Peer Review File

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Reviewer A:

Comment 1: This reviewer doubts the novelty of this study, because there are a plenty of previous studies that investigated survival risk analysis after surgical resection of perihilar cholangiocarcinoma. It is quite obvious that very early recurrence is closely related with a worse survival outcome in cancer surgery. The results of this study showed the following factors relevant with very early recurrence after surgery: age, preoperative CA19-9 level, tumor size, differentiation/grade, and lymph node metastasis. However, all of these are already known risk factors. Therefore, this reviewer does not think this manuscript worths publishing on this journal with its impact factor.

Reply 1: We thank the Reviewer for the comment. While prior research has identified several factors associated with survival risk among patients undergoing surgical resection for perihilar cholangiocarcinoma (pCCA), the current study provides a novel contribution by focusing specifically on the prediction of recurrence within 6 months post-surgery. This very early recurrence (VER) is a critical period influencing follow-up strategies and postoperative management, such as the receipt of adjuvant chemotherapy. We believe that a model targeting this specific timeframe offers new insights that differ from broader survival analyses reported in previous studies. In addition, to ensure the practical application of our findings in the clinical settings, we developed an online calculator based on the VER prediction model. This calculator is intended as a clinical decision-making tool, providing an accessible way for practitioners to assess VER risk quickly and conveniently.

Our study further distinguishes itself with the use of machine learning techniques, which allowed us to incorporate a complex array of interacting clinical variables with greater precision than traditional methods. This approach enhances the model's predictive accuracy by capturing nuanced relationships between risk factors, enabling a more comprehensive assessment of each patient's recurrence risk.

We conducted an additional analysis to develop a preoperative prediction model that integrated other factors not often used into the same online calculator for convenience. (See Page 11, Lines 1-12, Pages 19,20, Lines 14-5) This preoperative model highlighted the systemic immune-inflammation index (SII) as a significant predictor of recurrence following tumor markers, underscoring the relevance of inflammatory markers in risk stratification. (See Pages 14,15, Lines 9-2, Pages 17,18, Lines 23-11) We believe that incorporating SII, a factor less emphasized in prior models, provides a unique perspective that further strengthens our study's contribution to the field.

In summary, our study presents a novel and clinically relevant tool aimed at predicting very early recurrence, offering utility for patient management and stratification in ways that existing models do not.

Comment 2: The authors included pathological findings that could not be sufficiently evaluated before surgery but only done by surgical specimen. However, predictive analysis for very early recurrence after surgery should be done using variables that could be obtained before surgery.

As far as this reviewer understands, in this study, very early recurrence was defined as that was developed within 6 months after surgery because patients who developed very early recurrence were assumed to have little benefit from surgery due to the very bad survival outcome. Predictive factors for very early recurrence after surgery should be utilized for indication of surgery or systemic chemotherapy as an alternative therapeutic option for future patients, as the authors described as follows in the Introduction section: 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.

Reply 2: We thank the Reviewer for the comment. We agree that predictive models based solely on preoperative variables would be especially useful in guiding treatment decisions, including the surgical indication and consideration of alternative therapies. However, we chose to initially incorporate both postoperative pathological findings and preoperative data to achieve a high degree of accuracy to predict VER. This postoperative model has practical implications for guiding decisions on adjuvant chemotherapy and tailoring postoperative surveillance strategies, providing meaningful insights for patient care during the critical period following resection.

Recognizing the value of a preoperative-only predictive approach, we conducted an additional analysis to build a model exclusively using preoperative data. To develop the preoperative model, we used a subset of our cohort that included only patients from five facilities in which comprehensive preoperative examination data were available. This preoperative model allowed us to stratify patients into high- and low-risk groups for VER, supporting its potential utility in identifying patients who may be less likely to benefit from surgery. The model also demonstrated reasonable performance with an internal validation C-index of 0.70, indicating a solid predictive capacity. Using this preoperative model, we believe high-risk patients can be identified before surgery, potentially influencing clinical decisions such as offering preoperative systemic chemotherapy in lieu of upfront surgery for individuals with limited surgical benefit. We have added the additional analysis to the Method, Result, and Discussion sections. (see Page 11, Lines 1-12, Pages 14,15, Lines 9-2, Pages 17,18, Lines 23-11, Pages 19,20, Lines 14-5, **Supplementary Table S2**, **Supplementary Figure 2**, **Supplementary Figure 3**)

Comment 3: Table 1 shows that there were 7.1% of patients who underwent extrahepatic bile duct resection and 92.9% of patients who underwent liver resection. It is unclear if these are extrahepatic bile duct resection only or liver resection only, or how many patients there were who underwent both extrahepatic bile duct resection and liver resection. According to Table 1 as appeared, the study cohort seems to include more than 90% patients who underwent liver resection without extrahepatic bile duct resection, even though the surgery was performed to resect perihilar cholangiocarcinoma, and there are a lot (36.9%) of patients with margin positivity. If so, I suspect that the study cohort includes considerable rate of incomplete resection, because of the omission of extrahepatic bile duct resection. Please mention if indication of surgery, selection of the type of surgery, and surgical techniques were standardized among the institutions and if the use of intraoperative frozen section was evaluated for resected margin of the bile duct to pursue R0 resection in this study cohort. I do not think that the results

of this study can be widely applied to the clinical practice of other medical institutions that were not included in this study.

Reply 3: We thank the Reviewer for the comment. In this study, the standard surgical approach for pCCA involved a combination of liver resection and bile duct resection. Of note, 31 (7.1%) had extrahepatic bile duct resection only. In addition, a total of 237 (54.6%) patients underwent intraoperative frozen section analysis of margin status to evaluate bile duct margins, while a total of 37 (8.5%) patients did not. Information on intraoperative frozen section analysis was not available for the remaining 160 (36.9%) patients. We have described the details of the type of resection and information on intraoperative frozen section analysis in the Method section, Result section and **Table 1**. (see Page 8, Lines 6-10, Page 12, Line 3, **Table1**) This study was based on a large, international multi-center collaboration, and as such, surgical approaches and indications of surgery varied across institutions according to their individual protocols and surgeon preferences. Although an international multi-institutional database is a strength, we recognize that the lack of standardization may affect the generalizability of our findings. To address this limitation, we recommend that future prospective studies focus on standardizing surgical indications and techniques to validate the applicability of our model across diverse clinical settings. This point has been added to the Method and Limitation section for clarity. (see Pages 14,15, Lines 19-1, Page 20, Line 12-14)

Comment 4: Please describe a mortality rate after surgery for perihilar cholangiocarcinoma in the study cohort, as this is a highly-invasive surgery that should usually be done only at high volume center and also calculating system for early recurrence after surgery should not be casually used without considering standardized quality of surgery and operative mortality.

Reply 4: We thank the Reviewer for the comment. As requested, we have described the perioperative mortality rate. In this study, we excluded 28 (5.6%) patients who experienced death within 30 days. Among the analytic cohort (n=434), an additional 20 (4.3%) patients experienced death within 90 days. As such, among 496 patients with curative-intent surgery, the 90-day mortality was 9.7% (n=48). These outcomes have been added in the Result section. (see Page 11, Lines 18-21, Page 12, Line 10)

Comment 5: "Liver resection" is duplicated as one of the characteristics in Table 1. I guess the upper one should be corrected as "Type of resection".

Reply 5: We thank the Reviewer for the comment. As requested, we have changed the "type of resection" in **Table 1** and added the details of resection type. (see **Table 1**)

Comment 6: Please describe the number of patients with the pattern of recurrence.

Reply 6: We thank the Reviewer for the comment. To describe the pattern of recurrence, we categorized recurrence as either local or distant recurrence. Local recurrence was defined as a recurrence near the hepaticojejunostomy or in an area where surgical procedures had been

performed, including the liver hilum and hepatoduodenal ligament.[1] All other recurrences were defined as distant. Among the 269 patients who experienced recurrence, 90 (27.6%) patients had only local recurrence, 66 (24.5%) patients had only distant recurrence, and 26 (9.7%) patients had local and distant recurrences at initial recurrence. Unfortunately, one of the third patients (n=87, 32.3%) with recurrence had no data with the recurrence site. In addition, we have described the site of distant recurrence. These outcomes have been added to the Method section, the Result section, and **Supplemental Table S1**. (see Page 9, Lines 9-12, Page 12, Lines 19,20, **Supplemental Table S1**)

Comment 7: In the following sentence in the abstract, what those percentages mean should be explained, as those do not seem to mean the risk of recurrence within 6 months after resection: An XGBoost model was able to stratify patients relative to the risk of VER (low-risk: 94.6% vs. intermediate risk: 88.3% vs. high-risk: 40.0%; p<0.001).

Reply 7: We thank the Reviewer for the comment. To clarify the meaning of these percentages, the abstract has been revised to specify that the numbers represent 6-month recurrence-free survival. (see Page 3, Lines 15-17)

Comment 8: Please describe the number of patients who underwent right-sided and left-sided liver resection and trisectionectomy, respectively.

Reply 8: We thank the Reviewer for the comment. As requested, we have specified the number of patients who underwent right-sided and left-sided liver resections and trisectionectomies in **Table 1**. In this study, 50 patients (11.5%) underwent right hepatectomy, 22 patients (5.0%) underwent left hepatectomy, 69 patients (15.9%) underwent extended right hepatectomy, and 77 patients (17.7%) underwent extended left hepatectomy. Additionally, 64 patients (14.7%) and 67 patients (15.4%) underwent right and left trisectionectomies, respectively. (see **Table 1**)

Comment 9: Please clarify if this study included patients who underwent preoperative chemotherapy or not.

Reply 9: We thank the Reviewer for the comment. In this study, a total of 23 patients (5.3%) received neoadjuvant chemotherapy. These patients were included in the analysis, and there was no significant difference in the proportion of patients who received preoperative chemotherapy among individuals with and without VER. This outcome has been added to the method section, the result section, and **Table 1**. (see Page 8, Lines 4,5, Page 12, Lines 1,2, **Table 1**)

Comment 10: Please describe indication and regimens of postoperative adjuvant therapy..

Reply 10: We thank the Reviewer for the comment. The criteria for administering adjuvant chemotherapy were based on each institution's policy. Among the 160 patients who received adjuvant chemotherapy, 61 were treated with Gemcitabine-based regimens, 39 with capecitabine,

and 32 with other regimens. Information on the remaining 28 patients was not available. This information has been added to the Method and Result sections. (see Page 9, Lines 5,6, Page 12, Lines 11-14) Additionally, it has been noted in the Limitations section that variations in the criteria and types of postoperative adjuvant chemotherapy may impact prognosis. (see Page 20, Lines 9,10,12-14)

Reviewer B:

Comment 1: Although the method of analysis using AI is considered new, the data obtained are only well-known data and there is no new information. The information obtained lacks impact to the extent that it can be used to select patients for surgery.

Reply 1: We thank the Reviewer for the comment. While it is acknowledged that the data utilized in this study comprise well-established clinical and pathological factors, the primary innovation of our research lies in the creation of a risk model specifically aimed at predicting VER within 6 months following surgery. This tool addresses a critical gap in existing literature regarding the identification of patients at risk for such early recurrence within 12 months or 24 months. To enhance clinical applicability, we have also developed an online calculator that allows healthcare professionals to easily input patient data and obtain risk predictions. This tool is designed to facilitate informed decision-making regarding surveillance strategies and postoperative management, including the administration of adjuvant chemotherapy. Furthermore, as an additional analysis, we constructed a model that utilizes only preoperative factors to predict the likelihood of recurrence within 6 months. Notably, the SII recognized as a relatively new inflammatory marker, emerged as a significant factor for VER in this preoperative model. This calculator may assist clinicians in identifying patients at the highest risk of VER, thereby enabling them to consider alternative treatment options preoperatively for this cohort of patients with pCCA. These points and additional analysis have been incorporated into the Method, Result, and Discussion section. (see Page 11, Lines 1-12, Pages 14,15, Lines 9-2, Pages 17,18, Lines 23-11, Pages 19,20, Lines 14-5, **Supplementary Table S2**, **Supplementary Figure 2**, **Supplementary Figure 3**)

Comment 2: The data shown in Table 1 do not provide information on the quality of surgery, patient background, etc., so it is not possible to determine whether the data are reliable or not.

Reply 2: We thank the Reviewer for the comment. As requested, the information on preoperative systemic chemotherapy, details of surgical procedure, operative time, intraoperative blood loss, intraoperative frozen section analysis, and pathological stage were added in **Table 1.** In addition, **Supplementary Table S2** shows the patient characteristics of additional analysis, including preoperative laboratory and imaging data. We have added these modifications to the Method section, **Table 1**, and **Supplementary Table S2**. (see Page 8 Lines 4-11, **Table 1**, **Supplementary Table S2**)

Comment 3: Figure 3 says that the AJCC was compared to the AJCC, but it is unclear what the AJCC was compared to (it is not written in the method), so it cannot be evaluated.

Reply 3: We thank the Reviewer for the comment. In the current study, we compared the predictive ability of recurrence within 6 months after surgery between our model and the AJCC 8th Edition Staging System, which includes stages I, II, IIIA, IIIB, IIIC, and IVA. We have added the details of this comparison to the Method section and included the number of patients at each AJCC 8th Stage in **Table 1.** (see Page 10 Lines 19-21, **Table 1**)

Comment 4: If risk factors are calculated, the cutoff values should be clarified and the patient population that can be clearly excluded from surgery should be clearly stated.

Reply 4: We thank the Reviewer for the comment. In the postoperative model, patients with an estimated recurrence rate of less than 5.7% within 6 months were classified as low risk (n=186, 42.9%), while individuals with an estimated recurrence rate of 25% or more were classified as high risk (n=64, 14.7%). In the preoperative model, patients with an estimated recurrence rate of more than 8.1% within 6 months were classified as high risk (n=89, 45%). As requested, we have added these cut-offs to the Result section. (see Page 13, Lines 17-19, Page 14, Lines 21,22)