis, pathological stage, pathological tumor size, tumor differentiation (i.e., well, moderately differentiated versus poorly, undifferentiated), microvascular invasion (MVI), perineural invasion (PNI), pathological margin status, as well as postoperative severe complications and receipt of adjuvant chemotherapy. The American Joint Committee on Cancer (AJCC) 8th edition staging manual was used for T, N-category classification, and staging (23). Severity of postoperative complications was defined according to the Clavien-Dindo classification system (grade I–V); severe complications were defined as Clavien-Dindo classification ≥ III (24).

In this multi-institutional study, the indication of surgical treatment was guided by the protocols of each participating institution. The standard approach for pCCA generally involved a combination of liver resection and bile duct resection. If R0 resection was deemed achievable with extrahepatic bile duct resection alone, this approach was very seldomly used as certain institutions. Decisions regarding the type of resection and surgical techniques were, therefore, tailored to each institution and treating surgeon. Following curative-intent resection, patients were monitored for recurrence based on serum tumor markers and imaging, such as computed tomography and/or magnetic resonance imaging. Patients were followed once every 3 to 4 months during the first 3 years, once every 6 months during the 4th and 5th years, and then annually (16). The criteria for administering adjuvant chemotherapy were based on each institution's protocol. Recurrence-free survival (RFS) was defined as the time elapsed between the date of resection and recurrence confirmed on biopsy or evidence of a suspicious lesion on follow-up imaging; OS was defined as the time interval between the date of resection for pCCA and date of death or last follow-up. Recurrence was categorized as either local or distant. Local recurrence was defined as a recurrence at the hepaticojejunostomy or in an area where surgical procedures had been performed, including the liver hilum and hepatoduodenal ligament. All other recurrences were defined as distant (25). Treatment of tumor recurrence was based on consensus among the multidisciplinary team at each institution.

Statistical analysis

Descriptive statistics were presented as median values [interquartile range (IQR)] and frequency (%) for continuous and categorical variables, respectively. Continuous variables were compared using the Mann-Whitney *U* or Kruskal-Wallis tests, as appropriate. While categorical variables were compared with the Fishers exact test (χ^2). Multiple imputations with chain equations (MICE) procedures were utilized to handle missing values (26).

Survival was assessed using Kaplan-Meier curves along with log-rank tests and statistical significance was determined at α=0.05.

The XGBoost-algorithm-powered survival model was employed to develop a predictive model of VER following curative-intent resection of pCCA (27). XGBoost is an advanced implementation of the gradient boosting framework designed for speed and performance (28). This approach builds an ensemble of decision trees in which each new tree corrects the errors of the previous trees, resulting in a robust predictive model (28). Candidate variables for the XGBoost model, which were selected based on the literature, included age, preoperative jaundice, preoperative CA19-9 level, the number of harvested LN, AJCC T category, LN metastasis, tumor size, tumor differentiation, MVI, PNI, margin status, severe complication, and adjuvant chemotherapy (3,9,29-31). In the present study, hypermeters, which are used to control the learning process of ML models, were selected by grid search cross-validation (28). The c-index was calculated for the entire dataset followed by the bootstrapping resampling method (n=5,000) to assess the performance of the predictive model. SHapley Additive exPlanations (SHAP) values were used to interpret the predictions of the predictive model for VER (32). This approach is based on cooperative game theory and the concept of Shapley values, ensuring a fair distribution of "payout" (feature importance) among features (32). Subsequently, the patients were stratified into low-, intermediate-, or high-risk for VER using the model based on optimal cutoffs determined using the X-tile program (33). An easy-to-use web application to calculate risk at 6 months after resection was made freely available (https://junkawashima.shinyapps.io/VER_hilar/). The predictive ability of recurrence within 6 months after surgery was compared between the proposed predictive model and the AJCC 8th Edition Staging System, which includes stages I, II, IIIA, IIIB, IIIC, and IVA (23). Model discrimination was estimated using the area under the time-dependent receiver operating characteristic curve (time-dependent AUC) at 6 months after curative-intent resection.

An additional analysis to construct a preoperative predictive model was performed, which excluded data from three institutions that lacked preoperative examination information. This model incorporated preoperative clinical factors such as age, lymph node disease detected on preoperative imaging, portal vein or hepatic artery invasion observed on preoperative imaging, preoperative serum total bilirubin, systemic immune-inflammation index (SII), and CA19-9. The SII was calculated by multiplying the platelet-to-lymphocyte ratio by platelet counts (33). The preoperative predictive model was constructed using the XGBoost algorithm. The c-index was calculated for the additional analysis dataset, and the bootstrapping resampling method (n=5,000) was applied to evaluate the performance of the preoperative predictive model. SHAP values were applied to interpret the model's predictions for VER. Patients were then stratified into low- or high-risk groups for VER based on optimal cutoffs determined through the X-tile program, and the model was integrated into the online calculator. All statistical analyses were performed using R version 4.2.0 (R Project for Statistical Computing, Vienna, Austria).

Results

Baseline cohort characteristics

Overall, 496 patients underwent curative-intent surgery for pCCA; 28 patients were excluded due to 30-day postoperative mortality [the 30-day mortality: 5.6% (n=28)]; an additional 34 patients were excluded related to other exclusion criteria. Among 434 patients included in the analytic cohort, median patient age was 68.0 (IQR: 58.0–74.5) years and 255 (58.8%) patients were male (*Table 1*). Overall, most patients (n=329, 75.8%) had preoperative jaundice and some patients underwent PVE (n=107, 24.7%) with a median preoperative serum CA19-9 of 114.5 (IQR: 24.7–563.8) U/mL. Only a small number of patients (n=23, 5.3%) received preoperative systemic chemotherapy. Most patients underwent liver resection combined with bile duct resection (n=403, 92.9%) with lymphadenectomy (n=415, 95.6%), vascular resection (n=150, 34.6%); roughly half of the patients had ≥6 LNs harvested (n=247, 56.9%). On postoperative pathology, primary tumor was classified as T3/T4 disease (n=117, n=27.0%) with LN metastasis reported in 176 (40.6%) patients. Most patients had a moderate to well-differentiated tumor (n=331, 76.3%) with PNI (n=364, 83.9%) and a median size of 3.0 (IQR: 2.0–4.0) cm. Some patients had MVI (n=179, 41.2%) and a positive resection margin (n=160, 36.9%); a total of 169 patients (38.9%) experienced a postoperative severe complication, and 20 (4.3%) patients died within 90-day. Among the 160 (36.9%) patients who received adjuvant chemotherapy, 61 (14.0%) were treated with Gemcitabine-based regimens, 39 (9.0%) with capecitabine, and 32 (7.4%) with other regimens. Information on the remaining 28 (6.4%) patients

Table 1 Comparison of baseline characteristics and clinicopathological variables between patients with and without very early recurrence within 6 months after curative-intent resection perihilar cholangiocarcinoma

Characteristics	Total, n=434	Non-VER, n=369 (85.0%)	VER, n=65 (15.0%)	P value
Age, years, median (IQR)	68.0 (58.0–74.5)	68.0 (58.0–74.0)	69.0 (58.0–75.0)	0.38
Sex, male, n (%)	255 (58.8)	220 (59.6)	35 (53.8)	0.46
Year of surgery, n (%)				>0.99
2000–2010	119 (27.4)	101 (27.4)	18 (27.7)	
2011–2023	315 (72.6)	268 (72.6)	47 (72.3)	
Region, n (%)				0.24
Western	402 (92.6)	339 (91.9)	63 (96.9)	
Eastern	32 (7.4)	30 (8.1)	2 (3.1)	
Preoperative chemotherapy, n (%)	23 (5.3)	21 (5.7)	2 (3.0)	0.57
Jaundice, n (%)	329 (75.8)	275 (74.5)	54 (83.1)	0.18
Portal vein embolization, n (%)	107 (24.7)	94 (25.5)	13 (20.0)	0.43
CA19-9 (U/mL), median (IQR)	114.5 (24.7–563.8)	107.0 (23.0–560.0)	175.5 (42.7–830.0)	0.23
Type of resection, n (%)				–
Extrahepatic bile duct resection only	31 (7.1)	25 (6.8)	6 (9.2)	
Right hepatectomy	50 (11.5)	47 (12.7)	3 (4.6)	
Left hepatectomy	22 (5.0)	22 (6.0)	0 (0.0)	
Extended right hepatectomy	69 (15.9)	64 (17.3)	5 (7.7)	
Extended left hepatectomy	77 (17.7)	69 (18.7)	8 (12.3)	
Right trisectionectomy	64 (14.7)	46 (12.5)	18 (27.7)	
Left trisectionectomy	67 (15.4)	57 (15.4)	10 (15.4)	
Central hepatectomy	30 (6.9)	20 (5.4)	10 (15.4)	
Others	24 (5.5)	19 (5.1)	5 (7.7)	
Lymphadenectomy, n (%)	415 (95.6)	355 (96.2)	60 (92.3)	0.28
Combined vascular resection, n (%)	150 (34.6)	117 (31.7)	33 (50.8)	0.005*
Intraoperative frozen section analysis, n (%)				<0.001*
Yes	237 (54.6)	220 (59.6)	17 (4.6)	
No	37 (8.5)	36 (9.8)	1 (1.5)	
Unknown	160 (36.9)	113 (30.6)	47 (72.3)	
Intraoperative blood loss, mL, median (IQR)	524 (300–1,100)	500 (300–1,028)	1000 (462–1,665)	0.11
Operative time, minute, median (IQR)	540 (361–633)	540 (364–632)	536 (393–636)	0.76
Number of harvested LN, n (%)				0.08
<6	187 (43.1)	152 (41.2)	35 (53.8)	
≥6	247 (56.9)	217 (58.8)	30 (46.2)	
AJCC T category, n (%)				0.37
T1/T2	317 (73.0)	273 (74.0)	44 (67.7)	
T3/T4	117 (27.0)	96 (26.0)	21 (32.3)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Total, n=434	Non-VER, n=369 (85.0%)	VER, n=65 (15.0%)	P value
AJCC N category, n (%)				0.03*
N0	258 (59.4)	228 (61.8)	30 (46.2)	
N1/N2	176 (40.6)	141 (38.2)	35 (53.8)	
AJCC stage, n (%)				0.02*
Stage I	32 (7.4)	32 (8.7)	0 (0.0)	
Stage II	157 (36.2)	139 (37.7)	18 (27.7)	
Stage IIIA	53 (12.2)	42 (11.4)	11 (16.9)	
Stage IIIB	16 (3.7)	15 (4.1)	1 (1.5)	
Stage IIIC	142 (32.7)	113 (30.6)	29 (44.6)	
Stage IVA	34 (7.8)	28 (7.6)	6 (9.2)	
Tumor size, cm, median (IQR)	3.0 (2.0–4.0)	2.7 (2.0–4.0)	3.0 (2.2–4.0)	0.09
Tumor differentiation, n (%)				0.20
Well or moderate	331 (76.3)	286 (77.5)	45 (69.2)	
Poor	103 (23.7)	83 (22.5)	20 (30.8)	
Microvascular invasion, n (%)	179 (41.2)	144 (39.0)	35 (53.8)	0.04*
Perineural invasion, n (%)	364 (83.9)	305 (82.7)	59 (90.8)	0.15
Margin status, n (%)				<0.001*
R=0	274 (63.1)	246 (66.7)	28 (43.1)	
R=1	160 (36.9)	123 (33.3)	37 (56.9)	
Severe complications, n (%)	169 (38.9)	134 (36.3)	35 (53.8)	0.01*
Adjuvant chemotherapy, n (%)	160 (36.9)	141 (38.2)	19 (29.2)	0.21
Recurrence, n (%)	269 (62.0)	204 (55.3)	65 (100.0)	<0.001*

*, P value <0.05. VER, very early recurrence; IQR, interquartile range; CA19-9, carbohydrate antigen 19-9; LN, lymph node; AJCC, The American Joint Committee on Cancer.

was not available. Of note, roughly two-thirds of patients still experienced a recurrence (n=269, 62.0%).

Association of clinicopathologic characteristics and survival with VER

Overall, 65 patients (15.0%) experienced a VER. Among the 369 (85.0%) patients who did not have a VER, 204 patients (47.0%) had a recurrence >6 months after resection, while 165 individuals (38.1%) did not experience a recurrence during the follow-up period. The recurrence pattern at the time of initial recurrence was detailed in Table S1. After a median follow-up of 21.1 (IQR: 10.5–41.3) months, patients with VER demonstrated worse median OS (8.4, IQR 6.6–11.3 *vs.* 38.5, IQR 31.9–45.7) months and 3-year OS (9.2% *vs.* 32.3%) than individuals without VER (P<0.001) (*Figure 1*). Patients with VER were more likely to have had concomitant hepatic resection with vascular resection (n=33, 50.8% *vs.* n=117, 31.7%; P=0.005), as well as had experienced a severe postoperative complication (n=35, 53.8% *vs.* n=134, 36.3%; P=0.01). Patients with VER more frequently had LN metastases (n=35, 53.8% *vs.* n=141, 38.2%; P=0.03), MVI (n=35, 53.8% *vs.* n=144, 39.0%; P=0.04), and a positive resection margin (n=37, 56.9% *vs.* n=123, 33.3%; P<0.001) (*Table 1*).

Development and validation of the predictive model of VER

The contributions of the different variables in the XGBoost

model to predict VER following the resection of pCCA are presented in *Figure 2*. Notably, the five most important risk factors predictive of VER included LN metastasis, preoperative CA19-9 value, age, tumor size, and tumor differentiation; AJCC T stage, MVI, severe complications, and PNI were also associated with VER. The discriminative accuracy of the predictive model based on these factors was favorable in both the derivative [c-index: 0.74; 95% confidence interval (CI): 0.67–0.81] and validation (c-index: 0.77; 95% CI: 0.71–0.83) cohorts. Based on the predictive model, patients were categorized into three distinct risk groups using the X-tile program relative to VER: low-risk (n=186, 42.9%, 6-month RFS: 94.6%), intermediate-risk (n=184, 42.4%, 6-month RFS: 88.3%), and high-risk (n=64, 14.7%, 6-month RFS: 40.0%) (log-rank, P<0.001) (*Figure 3A*); an estimated incidence of recurrence less than 5.7% within 6 months was classified as low risk, while a rate of 25% or more was classified as high risk. Similarly, patients were also stratified relative to OS: low-risk (3-year OS: 75.3%), intermediate-risk (3-year OS; 19.5%), and high-risk (3-year OS; 4.6%) (log-rank, P<0.001) (*Figure 3B*). To facilitate the clinical applicability of the proposed risk model, an easy-to-use online calculator to predict VER of pCCA patients undergoing curative-intent resection was constructed and made available at: https://junkawashima.shinyapps.io/VER_hilar/ (Figure S1).

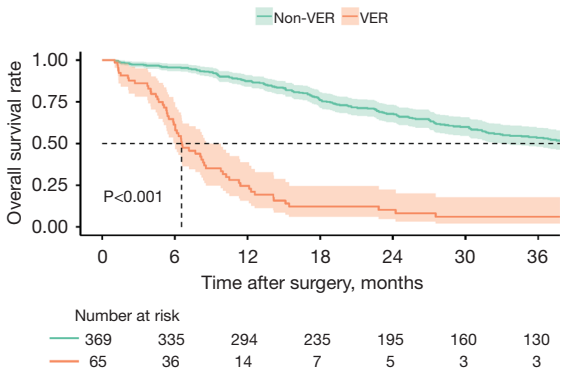

Figure 1 Kaplan-Meier curve demonstrating the differences in overall survival between patients with and without VER. VER, very early recurrence.

Notably, the predictive accuracy of AJCC staging system (c-index: 0.59, 95% CI: 0.54–0.65) performed poorly compared with the proposed ML model (c-index: 0.74; 95% CI: 0.67–0.81). In fact, the 6-month time-dependent AUC for AJCC staging system was only 0.62 (95% CI: 0.55–0.68) versus 0.80 (95% CI: 0.73–0.86) for the proposed ML VER predictive model (P<0.001) (*Figure 4*).

Additional analysis for development and validation of the preoperative predictive model

An additional analysis was conducted to develop a preoperative predictive model using data from 198 patients, among whom 18 (9.1%) individuals experienced VER (Table S2). The contributions of variables in the

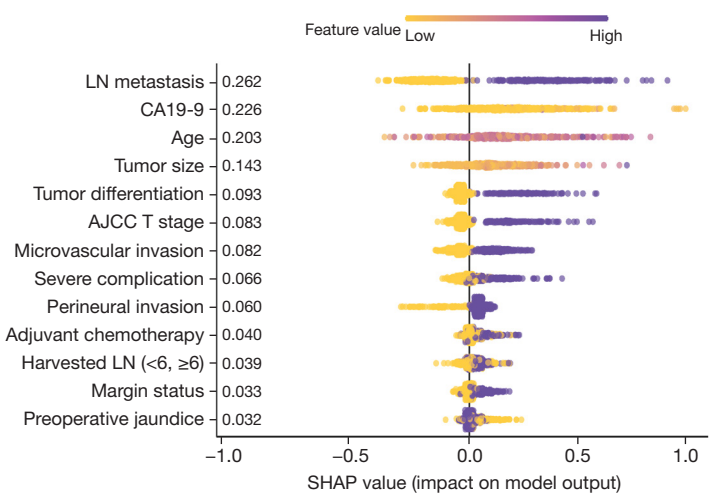

Figure 2 SHAP summary plot demonstrating weightages of pre and postoperative clinicopathological factors in predicting very early recurrence. LN, lymph node; CA19-9, carbohydrate antigen 19-9; AJCC, The American Joint Committee on Cancer; SHAP, SHapley Additive exPlanations.

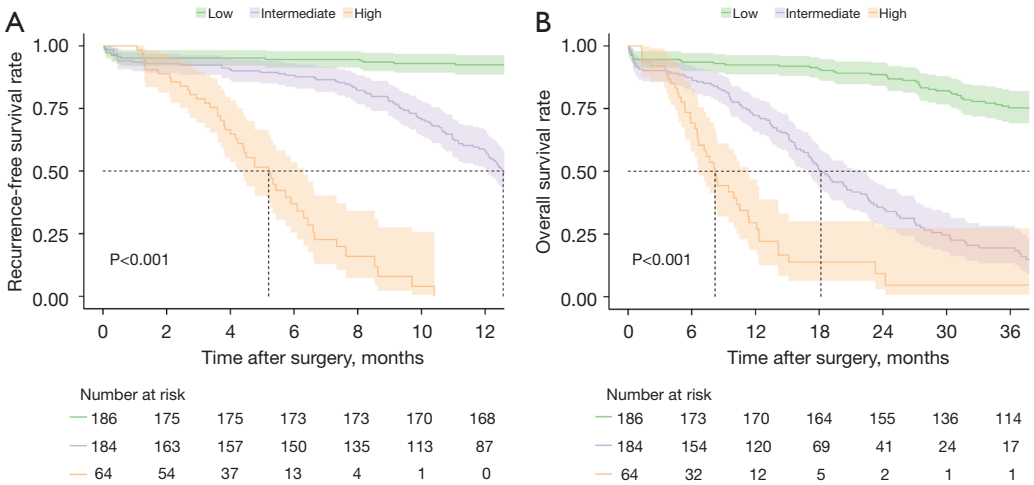

Figure 3 Kaplan-Meier curves demonstrating the differences in recurrence-free survival (A) and overall survival (B) stratified by risk group for very early recurrence according to postoperative risk model.

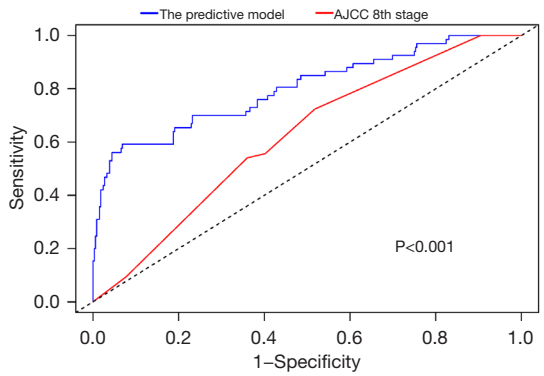

Figure 4 Time-dependent receiver operating characteristic curves at 6 months after curative-intent resection for the XGBoost model in the current study and the AJCC 8th staging system. AJCC, The American Joint Committee on Cancer; XGBoost, eXtreme gradient boosting.

preoperative model to predict VER were reported in Figure S2. Preoperative CA19-9 level, age, and SII were the three factors most strongly associated with likelihood of VER. The model demonstrated good discriminative accuracy with a c-index of 0.70 (95% CI: 0.59–0.80) in the derivation cohort and 0.69 (95% CI: 0.60–0.79) in the internal validation cohort. Using the X-tile program, patients were stratified into low-risk (n=109, 55%; 6-month RFS: 95.4%, 12-month RFS: 89.0%) versus high-risk (n=89, 45%; 6-month RFS: 83.8%, 12-month RFS: 50.6%) relative to VER (log-rank, P<0.001) (Figure S3A). Patients were also stratified relative to OS: low-risk (3-year OS: 78.7%) and high-risk (3-year OS; 27.5%) (log-rank, P<0.001) (Figure S3B).

Discussion

Recurrence after curative-intent surgery for pCCA can be high with an incidence ranging from 44.0–83.2% (3-5). Unfortunately, recurrence after resection of pCCA can occur early with a subset of patients experiencing recurrent disease within one year after surgery (3-5,7-9). Several previous studies have used the term VER to characterize recurrence within 6 months following resection for ICC, hepatocellular carcinoma (HCC), and colorectal liver metastases (16,19-22). These studies demonstrated poor prognosis of patients with VER, emphasizing the importance of predicting VER in terms of consideration for perioperative systemic chemotherapy, clinical trials, and other non-surgical treatments (16,19,20). However, the oncological outcome and risk factors of VER have not been defined among patients undergoing curative-intent surgery for pCCA. The current study was important because we demonstrated that 15.0% of patients with pCCA had VER and, in turn, a very poor prognosis. We developed and validated a predictive model to calculate risk of VER using a ML approach that leveraged data from a large, international cohort of patients from major Eastern and Western hospitals from around the world. Using this artificial intelligence predictive model, patients were categorized into low-, intermediate-, and high-risk categories who had an incrementally worse 6-month RFS (94.6%, 88.3%, and

40.0%, P<0.001). A preoperative predictive model was also developed that had good discrimination. Furthermore, an online calculator was developed that physicians can easily access to estimate individualized risk of VER in the pre- and postoperative setting. To our knowledge, this is the first study to provide a clinical prediction tool to assess the likelihood of VER among patients undergoing curative-intent surgery for pCCA.

Surgical resection for pCCA is challenging because the tumor arises in an anatomical complex location that involve the bile ducts and abut the hepatic artery and portal vein; many cases require major liver resection with bile duct and portal vein reconstruction, which may impede postoperative recovery and lead to a higher incidence of complications (34). Indeed, a recent systematic review reported a pooled severe morbidity and 90-day mortality among patients who underwent curative intent surgery of 40.0% and 9.0%, respectively (35). In addition, pCCA is a highly aggressive malignancy with a 5-year survival of 8.0–39.7% (3). For patients who undergo curative-intent surgery, early recurrence is associated with a particularly poor prognosis (3,5,35). Zhao *et al.* reported that patients with recurrence within a year had a median OS of 15 months (95% CI: 12.3–17.7 months) (5). In the current study, 15.0% of patients who underwent curative-intent resection for pCCA recurred within 6 months; these patients had a very poor median OS of 8.4 months and 3-year survival of only 9.2%, which was a worse prognosis than early recurrence related to other malignant diagnoses (5,36). Of note, a recent phase 3 randomized clinical trial demonstrated that patients with advanced biliary tract cancer receiving systemic chemotherapy with gemcitabine and cisplatin, with or without pembrolizumab, had a median OS of 12.7 and 10.9 months, respectively, which was comparable to the outcomes of patients with VER in the current study (37). Given the aggressive nature of pCCA and the substantial surgical risks, it is important to balance the potential benefits of surgery against the likelihood of VER. As such, predicting VER is important in terms of the selection of patients likely to benefit the most from resection. In addition, tools such as the proposed online calculator can help to individualize management of perioperative treatment and surveillance according to the risk of recurrence in the early postoperative period.

In the current study, SHAP values were used to interpret the associations of each clinicopathological factor with the estimated risk of VER for patients with pCCA. Among the prognostic factors for pCCA, patient age, LN metastasis, preoperative CA19-9, tumor size, and tumor differentiation were the most important factors of VER based on the XGBoost based-postoperative predictive model (3,9,29-31). Among these factors, LN metastasis had the highest weight to predict the risk of VER. This finding was in line with a meta-analysis on prognostic factors of early recurrence for pCCA by Tian *et al.* that demonstrated LN metastasis was the factor most strongly associated with early recurrence (3). Likewise, CA19-9 also demonstrated an important role in prognosis, as noted in previous studies (38,39). CA19-9 is a well-known tumor biomarker, which reflects the aggressive tumor biology in cholangiocarcinoma. Notably, a systematic review of prognostic biomarkers in pCCA demonstrated preoperative CA19-9 was strongly associated with lower OS in ten out of thirteen studies and poorer RFS in four studies (38). In the current study, patients age also was associated with pCCA VER, which was consistent with other studies demonstrating the prognostic effect of age on survival outcomes (16,36,40). Other factors predictive of VER included tumor size and differentiation, which was consistent with other reports (3,29-31). For instance, Zhang *et al.* demonstrated that prognostic stratification by tumor diameter outperformed AJCC staging system (29). Additionally, a recent meta-analysis noted that poorly differentiated tumors were associated with more than a two-fold increased risk of early recurrence among patients with pCCA (3). Collectively, these pathological factors reflect the malignancy potential of pCCA, and the potential ability to use these factors collectively to more accurately predict VER. In the preoperative predictive model, both age and CA19-9 were clinical factors strongly associated with VER, which was consistent with the postoperative predictive model. Notably, SII, a relatively recent inflammatory biomarker, also was an important predictive factor (33). Inflammation is a crucial driver in tumor biology, promoting extracellular matrix breakdown, cancer progression, immunosuppression, and angiogenesis, all of which support metastatic spread (41,42). Initially identified as a prognostic marker in HCC, SII has since been applied to other gastrointestinal cancers (33). In the field of cholangiocarcinoma, some investigators have demonstrated SII to be a prognostic factor independent of other conventional clinicopathological factors (33,43,44). For instance, Toyoda *et al.* reported that high SII values were associated with a 1.46-fold increase in recurrence among patients with extrahepatic bile duct cancer (44). Collectively, these findings suggest that SII may capture the inflammatory microenvironment of pCCA tumors and

potentially help predict VER risk.

Of note, the XGBoost-based postoperative predictive model demonstrated favorable discriminative accuracy for the entire cohort (c-index: 0.74; 95% CI: 0.67–0.81), as well as the bootstrapped resampled internal cohort (c-index: 0.77; 95% CI: 0.71–0.83). Moreover, the model stratified patients incrementally into three distinct groups relative to VER and OS: low-risk (6-month RFS: 94.6%, 3-year OS: 75.3%), intermediate-risk (6-month RFS: 88.3%, 3-year OS: 19.5%), and high-risk (6-month RFS: 40.0%, 3-year OS: 4.6%) (*Figure 3*). Traditional simple risk factors such as LN metastasis, CA19-9 levels, and AJCC Staging system may not fully identify risk of VER when used separately as single prognostic indicators (3,23,38,39). Specifically, the real-world clinical environment represents a web of interrelated and confounding factors that may influence patient outcomes in complex ways. To address these reality and achieve a more tailored and accurate prognostic prediction, the use of ML techniques has become increasingly popular (45). The improved performance of the XGBoost model mostly derives from its decision tree architecture, which has the ability to capture independently nuanced relationships among variables (28). Among these ML techniques, the XGBoost statistical approach may be superior to other ML techniques in terms of prediction accuracy (32,46). In fact, XGBoost-based models have been used to predict risk of cardiac surgery-associated acute kidney damage and postoperative pancreatic fistula with high discriminatory accuracy (28,47). In the current study, the proposed XGBoost-based postoperative predictive model outperformed the AJCC 8th staging system with respect to c-index and time-dependent AUC at 6 months after resection (*Figure 4*). Furthermore, to make this complicated predictive model accessible, an easy-to-use, online calculator was developed. An easy-to-use online calculator can facilitate use by clinicians by allowing the simple input of individual data points with subsequent real-time predictions of VER risk. The ease of use and immediate feedback provided by the calculator may help clinical decision-making, particularly in augmenting surveillance strategies and guiding the use of perioperative chemotherapy.

To assess the VER risk preoperatively, we also developed an XGBoost-based preoperative predictive model. Although the predictive ability was slightly inferior to that of the postoperative predictive model, the preoperative model demonstrated reasonable discriminative accuracy with a c-index of 0.70 (95% CI: 0.59–0.80) in the derivation cohort and 0.69 (95% CI: 0.60–0.79) in the internal validation cohort. Given the aggressive nature of pCCA and the significant surgical risks involved, it may be beneficial to consider preoperative systemic chemotherapy for high-risk VER patients. This approach mirrors the standard practice for pancreatic ductal adenocarcinoma, which also carries a poor prognosis due to its aggressive behavior (48). Preoperative systemic chemotherapy can serve both therapeutic and selection roles, helping to determine which patients are most likely to benefit from curative-intent surgery (16,33). In fact, neoadjuvant therapy has been demonstrated to be effective in increasing disease-free survival among patients with pCCA (49). By providing risk estimates for VER with reasonable accuracy, the predictive tool may assist the multidisciplinary team in decision-making regarding preoperative chemotherapy for pCCA patients, offering valuable guidance in tailoring treatment strategies.

The findings of this current study should be interpreted in light of several limitations. Even though the multi-institutional nature of the database was a strength, there may have been some heterogeneity in patient selection and surgical techniques among the different participating centers. In particular, variations in the indications and types of adjuvant chemotherapy across institutions and over time may have influenced the results. Additionally, while the predictive model for VER performed well in both the training and internal validation cohorts using bootstrapping resampling, future prospective studies should be conducted to standardize surgical indications, techniques, and postoperative management, as well as to validate the proposed models externally. A preoperative prediction model for VER was developed; however, only 198 cases had sufficient preoperative test information, resulting in a relatively small sample size. Future work should aim to build the preoperative prediction model for VER in a larger cohort to enhance its robustness and applicability.

Conclusions

In conclusion, 15% of patients undergoing curative-intent resection for pCCA developed VER, which was associated with a dismal prognosis. Various patient-, tumor-, and treatment-specific factors were associated with VER among patients with pCCA. These factors were utilized to develop ML prediction models to categorize patients into groups relative to risk of VER and survival with high accuracy. Furthermore, an easy-to-use, online calculator

was made available to help with the selection of patients likely to benefit the most from resection, as well as counsel individuals about the anticipated risk of recurrence in the early post-operative period.

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Footnote

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