

RESEARCH

A Radiomic Nomogram Based on CT Images to Predict Survival Outcomes in Intrahepatic Cholangiocarcinoma Patients after Resection

Junli Wang¹, Mengye He², Jing Ni¹, Xiaochen Zhang², Yuguo Wei³, Ke Sun⁴ and Wenbo Xiao^{1*}

*Correspondence:

xiaowb.111@163.com

¹Department of Radiology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Full list of author information is available at the end of the article

Abstract

Background: The purpose of this study was to establish a radiomics nomogram based on multiphase contrast-enhanced computed tomography (CT) to demonstrate the outcome of the patients after resection of intrahepatic cholangiocarcinoma (ICC).

Methods: A cohort of 96 (7:3 in the training/validation cohort) ICC patients was enrolled in this study. All patients underwent a preoperative enhanced CT examination and then accepted the ICC resection. Radiomic features were extracted from arterial phase (AP) and portal venous phase (PVP) contrast-enhanced CT images. The least absolute shrinkage and selection operator (LASSO) Cox regression was used to select the features. Radiomic features and clinical data were combined to build the nomogram to predict the overall survival (OS). ICC patients were divided into high- and low- risk groups based on their probability of survival. The Kaplan–Meier analysis and the log-rank test were applied to analyze the patients, difference from different risk groups.

Results: The C-index of the radiomics and clinical-nomogram for the prediction of OS in ICC patients was 0.869 and 0.632, 0.873 and 0.628 in the training and validation cohorts, respectively. The C-index of the combined nomogram for the prediction of OS in ICC patients was 0.912 and 0.696 in the training and validation cohorts, respectively. The calibration curve indicated that the predicted survival time was close to the actual survival time. Decision curve analysis showed that the combined nomogram has better clinical prediction than clinical or radiomics features alone. For ICC patients after surgical resection, the combined model showed that the low-risk group and high-risk group had a significant statistical difference in both the training cohort ($p < 0.001$) and the validation cohort ($p = 0.01$).

Conclusion: Based on the application of preoperative enhanced CT radiomics in ICC, this study proposed a new personalized clinical decision nomogram, which can be used to predict the survival state of patients and play a certain role in assisting clinical treatment decision-making.

Keywords: Intrahepatic cholangiocarcinoma; Computed tomography; Radiomics; Nomogram; Survival

Background

Intrahepatic cholangiocarcinoma (ICC) arises within the second-order bile duct branches and peripheral branches and accounts for 5% to 30% of all primary liver malignancies [1, 2, 3]. It is a highly aggressive malignancy associated with high

mortality and increasing global incidence in recent years [4]. Currently, surgical resection remains the best treatment choice. However, most ICC patients were usually diagnosed in advanced clinical stages, and only one third of patients could accept surgical resection. Unfortunately, the postoperative prognosis was disappointing, with the five-year survival and OS ranging from 15% to 40% [5]. Even for patients with localized ICC who undergo prompt surgical resection, the chances of recurrence and/or distant metastases remain unacceptably high [6]. Meanwhile, adjuvant therapy (AT) can only bring some survival benefits for unresectable patients, but whether postoperative AT is beneficial to patients after surgical resection is still controversial [7].

For the poor outcomes of ICC patients, accurate clinical staging is critical for predicting survival and selecting treatment options. Many recent studies have shown that the number of lesions, vascular invasion (e.g., microvascular or major vascular invasion), positive surgical margin, and lymph node metastasis are all important factors in ICC prognosis [8, 9]. Therefore, imaging plays an important role in preoperation diagnosis and treatment of patients with suspected ICC. Multiphase contrast-enhanced multi-detector CT has high spatial resolution and advanced postprocessing techniques and has served as the standard imaging modality for the preoperative assessment of ICC [10]. Meanwhile, the use of multi-detector CT can provide a comprehensive assessment and staging information of the primary tumor, the vascular and lymph node status, and the presence and extent of tumor invasion into the adjacent structures. In addition, based on the qualitative imaging features of ICC on CT, a better prediction of prognosis was identified in the survival outcomes of surgical patients [11]. However, the evaluation of these images is mostly dependent on the physicians' experience, which will affect the accuracy of the preoperative diagnosis. Therefore, there is an urgent need for an accurate and effective diagnostic method with higher clinical applicability and universality to preoperatively evaluate the OS.

In recent years, radiomics as an emerging and promising field, has shown discriminating capabilities in the stratification of tumor histology, tumor grades or stages, prognosis evaluation, and clinical treatment outcomes by extracting and mining large numbers of quantitative features from images [12, 13]. In addition, the nomograms have been widely used as a reliable prediction tool to estimate prognosis in oncology and medicine by incorporating quantitative risk factors of clinical events [14]. Therefore, In this study, we extracted radiomic features from preoperative CT images of ICC in AP and PVP, respectively. Then, we established a radiomics nomogram combined with clinicopathological factors to predict the survival status of ICC patients after resection.

Methods

Patients

In this retrospective study, we reviewed clinical and pathological records, and AP and PVP contrast-enhanced CT images of ICC patients who underwent surgical resection between January 2011 and December 2018. The patients' inclusion criteria were as follows: a) a Multiphase enhanced CT examination within 1 month prior to surgery or biopsy, b) no anti-tumor treatment received before the CT examination,

c) with surgical or biopsy specimens confirmed by pathology, d) with well-preserved imaging data, clinical and pathological records. The exclusion criteria were as follows: a) with recurrent ICC; (b) who underwent antitumor treatments before the contrast-enhanced CT scan; and (c) with partial loss or poor CT images that could not be used for region of interest (ROI) delineation.

CT image acquisition

All enrolled patients underwent contrast-enhanced CT. All CT scans were performed on three CT scanners, including a 16-slice CT (Toshiba Medical Systems), a 64-slice CT (Revolution EVO, General Electric Medical Systems), and a 256-slice CT (Philips Healthcare). CT scans used the same scanning parameters: tube voltage of 120 kV, tube current of 125 - 300 mAs, pitch of 0.6 - 1.25mm, slice thickness of 3 - 5 mm, and reconstruction interval of 3 - 5 mm. Each patient was bolus-injected (1.5 mL/kg) with the nonionic contrast agent Ultravist (Bayer Schering Pharma) with a high-pressure syringe at 3.0 mL/s. The AP and PVP were scanned at 25 to 35 seconds and 55 to 75 seconds after injection, respectively.

ROI segmentation

CT images of AP and PVP with a thickness of 3 mm were retrieved for image feature extraction. Before radiomic features extraction, image resampling and gray-level normalization were carried out to standardize different image specifications [15]. All image data were resampled to a $1 \times 1 \times 1$ mm voxel space size. The gray scale was standardized to 64 levels to calculate the radiomic features.

The segmentation of tumors' region of interest (ROI) was contoured manually using ITK-SNAP software (version 3.8.0, <http://www.itksnap.org/> [16]). The tumor boundary was outlined on each slice for both axial AP and PVP images by an abdominal radiologist (J.W., 9 years of experience in the abdominal imaging) and validated by another radiologist (W.X., more than 20 years of clinical experience in abdominal imaging). The two radiologists were aware of the final pathologic result, but they were blinded to the exact pathologic type and TNM stage.

Feature Extraction and Selection

Radiomic features including firstorder features, shape features, Gray-level Co-occurrence Matrix (GLCM) features, Gray Level Size Zone Matrix (GLSZM) features, Gray Level Run Length Matrix (GLRLM) features, were extracted from the AP and PVP CT images separately based on segmented tumor ROI using the Artificial Intelligence Kit Version 3.0.1.A (GE Healthcare, China), which based on pyradiomics, and complies IBSI [17]. Ultimately, a total of 293×2 radiomic features were calculated and standardized. For the purpose of dimension reduction, a univariate Cox regression analysis model was used to select the significant predictors from all the extracted image features. The correlation analysis between features was adopted, and one of the features with a correlation higher than 0.9 was retained to reduce the redundancy. Then, the survival analysis model was constructed by the least absolute shrinkage and selection operator (LASSO) Cox regression analysis model. For each patient, a radiomics score (rad score) was produced using a linear combination of selected features that were weighted by their coefficients [18].

Construction of the Radiomics Nomogram and Its Performance

For clinical data, the univariate Cox regression analysis model was first used to select the significant predictors. Then, the multivariate Cox regression analysis model was adopted to develop the clinical survival analysis model.

The rad score from the radiomic model and predictors from the clinical survival model were used to construct the radiomics nomogram. In the training and validation cohorts, Harrell's C index was calculated to evaluate the predictive performance of the radiomics nomogram. The C-index is a number that varies from 0.5 to 1.0, with 0.5 denoting a random data distribution and 1.0 denoting that the model's results correctly match the observed survival data. Also, the radiomics nomogram calibration curves of the patient's 3-year OS were drawn [19]. The calibration curve showed the difference between the observed probabilities and the survival probability predicted by the nomogram. A decision curve was also applied to determine the clinical practicability of radiomics nomogram by quantifying the net benefits under different threshold probabilities. The specific research process was shown in Figure 1.

Statistical Analysis

All statistical analyses were performed using the R software (version 4.0.2, www.r-project.org) and Python (version 3.5.6). Mann-Whitney U test and χ^2 test were used to determine whether there was a significant difference in the values of clinical-pathologic variables. A two-tailed p -value <0.05 indicated statistical significance. The Kaplan–Meier analysis and a log-rank test were used to analyze the survival time and the difference between the patients from the high-risk group and the low-risk group, in the training and the validation sets respectively.

Results

Clinical characteristics

Clinical characteristics of the training and validation cohorts were shown in Supplementary Table 1. There were no significant differences in age, sex, clinical symptom, chronic hepatopathy, tumor markers level, or clinical stage etc., between the two cohorts ($p > 0.05$), indicating that grouping was reasonable. But as shown in Supplementary Table 2, there were significant differences in age, clinical symptoms, Alb, CEA, CA 12-5, vascular invasion (including MVI and major vascular invasion), TNM stage, postoperative recurrence, OS, and radscore between the survived and died cohorts ($p < 0.05$).

Important Radiomics Feature Selection and Radiomics Signature Construction

Totally, there were 293×2 radiomics features were extracted from AP and PVP CT images separately. We used the LASSO regression model for feature selection (Figure 2A, B). Finally, nine important features were selected as follows (Figure 2C):

Then the rad score were calculated as follows:

$$\begin{aligned} \text{Radscore} = & 0.227V_log_sigma_2.0_mm_3D_glszm_LargeAreaLowGrayLevelEmphasis \\ & + 0.124A_log_sigma_3.0_mm_3D_firstorder_90Percentile \\ & + 0.112V_log_sigma_3.0_mm_3D_gldm_LargeDependenceLowGrayLevelEmphasis \end{aligned}$$

- 0.071V_original_firstorder_RootMeanSquared
- 0.172A_original_gldm_DependenceNonUniformityNormalized
- 0.396V_log_sigma_3.0_mm_3D_gldm_LargeDependenceHighGrayLevelEmphasis
- 0.484A_log_sigma_3.0_mm_3D_ngtdm_Contrast
- 0.487V_original_shape_Sphericity
- 0.788V_original_firstorder_90Percentile.

The Kaplan–Meier analysis of the radiomic model was plotted to analyze the survival time between the patients from the high-risk group and the low-risk group in the training and validation sets, respectively. The results of the log rank test showed that there were significant differences between the two risk groups in the training set ($p < 0.01$, log-rank test) and the test set ($p = 0.056$, log-rank test). The specific results were shown in Supplementary Figure 1.

Development of the Combined Nomogram and Its Evaluation Performance

For all clinical data, we used the univariate Cox regression analysis model to select the significant predictor with $P < 0.05$, and then utilized the multivariate Cox regression analysis model to construct the clinical nomogram (Figure 3A). The Kaplan–Meier curve showed that the combined model could effectively distinguish between high- and low-risk patients in the test cohort ($p < 0.0001$, log-rank test) (Figure 3B), but there was no statistical significance between low- and high-risk group in the validation cohort (Figure 3C, $p = 0.31$, log-rank test).

Combining the rad score with the clinically significant predictors, a combined model was constructed based on multivariate Cox regression analysis (Figure 4A). In the training and validation cohorts, the C index of the combined model was 0.912 and 0.696, respectively (Table 1). The Kaplan–Meier curve demonstrated that the model score could effectively distinguish between high- and low-risk patients in both the train cohort (Figure 4B, $p < 0.0001$, log-rank test) and validation cohort (Figure 4C, $p = 0.01$, log-rank test). The result of calibration curve indicated that the predicted probability was very close to the actual survival time of ICC patients (Figure 4D). The decision curve analysis showed that the combined nomogram was better than the radiomics and clinical models and had a higher overall net benefit (Figure 4E).

Discussion

In this study, we developed a combined model based on AP and PVP CT radiomics features combined with clinicopathological factors to predict the survival status of ICC patients after resection, with the aim of helping identify the patient who might benefit most from the surgical method and achieve personalized treatment.

And, while the clinical nomogram based on clinical data effectively distinguishes between high- and low-risk patients in the test cohort ($p < 0.0001$, log-rank test), it had no statistical significance between low- and high-risk groups in the validation cohort ($p = 0.31$, log-rank test), which could be attributed to overfitting. However, after adding the radiomics score to the clinical model, the combined model had better predictive performance for OS, and the C-index were 0.912 and 0.696 in the training and validation cohort, respectively. What's more, the results indicated that radscore and several clinical variables, including clinical symptoms, ALT, PLT,

CEA, TNM stage, resection margins, and postoperative recurrence, were associated with OS. In addition, combined with the clinical characteristics of survival and death cohorts shown in Supplementary Table 2, we believe that the radscore and some clinical factors, including clinical symptoms, CEA, TNM stage, and postoperative tumor recurrence, are closely related to the prognosis of ICC patients after surgery. Moreover, the Kaplan-Meier curve showed that the combined model could effectively distinguish between high- and low-risk patients in test cohort ($p < 0.0001$, log-rank test) and validation cohort ($p = 0.01$, log-rank test). The results showed that imaging examination was of great significance in evaluating tumor status compared with clinical features. It also indicated the potential of radiomics in predicting the survival outcome of preoperative ICC.

Most ICC patients are usually asymptomatic in the early stage. When they have abdominal pain, fatigue, malaise, biliary obstruction and other symptoms, they are already in the advanced stage [20]. Our study showed that the prognosis of older ICC patients with first clinical symptoms was poor, and the first clinical symptoms were also one of the important predictors of postoperative prognosis of ICC, which might be related to the poor physical condition of older patients and the late stage or metastasis of tumor. Some studies also showed that the prognosis of elderly patients with ICC was worse than that of young people [21, 22]. In addition, there is ample evidence that aging is related to the decline of immune system function, many infections and chronic diseases [23].

Tumor markers are well-established tools for assisting in diagnosis, predicting prognosis, and detecting recurrence [24, 25]. In our study, we found that serum biomarkers Alb, CEA, and CA125 were related to the prognosis of patients, among which CEA was an important clinical predictor related to OS in ICC patients. Previously, Alb level was considered to be the most important factor in evaluating liver reserve. Li et al. [26] found that hypoalbuminemia was associated with low survival in ICC patients, which was consistent with our research. At present, it was considered that serum CA125 might have better clinical application in adenocarcinoma [27]. A recent study has shown that preoperative serum CA125 could be used to predict the prognosis of hilar cholangiocarcinoma after radical resection [28]. In addition, a previous study showed that higher levels of CA19-9 and CEA were related to the advanced TNM stages and poor prognosis of ICC patients [29]. But we also found the serum CA19-9 had no significant contribution in the clinical model and combined model. Also, there were some contradicting studies [30, 31], a meta-analysis indicated that serum tumor markers did not help predict postoperative prognosis in patients with ICC [32]. Furthermore, our study also found that the increase of ALT and PLT levels were also significant predictors of postoperative prognosis in ICC patients. The rise of serum ALT levels might be related to hepatocyte injury in advanced tumor [33]. A previous study has also shown that platelets are related to tumor recurrence and prognosis, which may be related to platelet activation and uncontrolled tumor angiogenesis, because platelets can release angiogenic factors, such as vascular endothelial growth factor [34, 35].

At present, surgery is still the first-line method of ICC treatment and the best cure opportunity for ICC. At the same time, it is consensus that a negative margin predicts a better result in comparison with a positive margin. Also, our study

indicated that the surgical margin was related to the prognosis of ICC patients. A meta-analysis [36] indicated that ICC patients with negative margins of 10mm or more, compared with patients with negative margins less than 10mm, enjoyed a long-term survival (HR 1.59, 95%CI : 1.09–2.32). Another study [37] showed that wide resection margins, narrow margins and R1 resections had no significant difference in OS or recurrence-free survival (RFS), but compared with the unresectable group, all of these groups showed significant advantages. Therefore, even if only a narrow margin can be obtained, extended resection should be performed. Nevertheless, the high incidence of postoperative recurrence is a main factor affecting the overall prognosis of ICC patients after surgical resection[38]. Our study also showed that patients with postoperative recurrence had a poor prognosis.

Nowadays, AT, including chemotherapy, radiotherapy, transarterial chemoembolization (TACE), and comprehensive treatment, is still undergoing much debate about whether ICC patients can benefit from AT after radical resection [7, 39, 40]. Our study indicated that postoperative adjuvant therapy in ICC patients did not play a significant role in clinical models or combined models. Nevertheless, a recent multicenter retrospective study found that patients who received AT had longer median OS and DFS than patients not receive AT [41]. However, this study did not show which AT made ICC patients more likely to benefit from it than the other, or which AT method was the most effective. Recently, targeted therapy and immunotherapy are developing rapidly and have achieved great progress in several human malignant tumors[7]. What's more, the additional information extracted by radiomics can reveal the spatial heterogeneity within the tumor and can be used to predict tumor type, tumor stage and prognosis [42]. Our study also found that the prognosis of patients with vascular infiltration (including MVI and major vascular invasion) and a high TNM stage was poor, and the TNM stage was a significant predictor of the prognosis of ICC patients. Previous studies have confirmed that tumor size, multiple tumors, lymph node metastasis, vascular infiltration and poor tumor differentiation are related to the prognosis of ICC [8, 9, 43]. Therefore, preoperative prediction of survival in ICC patients may facilitate clinical decision-making. In this case, the prediction models and nomograms proposed in clinical practice or future clinical trials may help to identify the optimal candidates for surgery or high-risk patients.

Our study had several limitations. First, this study used a small sample and a retrospective design, so there may be potential selection bias. Moreover, the sample size was not large enough which also caused the problem of overfitting in the test cohort. Second, this study was conducted in a single center, and the results need to be externally validated in other centers. Third, there was no stratified analysis of whether ICC patients received AT after operation, which could have resulted in some discrepancies. In the follow-up study, we will increase the sample size, conduct multicenter and prospective researches, and design hierarchical analysis of relevant clinical, pathological, and radiomics features in order to obtain more conclusive data on the prognosis of ICC patients.

Conclusion

In conclusion, a rad score based on enhanced CT combined with clinicopathological factors can predict the postoperative survival outcomes of ICC patients. The predic-

tion result of the radiomics nomogram might contribute to clinical decision-making and identify the subgroups of patients who benefit most from surgery.

Abbreviations

AFP: fetoprotein; AJCC: the American Joint Committee on Cancer; Alb: albumin; ALT: alanine aminotransferase; AP: arterial phase; AST: aspartate aminotransferase; AT: adjuvant therapy; CA12-5: carbohydrate antigen 12-5; CA19-9: carbohydrate antigen CA19-9; CEA: carcinoembryonic antigen; CT: computed tomography; GLB: globulin; GLCM: Gray-level Co-occurrence Matrix; GLRLM: Gray Level Run Length Matrix; GLSZM: Gray Level Size Zone Matrix; ICC: intrahepatic cholangiocarcinoma; LASSO: the least absolute shrinkage and selection operator; LYM: lymphocyte count; MDT: multidisciplinary team; MVI: microvascular invasion OS: overall survival; PLT: platelet count; PVP: portal venous phase; RFS: recurrence-free survival ROI: region of interest; TACE: transarterial chemoembolization; TBIL: total bilirubin

Declarations

Ethics approval and consent to participate

All procedures performed in the study were in accordance with the Helsinki declaration and guidelines. The Clinical Research Ethics of the First Affiliated Hospital, Zhejiang University School of Medicine approved this retrospective study (REC/2021/934) and waived the need for patients' informed permission due to its retrospective nature.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets analyzed in this study are available from the corresponding author on request.

Competing interests

The authors declare that they have no competing interests

Funding

This study was supported by the horizontal project of Zhejiang University (No. K-20212766). The funding sponsor had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

Acknowledgements

We sincerely appreciate Dr. Shaofeng Duan of GE healthcare for his guidance in this study.

Authors' contributions

WJ, MH, XZ, XW, and ZX: conception and design. WJ, NJ, WY, and SK: data analysis and interpretation. WJ, MH, and WY: manuscript writing. All authors: review and editing.

Author details

¹Department of Radiology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.

²Department of Medical Oncology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China. ³Institute of Precision Medicine, GE Healthcare China, Shanghai, China. ⁴Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.

References

1. Krasinskas, A.M.: Cholangiocarcinoma. *Surgical pathology clinics* **11**(2), 403–429 (2018)
2. L.C.S.G.J.: Primary liver cancer in japan. clinicopathologic features and results of surgical treatment. *Annals of Surgery* **211**(3), 277–287 (1990)
3. Kaczynski, J., Hansso, G., Wallerstedt, S.: Incidence, etiologic aspects and clinicopathologic features in intrahepatic cholangiocellular carcinoma: a study of 51 cases from a low-endemicity area. *Acta Oncologica* **37**(1), 77–83 (1998)
4. Spolverato, G., Vitale, A., Cucchetti, A., Popescu, I., Marques, H.P., Aldrighetti, L., Gamblin, T.C., Maithel, S.K., Sandroussi, C., Bauer, T.W., *et al.*: Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer* **121**(22), 3998–4006 (2015)
5. Bridgewater, J., Galle, P.R., Khan, S.A., Llovet, J.M., Park, J.-W., Patel, T., Pawlik, T.M., Gores, G.J.: Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *Journal of hepatology* **60**(6), 1268–1289 (2014)
6. Cloyd, J.M., Ejaz, A., Pawlik, T.M.: The landmark series: intrahepatic cholangiocarcinoma. *Annals of Surgical Oncology* **27**(8), 2859–2865 (2020)
7. Chun, Y.S., Javle, M.: Systemic and adjuvant therapies for intrahepatic cholangiocarcinoma. *Cancer Control* **24**(3), 1073274817729241 (2017)
8. Lee, A.J., Chun, Y.S.: Intrahepatic cholangiocarcinoma: the ajcc/uicc 8th edition updates. *Chin Clin Oncol* **7**(5), 52 (2018)

9. Hwang, S., Lee, Y.-J., Song, G.-W., Park, K.-M., Kim, K.-H., Ahn, C.-S., Moon, D.-B., Lee, S.-G.: Prognostic impact of tumor growth type on 7th ajcc staging system for intrahepatic cholangiocarcinoma: a single-center experience of 659 cases. *Journal of Gastrointestinal Surgery* **19**(7), 1291–1304 (2015)
10. Joo, I., Lee, J.M., Yoon, J.H.: Imaging diagnosis of intrahepatic and perihilar cholangiocarcinoma: recent advances and challenges. *Radiology* **288**(1), 7–13 (2018)
11. Aherne, E.A., Pak, L.M., Goldman, D.A., Gonen, M., Jarnagin, W.R., Simpson, A.L., Do, R.K.: Intrahepatic cholangiocarcinoma: can imaging phenotypes predict survival and tumor genetics? *Abdominal Radiology* **43**(10), 2665–2672 (2018)
12. Parmar, C., Grossmann, P., Bussink, J., Lambin, P., Aerts, H.J.: Machine learning methods for quantitative radiomic biomarkers. *Scientific reports* **5**(1), 1–11 (2015)
13. Yang, C.M., Shu, J.: Cholangiocarcinoma evaluation via imaging and artificial intelligence. *Oncology* **99**(2), 72–83 (2021)
14. Balachandran, V.P., Gonen, M., Smith, J.J., DeMatteo, R.P.: Nomograms in oncology: more than meets the eye. *The lancet oncology* **16**(4), 173–180 (2015)
15. Huynh, E., Coroller, T.P., Narayan, V., Agrawal, V., Hou, Y., Romano, J., Franco, I., Mak, R.H., Aerts, H.J.: Ct-based radiomic analysis of stereotactic body radiation therapy patients with lung cancer. *Radiotherapy and Oncology* **120**(2), 258–266 (2016)
16. Yushkevich, P.A., Piven, J., Hazlett, H.C., Smith, R.G., Ho, S., Gee, J.C., Gerig, G.: User-guided 3d active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage* **31**(3), 1116–1128 (2006)
17. Van Griethuysen, J.J., Fedorov, A., Parmar, C., Hosny, A., Aucoin, N., Narayan, V., Beets-Tan, R.G., Fillion-Robin, J.-C., Pieper, S., Aerts, H.J.: Computational radiomics system to decode the radiographic phenotype. *Cancer research* **77**(21), 104–107 (2017)
18. Huang, Y.-q., Liang, C.-h., He, L., Tian, J., Liang, C.-s., Chen, X., Ma, Z.-l., Liu, Z.-y.: Development and validation of a radiomics nomogram for preoperative prediction of lymph node metastasis in colorectal cancer. *Journal of clinical oncology* **34**(18), 2157–2164 (2016)
19. Yang, L., Yang, J., Zhou, X., Huang, L., Zhao, W., Wang, T., Zhuang, J., Tian, J.: Development of a radiomics nomogram based on the 2d and 3d ct features to predict the survival of non-small cell lung cancer patients. *European Radiology* **29**(5), 2196–2206 (2019)
20. Blechacz, B.: Cholangiocarcinoma: current knowledge and new developments. *Gut and liver* **11**(1), 13 (2017)
21. Mavros, M.N., Economopoulos, K.P., Alexiou, V.G., Pawlik, T.M.: Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. *JAMA surgery* **149**(6), 565–574 (2014)
22. Antwi, S.O., Mousa, O.Y., Patel, T.: Racial, ethnic, and age disparities in incidence and survival of intrahepatic cholangiocarcinoma in the united states; 1995–2014. *Annals of hepatology* **17**(2), 274–285 (2018)
23. Jura, M., Kozak, L., *et al.*: Obesity and related consequences to ageing. *Age* **38**(1), 1–18 (2016)
24. Fang, T., Wang, H., Wang, Y., Lin, X., Cui, Y., Wang, Z.: Clinical significance of preoperative serum cea, ca125, and ca19-9 levels in predicting the resectability of cholangiocarcinoma. *Disease markers* **2019** (2019)
25. Moro, A., Mehta, R., Sahara, K., Tsilimigras, D.I., Paredes, A.Z., Farooq, A., Hyer, J., Endo, I., Shen, F., Guglielmi, A., *et al.*: The impact of preoperative ca19-9 and cea on outcomes of patients with intrahepatic cholangiocarcinoma. *Annals of Surgical Oncology* **27**(8), 2888–2901 (2020)
26. Li, H., Wu, J.-s., Wang, X.-t., Lv, P., Gong, L.-s., Liu, G., Tian, B.-n., Li, Y.-y., Jiang, B.: Factors predicting surgical resection in patients with intrahepatic cholangiocarcinoma and cirrhosis. *Journal of Investigative Surgery* **27**(4), 219–225 (2014)
27. Fang, T., Wang, H., Wang, Y., Lin, X., Cui, Y., Wang, Z.: Clinical significance of preoperative serum cea, ca125, and ca19-9 levels in predicting the resectability of cholangiocarcinoma. *Disease markers* **2019** (2019)
28. Xu, Z.-L., Ou, Y.-J., Dai, H.-S., Wan, K., Bie, P., Chen, Z.-Y., Zhang, L.-D., Zhang, C.-C.: Elevated preoperative ca125 levels predicts poor prognosis of hilar cholangiocarcinoma receiving radical surgery. *Clinics and research in hepatology and gastroenterology* **45**(6), 101695 (2021)
29. Tian, M., Liu, W., Tao, C., Tang, Z., Zhou, Y., Song, S., Jin, L., Wang, H., Jiang, X., Zhou, P., *et al.*: Prediction of overall survival in resectable intrahepatic cholangiocarcinoma: Isicc-applied prediction model. *Cancer science* **111**(4), 1084–1092 (2020)
30. Loosen, S.H., Roderburg, C., Kauertz, K.L., Koch, A., Vucur, M., Schneider, A.T., Binnebösel, M., Ulmer, T.F., Lurje, G., Schoening, W., *et al.*: Cea but not ca19-9 is an independent prognostic factor in patients undergoing resection of cholangiocarcinoma. *Scientific reports* **7**(1), 1–10 (2017)
31. Bergquist, J.R., Ivanics, T., Storlie, C.B., Groeschl, R.T., Tee, M.C., Habermann, E.B., Smoot, R.L., Kendrick, M.L., Farnell, M.B., Roberts, L.R., *et al.*: Implications of ca19-9 elevation for survival, staging, and treatment sequencing in intrahepatic cholangiocarcinoma: a national cohort analysis. *Journal of surgical oncology* **114**(4), 475–482 (2016)
32. Mavros, M.N., Economopoulos, K.P., Alexiou, V.G., Pawlik, T.M.: Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. *JAMA surgery* **149**(6), 565–574 (2014)
33. Bartella, I., Dufour, J.-F.: Clinical diagnosis and staging of intrahepatic cholangiocarcinoma. *J Gastrointest Liver Dis* **24**(4), 481–489 (2015)
34. Watanabe, A., Araki, K., Hirai, K., Kubo, N., Igarashi, T., Tsukagoshi, M., Ishii, N., Hoshino, K., Kuwano, H., Shirabe, K.: A novel clinical factor, d-dimer platelet multiplication, may predict postoperative recurrence and prognosis for patients with cholangiocarcinoma. *Annals of surgical oncology* **23**(5), 886–891 (2016)
35. Caine, G.J., Lip, G.Y., Stonelake, P.S., Ryan, P., Blann, A.D.: Platelet activation, coagulation and angiogenesis in breast and prostate carcinoma. *Thrombosis and haemostasis* **92**(07), 185–190 (2004)
36. Tang, H., Lu, W., Li, B., Meng, X., Dong, J.: Influence of surgical margins on overall survival after resection of intrahepatic cholangiocarcinoma: A meta-analysis. *Medicine* **95**(35) (2016)
37. Bartsch, F., Baumgart, J., Hoppe-Lotichius, M., Straub, B.K., Heinrich, S., Lang, H.: Intrahepatic cholangiocarcinoma—influence of resection margin and tumor distance to the liver capsule on survival. *BMC surgery* **20**(1), 1–10 (2020)

38. Chan, K.-M., Tsai, C.-Y., Yeh, C.-N., Yeh, T.-S., Lee, W.-C., Jan, Y.-Y., Chen, M.-F.: Characterization of intrahepatic cholangiocarcinoma after curative resection: outcome, prognostic factor, and recurrence. *BMC gastroenterology* **18**(1), 1–8 (2018)
39. Lee, G.C., Ferrone, C.R., Tanabe, K.K., Lillemoe, K.D., Blaszkowsky, L.S., Zhu, A.X., Hong, T.S., Qadan, M.: Predictors of adjuvant treatment and survival in patients with intrahepatic cholangiocarcinoma who undergo resection. *The American Journal of Surgery* **218**(5), 959–966 (2019)
40. Edeline, J., Bonnetain, F., Phelip, J.M., Watelet, J., Hammel, P., Joly, J.-P., Ben Abdelghani, M., Rosmorduc, O., Bouhier-Leporrier, K., Jouve, J.-L., et al.: Gemox versus surveillance following surgery of localized biliary tract cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. *American Society of Clinical Oncology* (2017)
41. Wang, L., Deng, M., Ke, Q., Lou, J., Zheng, S., Bi, X., Wang, J., Guo, W., Li, F., Wang, J., et al.: Postoperative adjuvant therapy following radical resection for intrahepatic cholangiocarcinoma: A multicenter retrospective study. *Cancer Medicine* **9**(8), 2674–2685 (2020)
42. King, M.J., Hectors, S., Lee, K.M., Omidele, O., Babb, J.S., Schwartz, M., Tabrizian, P., Taouli, B., Lewis, S.: Outcomes assessment in intrahepatic cholangiocarcinoma using qualitative and quantitative imaging features. *Cancer Imaging* **20**(1), 1–15 (2020)
43. Mejia, J.C., Pasko, J.: Primary liver cancers: intrahepatic cholangiocarcinoma and hepatocellular carcinoma. *Surgical Clinics* **100**(3), 535–549 (2020)

Figures

Figure 1 The workflow of model development

Figure 2 The optimal subset of radiomics features were extracted as shown. (A)The hyperparameter/lambda was determined using the partial likelihood deviation as the standard, (B)and the optimization/lambda (vertical dotted line) was utilized to choose the features with non-zero coefficients. (C)The LASSO algorithm chose nine radiomics features that contributed the most to the prognosis prediction model.

Figure 3 (A) A clinical logistic regression model for prediction of 1-3 years overall survival for ICC patients. (B) The Kaplan-Meier curve showed that the model could effectively distinguish between high- and low-risk patients in test cohort ($p < 0.0001$, log-rank test), (C) but there was no statistical significance between low- and high-risk group in validation cohort ($p = 0.31$, log-rank test)

Figure 4 (A) A combined logistic regression model for prediction of 3-year overall survival for ICC patients. The Kaplan-Meier curve showed that the model could effectively distinguish between high- and low-risk patients in test cohort (B, $p < 0.0001$, log-rank test) and validation cohort (C, $p = 0.01$, log-rank test). (D) The result of calibration curve showed that the prediction probability was very close to the actual survival time of patients. (E) The decision curve analysis of each model showed that the combined nomogram was better than radiomics and clinical model, and had a higher overall net benefit

Tables

Table 1 The comparison of prognostic accuracy between the combined model and two other prediction models

C-index	Training set	Test set
Radiomics	0.869(se = 0.026)	0.632(se = 0.072)
Clinical	0.873(se = 0.026)	0.628(se = 0.073)
Combined	0.912(se = 0.018)	0.696(se = 0.067)

Additional Files

Additional file 1 — Supplementary Figure 1

Kaplan–Meier analysis for high- and low-risk group. The left figure is the training set (A, $p < 0.01$, log-rank test) and the right figure is the test set (B, $p = 0.056$, log-rank test).

Additional file 2 — Supplementary Table 1

Clinical characteristics of the training and validation cohorts

Additional file 3 — Supplementary Table 2

Clinical characteristics of the survived and died cohorts.