Retrospective Study

Comprehensive radiomics nomogram for predicting survival of patients with combined hepatocellular carcinoma and cholangiocarcinoma

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Abstract

BACKGROUND

Combined hepatocellular carcinoma (HCC) and cholangiocarcinoma (cHCC-CCA) is defined as a single nodule showing differentiation into HCC and intrahepatic cholangiocarcinoma and has a poor prognosis.

AIM

To develop a radiomics nomogram for predicting post-resection survival of patients with cHCC-CCA.

METHODS

Patients with pathologically diagnosed cHCC-CCA were randomly divided into training and validation sets. Radiomics features were extracted from portal venous phase computed tomography (CT) images using the least absolute shrinkage and selection operator Cox regression and random forest analysis. A nomogram integrating the radiomics score and clinical factors was developed using univariate analysis and multivariate Cox regression. Nomogram performance was assessed in terms of the C-index as well as calibration, decision, and survival curves.

RESULTS
INTRODUCTION

Combined hepatocellular carcinoma (HCC) and cholangiocarcinoma (cHCC-CCA), which arises in hepatic progenitor cells, accounts for 0.8%-6.5% of primary liver carcinoma cases[1-5]. The World Health Organization defines the condition as the presence of a single nodule showing differentiation into HCC and intrahepatic cholangiocarcinoma (ICC)[6,7]. There is disagreement in the literature on whether the prognosis of cHCC-CCA patients is worse or similar to that of patients with only HCC. Several studies concur that the prognosis of cHCC-CCA patients is comparable to that of patients with only ICC[8-11]. Studies vary regarding the prognosis of cHCC-CCA patients after potentially curative resection, with 5-year postoperative overall survival (OS) rates ranging from 8% to 63%. A reliable method to predict prognosis after resection may help select cHCC-CCA patients more likely to benefit from surgery. Radiomics can also differentiate cHCC-CCA from common HCC or ICC[18,22], although no radiomics models have been established for predicting long-term survival of cHCC-CCA patients after resection.

CT and clinical data of 118 patients were included in the study. The radiomics score, vascular invasion, anatomical resection, total bilirubin level, and satellite lesions were found to be independent predictors of overall survival (OS) and were therefore included in an integrative nomogram. The nomogram was more strongly associated with OS (hazard ratio: 8.155, 95% confidence interval: 4.498-14.785, P < 0.001) than a model based on the radiomics score or only clinical factors. The area under the curve values for 1-year and 3-year OS in the training set were 0.878 and 0.875, respectively. Patients stratified as being at high risk of poor prognosis showed a significantly shorter median OS than those stratified as being at low risk (6.1 vs 81.6 mo, P < 0.001).

CONCLUSION

This nomogram may predict survival of cHCC-CCA patients after hepatectomy and therefore help identify those more likely to benefit from surgery.

Key Words: Radiomics; Nomogram; Combined hepatocellular carcinoma and cholangiocarcinoma; Risk strata; Prognosis

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INTRODUCTION

Combined hepatocellular carcinoma (HCC) and cholangiocarcinoma (cHCC-CCA), which arises in hepatic progenitor cells, accounts for 0.8%-6.5% of primary liver carcinoma cases[1-5]. The World Health Organization defines the condition as the presence of a single nodule showing differentiation into HCC and intrahepatic cholangiocarcinoma (ICC)[6,7]. There is disagreement in the literature on whether the prognosis of cHCC-CCA patients is worse or similar to that of patients with only HCC. Several studies concur that the prognosis of cHCC-CCA patients is comparable to that of patients with only ICC[8-11]. Studies vary regarding the prognosis of cHCC-CCA patients after potentially curative resection, with 5-year postoperative overall survival (OS) rates ranging from 8% to 63%[12-15]. A reliable method to predict prognosis after resection may help select cHCC-CCA patients more likely to benefit from surgery.

Radiomics is a promising comprehensive analysis to predict the prognosis of liver cancer patients after hepatectomy, which is a post-processing method to quantitatively evaluate imaging features in order to assess cancer heterogeneity non-invasively and objectively[16,17]. Radiomics features have proven effective in predicting the survival of patients with HCC or ICC alone[18-21]. Radiomics can also differentiate cHCC-CCA from common HCC or ICC[18,22], although no radiomics models have been established for predicting long-term survival of cHCC-CCA patients after resection.
The predictive performance of radiomics features may improve when combined with clinical factors, as demonstrated for patients with ICC\cite{[23-25]}. Therefore, the current study aimed to construct and validate a nomogram based on radiomics and clinical features for predicting postoperative survival of cHCC-CCA patients. This prognostic model may help guide treatment decisions for these patients.

**MATERIALS AND METHODS**

**Study design and patient selection**
This retrospective study was approved by the West China Hospital Ethics Committee, and the requirement for informed consent was waived. All patients agreed to undergo medical examination and were informed that their anonymized medical data would be analyzed and published for the purposes of medical research. We retrospectively reviewed the data of all patients: (1) Who were diagnosed with cHCC-CCA based on the 2019 guidelines of the World Health Organization which defined cHCC-CCA as a single nodule showing differentiation into HCC and ICC; (2) Who underwent hepatectomy with curative intent at West China Hospital between February 2012 and May 2017; and (3) For whom complete medical records were available during hospitalization and during follow-up, as well as computed tomography (CT) data within 2 wk before surgery.

Patients were excluded if they were diagnosed with morphologically typical HCC or ICC based on the expression of markers for cholangiocytes, hepatocytes, or progenitor cells (e.g., keratins 7 and 19 based on immunostaining). Patients were considered to have common HCC if they showed trabecular growth (often accompanied by bile production), hyaline bodies, prominent nucleoli, immunoreactivity against HepPar1 or alpha-fetoprotein, and expression of keratin 19\cite{[26,27]}. Patients presenting typical adenocarcinoma together with abundant stroma and mucin production were considered to have ICC only. Patients diagnosed with cholangiocellular carcinoma were excluded from this study as the latest guidelines\cite{[7]} no longer consider this condition a subtype of cHCC-CCA.

Patients were also excluded if they had received transcatheter arterial chemoembolization or any other type of chemotherapy before CT, or if they had other malignancies simultaneously with cHCC-CCA. The primary endpoint of this study was OS, defined as the time from the date of surgery until the date of all-cause death or last follow-up. Patients were routinely followed at 1 mo after surgery and then every 3-6 mo thereafter, until April 30, 2020.

**Computed tomography examination**
Enhanced CT of the abdomen was performed with a single 64-detector row scanner (Brilliance 64, Philips Medical Systems, Eindhoven, The Netherlands) in all the patients. The scan parameters were as follows: Beam pitch, 0.891; tube voltage, 120 kV; tube current, 200 mA; detector collimation, 0.75 mm; slice thickness, 1.0 mm; reconstruction increment, 5.0 mm; and rotation time, 0.42 s. Arterial phase scanning began at 25 s and portal venous phase scanning began at 60 s\cite{[22]}.

**Extraction of radiomics features**
All patients were randomly divided into a training set and validation set at a ratio of 7:3. All CT images from portal venous phase scanning were loaded into LIFEx software (version 3.74; CEA-SHFJ, Orsay, France)\cite{[28]}. Working independently, two radiologists manually drew regions of interest for each patient within the hepatic neoplasm in all portal venous phase CT images. Radiomics features in the CT images were screened using the Least Absolute Shrinkage and Selection Operator (LASSO) and Cox regression, followed by random forest analysis\cite{[29]}. The selected radiomics features were linearly combined with their own weighting coefficients, generating a radiomics score for each patient.

**Selection of clinical factors**
All clinical variables in the training set were subjected to univariate analysis followed by multivariate Cox analysis with step-wise selection in order to identify independent predictors of OS. In these analyses, total bilirubin level was converted into a categorical variable.
Development and validation of an integrative nomogram

To develop the nomogram, radiomics scores were categorized as “high” or “low” based on whether they were greater or smaller than the median score. Then the nomogram was constructed based on the radiomics score and the clinical risk factors identified in multivariate Cox regression. Within the nomogram, each variable was scored ranging from 0 to 100, and the variable associated with the greatest hazard ratio (HR) was assigned 100 points\[30\]. Using the nomogram, we classified patients as being at high or low risk based on the maximum Youden index\[31\].

The performance of the nomogram was assessed in terms of a calibration curve related to the predicted and observed OS, the C-index used to assess model discrimination, and receiver operating characteristic (ROC) curve\[32\]. The clinical usefulness of the nomogram was assessed using decision curve analysis\[33\].

Statistical analysis

Differences in continuous variables were assessed for significance using the Wilcoxon rank-sum test if the data were skewed, or Student’s t test if the data showed a normal distribution. Differences in categorical variables were assessed using the χ² or Fisher’s exact test. OS was plotted using the Kaplan-Meier method, and groups were compared using the log-rank test. All statistical analyses were performed with EmpowerStats (version 2.20; 2011 X&Y Solutions) and R software (version 4.0.0; The R Foundation). The following packages in R were used: glmnet, cmprsk, rms, survival, rmda, and devtools. Differences with P < 0.05 were considered statistically significant.

RESULTS

Patients

A total of 118 eligible patients (86.4% men) were enrolled (Table 1). Their mean age was 51.6 years, and 90 patients had been diagnosed when they were younger than 60 years. Follow-up data were complete for 110 patients, who were followed for a median of 25.1 mo (95% confidence interval [CI]: 17.3-59.7 mo). Median OS was 21.6 mo, and OS rates were 61.0% at 1 year, 48.3% at 3 years, and 37.4% at 5 years.

Patients were randomly assigned to either the training or validation set, and the two sets did not differ significantly in terms of clinical features, except for tumor size, American Joint Committee on Cancer stage and T stage. OS rates at 1 and 3 years were 58.3% and 46.4% in the training set, compared to 67.7% and 52.9% in the validation set.

Feature selection and construction of radiomics score

The integrative nomogram flow chart is depicted in Figures 1 and 2. For each patient, data on 49 radiomics features were extracted from portal venous phase CT images. Among these 49 features, LASSO regression selected nine with non-zero coefficients, of which random forest analysis selected three (MeanValue, NGLDM Busyness and GLZLM HGZE) (Supplementary Table 1) that showed the highest prediction values (variable importance > 0.01, Figure 3A). Radiomics scores were calculated based on these three features, and scores were subsequently categorized into “high” or “low” based on whether they were lower or higher than the median score (Figure 3).

Selection of prognostic clinical factors

In total, 31 clinical variables were initially considered in the univariate analysis; and seven variables with P < 0.1 were then entered into the multivariate Cox analysis (Table 2). The multivariate analysis identified four predictors of OS: Vascular invasion, anatomical resection, total bilirubin level, and satellite lesions. Total bilirubin level (> 17.1 μmol/L) resulted in a larger HR (13.94) than the other three risk factors. Nevertheless, all four factors were subsequently included in the nomogram.

Construction and validation of a radiomics nomogram model

Based on the above-mentioned four clinical factors and the radiomics score, we developed a comprehensive integrative nomogram to predict 1-year and 3-year OS of cHCC-CCA patients after surgical resection with curative intent (Figure 4A). The area under the ROC curve (AUC) for 1-year OS was 0.878 in the training set and 0.937 in the validation set (Figure 4B). The calibration curve of 1-year OS showed good agreement between predicted and observed values in both the training and validation sets (Figure 4C). The AUC for 3-year OS was 0.875 in the training set and 0.866 in the validation set. The C-index was 0.807 (95%CI: 0.756-0.858) in the training set and 0.820
In decision curve analysis, the nomogram showed higher “net benefit” than a model based only on the four clinical factors or models based on “treat-all-patients” or “treat-no-patients” approaches. These results were observed at nearly all threshold probabilities in the training set (Figure 6A) and validation set (Figure 6B).
| Variable                        | Entire cohort (n = 118) | Training set (n = 84) | Validation set (n = 34) | P value |
|--------------------------------|--------------------------|-----------------------|--------------------------|---------|
| Male sex                       | 102 (86.4)               | 73 (86.9)             | 29 (85.3)                | 0.817   |
| Age, yr                        | 51.6 ± 10.5              | 51.2 ± 10.5           | 52.7 ± 10.6              | 0.484   |
| Hypertension                   | 11 (9.3)                 | 7 (8.3)               | 4 (11.8)                 | 0.561   |
| Diabetes mellitus              | 7 (5.9)                  | 6 (7.1)               | 1 (2.9)                  | 0.382   |
| Hepatitis B/C                  | 61 (51.7)                | 40 (47.6)             | 21 (61.8)                | 0.164   |
| Child-Pugh, A/B                | 116/2                    | 83/1                  | 33/1                     | 0.495   |
| Liver cirrhosis                | 47 (39.8)                | 35 (41.7)             | 12 (35.3)                | 0.522   |
| Hypersplenia                   | 15 (12.7)                | 11 (13.1)             | 4 (11.8)                 | 0.844   |
| ALT (U/L)                      | 55.2 ± 100.4             | 46.1 ± 29.3           | 77.6 ± 181.1             | 0.807   |
| AST (U/L)                      | 59.8 ± 136.6             | 48.1 ± 28.8           | 88.6 ± 250.7             | 0.513   |
| ALB (g/L)                      | 42.1 ± 4.6               | 42.3 ± 4.0            | 41.5 ± 5.7               | 0.643   |
| TB (mmol/L)                    | 15.9 ± 10.1              | 15.7 ± 10.1           | 16.5 ± 10.0              | 0.597   |
| AFP (ng/mL)                    | 285.2 ± 475.1            | 256.3 ± 454.6         | 356.5 ± 522.4            | 0.156   |
| CA19-9 (U/mL)                  | 106.8 ± 251.2            | 109.7 ± 258.3         | 99.6 ± 236.2             | 0.184   |
| CA125 (U/mL)                   | 117.0 ± 624.6            | 152.9 ± 727.5         | 18.3 ± 11.9              | 0.541   |
| CEA (ng/mL)                    | 6.4 ± 30.3               | 7.5 ± 35.5            | 3.4 ± 3.2                | 0.444   |
| Liver fibrosis                 |                          |                       |                          | 0.871   |
| No significant fibrosis        | 15 (13.8)                | 11 (13.8)             | 4 (13.8)                 |         |
| Significant fibrosis           | 37 (33.9)                | 26 (32.5)             | 11 (37.9)                |         |
| Advanced fibrosis              | 57 (52.3)                | 43 (53.8)             | 14 (48.3)                |         |
| Not mentioned                  | 8 (6.8)                  | 3 (3.6)               | 5 (14.7)                 |         |
| Tumor size, ≤ 5 cm             | 38 (32.2)                | 20 (23.8)             | 18 (52.9)                | 0.002   |
| Tumor number, ≥ 2              | 67 (56.8)                | 52 (61.9)             | 15 (44.1)                | 0.077   |
| Satellite lesions              | 42 (35.6)                | 29 (34.5)             | 13 (38.2)                | 0.703   |
| Vascular invasion              | 46 (39.0)                | 35 (41.7)             | 11 (32.4)                | 0.347   |
| Lymph node infiltration        | 15 (12.7)                | 10 (11.9)             | 5 (14.7)                 | 0.679   |
| Differentiation                |                          |                       |                          | 0.578   |
| Well                           | 44 (37.3)                | 30 (35.7)             | 14 (41.2)                |         |
| Moderate                       | 22 (18.6)                | 18 (21.4)             | 4 (11.8)                 |         |
| Poor                           | 1 (0.8)                  | 1 (1.2)               | 0 (0.0)                  |         |
| Undifferentiated               | 51 (43.2)                | 35 (41.7)             | 16 (47.1)                |         |
| 8th AJCC stage                 |                          |                       |                          | 0.027   |
| I                              | 9 (7.6)                  | 7 (8.3)               | 2 (5.9)                  |         |
| II                             | 28 (23.7)                | 14 (16.7)             | 14 (41.2)                |         |
| III                            | 66 (55.9)                | 53 (63.1)             | 13 (38.2)                |         |
| IV                             | 15 (12.7)                | 10 (11.9)             | 5 (14.7)                 |         |
| T stage                        |                          |                       |                          | 0.042   |
| T1                             | 13 (11.0)                | 9 (10.7)              | 4 (11.8)                 |         |
| T2                             | 29 (24.6)                | 15 (17.9)             | 14 (41.2)                |         |
| T3                             | 45 (38.1)                | 37 (44.0)             | 8 (23.5)                 |         |
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| T4  | 31 (26.3) | 23 (27.4) | 8 (23.5) | 0.762 |
|-----|-----------|-----------|----------|-------|
| N0  | 103 (87.3) | 74 (88.1) | 29 (85.3) |       |
| N1  | 15 (12.7)  | 10 (11.9) | 5 (14.7)  |       |
| Transfusion | 17 (14.4) | 14 (16.7) | 3 (8.8) | 0.388 |
| Blood loss ≤ 400 mL | 71 (60.2) | 49 (58.3) | 22 (64.7) | 0.522 |
| Margin, R1 | 13 (11.0) | 9 (10.7) | 4 (11.8) | 0.869 |
| Surgical method | 0.285 |
| Major resection | 57 (48.3) | 44 (52.4) | 13 (38.2) |       |
| Minor resection | 50 (42.4) | 32 (38.1) | 18 (52.9) |       |
| Resection + ablation | 11 (9.3) | 8 (9.5) | 3 (8.8) |       |
| Anatomical resection | 50 (43.9) | 39 (48.1) | 11 (33.3) | 0.148 |
| Postoperative TACE | 35 (29.7) | 28 (33.3) | 7 (20.6) | 0.17 |
| Hospital stay (d) | 12.2 ± 4.5 | 12.3 ± 4.4 | 11.9 ± 5.0 | 0.608 |
| Overall survival (mo) | 30.8 ± 26.3 | 29.6 ± 26.2 | 33.6 ± 26.9 | 0.462 |

| Values are n, n (%), or mean ± SD, unless otherwise noted. |
|----------------------------------------------------------------|
| AFP: Alpha fetoprotein; AJCC: American Joint Committee on Cancer; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CEA: Carcinoembryonic antigen; TACE: Transhepatic arterial chemotherapy and embolization; TB: Total bilirubin. |

Risk stratification using the nomogram

A total risk score was calculated for each patient by summing the scores for each variable in the nomogram. The maximum Youden index of 105 points in the nomogram led us to determine a cut-off value of 39.66, and patients were categorized as being at “high” or “low” risk based on whether their risk score was above or below this cut-off. Kaplan-Meier curves showed that OS was significantly longer for low-risk patients than for high-risk patients, regardless of whether the analysis included all patients (Figure 6C) or only the training set (Figure 6D) or validation set (Figure 6E). Across all patients, OS rates at 1 year were 10.8% for the high-risk group and 84.0% for the low-risk group (P < 0.001), while the corresponding OS rates at 3 years were 2.7% and 69.1%, respectively (P < 0.001).

Table 3 compares HRs obtained with the integrated nomogram, the radiomics score alone, or a model based only on clinical factors. The model based only on the four clinical risk factors resulted in an HR of 2.65 (95%CI: 1.53-4.60), even though total bilirubin level resulted in an HR of 13.94 (95%CI: 3.56-54.60) in multivariate analysis. The nomogram HR was higher than that provided by models based on the radiomics score or on clinical factors alone.

DISCUSSION

In the present study, we developed a comprehensive integrative nomogram that takes into account CT radiomics scores and four clinical risk factors that independently predict OS (vascular invasion, anatomical resection, total bilirubin, and satellite lesions), and we showed that this nomogram can predict OS in cHCC-CCA patients following potentially curative hepatectomy. The AUC for 1-year OS was 0.878 in the training set and 0.937 in the validation set. To our knowledge, this is the first CT-based radiomics model to predict postoperative survival of cHCC-CCA patients.

Our results extend the number of situations in which radiomics has shown potential in predicting the survival of patients with liver tumors[34,35]. The patients in our study who were assigned a high radiomics score had a 5.91-fold higher risk of death than those with a low score, consistent with a previously reported association between high radiomics score and risk of recurrence in patients with HCC or ICC[24,36]. These findings imply that radiomics scores may be able to identify patients preoperatively who are more likely to benefit from surgical resection.
Table 2 Univariate analysis and multivariate Cox regression to identify clinical factors associated with overall survival after curative hepatectomy

| Variable                             | Univariate analysis | Multivariate analysis |
|--------------------------------------|---------------------|-----------------------|
|                                      | HR (95%CI)          | P value               | HR (95%CI)          | P value               |
| Male sex                             | 0.470 (0.203-1.088) | 0.078                 | 1.767 (0.244-1.316) | 0.186                 |
| Age, yr                              |                     |                       |                      |                       |
| ≥ 60                                 | Ref.                |                       |                      |                       |
| > 60                                 | 1.173 (0.644-2.139) | 0.602                 |                       |                       |
| Liver cirrhosis                      |                     |                       |                      |                       |
| Absent                               | Ref.                |                       |                      |                       |
| Present                              | 1.370 (0.852-2.203) | 0.194                 |                       |                       |
| AFP (ng/mL)                          | 0.990 (0.597-1.643) | 0.970                 |                      |                       |
| CA 19-9 (U/mL)                       | 0.987 (0.586-1.662) | 0.960                 |                      |                       |
| Albumin (g/L)                        | 2.496 (0.997-6.244) | 0.051                 | 1.025 (0.968-1.085) | 0.403                 |
| TB (μmol/L)                          |                      |                       |                      |                       |
| ≤ 34                                 | Ref.                |                       | Ref.                 |                       |
| > 34                                 | 17.994 (4.726-68.509)| < 0.001               | 13.943 (5.561-54.602)| < 0.001               |
| Tumor number, multiple               | 0.766 (0.473-1.240) | 0.277                 |                      |                       |
| Satellite lesions                    |                     |                       |                      |                       |
| Absent                               | Ref.                |                       | Ref.                 |                       |
| Present                              | 2.037 (1.267-3.268) | 0.003                 | 1.762 (1.079-2.877) | 0.024                 |
| Vascular invasion                    |                     |                       |                      |                       |
| Absent                               | Ref.                |                       | Ref.                 |                       |
| Present                              | 2.009 (1.247-3.259) | 0.004                 | 1.725 (1.049-2.834) | 0.032                 |
| T stage                              |                      |                       |                      |                       |
| T1                                   | Ref.                |                       |                      |                       |
| T2                                   | 1.171 (0.705-1.942) | 0.542                 |                      |                       |
| T3                                   | 2.424 (0.704-8.348) | 0.161                 |                      |                       |
| T4                                   | 3.823 (1.158-12.615)| 0.028                 |                      |                       |
| Anatomy resection                    |                     |                       |                      |                       |
| Yes                                  | Ref.                |                       | Ref.                 |                       |
| No                                   | 2.011 (1.344-3.006) | 0.006                 | 1.731 (1.083-2.767) | 0.028                 |
| Margin                               |                      |                       |                      |                       |
| R0                                   | Ref.                |                       |                      |                       |
| R1                                   | 1.032 (0.446-2.387) | 0.941                 |                      |                       |
| Postoperative TACE                    |                     |                       |                      |                       |
| Yes                                  | Ref.                |                       |                      |                       |
| No                                   | 1.597 (0.924-2.759) | 0.093                 | 1.6051 (0.3546-1.0947)| 0.100                 |

AFP: Alpha-fetoprotein; CI: Confidence interval; HR: Hazard ratio; Ref.: Reference; TB: Total bilirubin; TACE: Transhepatic arterial chemotherapy and embolization.

Our results further support previous work indicating that combining clinical variables with radiomics features may predict prognosis better than either the variables or the features separately[37,38]. Combining the radiomics score with clinical variables allowed us to classify patients into a high-risk group that had an 8.16-fold
higher risk of death than the low-risk group, with the two groups showing a median OS of 6.1 and 81.6 mo, respectively ($P < 0.001$). This integrative nomogram may help identify cHCC-CCA patients who are more likely to benefit from resection.

The rate of vascular invasion in our patients was 39.0%, similar to previous studies and within the prevalence of 9%-89.5% reported for cHCC-CCA[3,39,40]. As shown in Supplementary Figure 1, the OS rate at 3 years was 56.8% among our patients without vascular invasion, compared to only 36.8% among those with invasion, consistent with the association between vascular invasion and worse postoperative prognosis[2,13,41]. Indeed, vascular invasion has been shown to be an independent predictor of postoperative survival in patients with combined hepatocellular-cholangiocarcinoma and it increases the risk of death in these patients by 1.6-fold to 5.2-fold[42,43].

In addition, elevated total bilirubin level (> 34 μmol/L) and no anatomic surgical resection were considered to be independent risk factors related to the poor prognosis of cHCC-CCA patients. Total bilirubin level is one element of the Child-Pugh classi-

### Table 3 Comparison of hazard ratios describing risk for different predictive models

| Model                      | HR (95%CI)       | $P$ value |
|----------------------------|------------------|-----------|
| Radiomics score            |                 | < 0.001   |
| Low risk                   | Ref.             |           |
| High risk                  | 5.908 (3.285-10.626) |           |
| Clinical model             |                 | < 0.001   |
| Low risk                   | Ref.             |           |
| High risk                  | 2.653 (1.532-4.595) |           |
| Radiomics nomogram         |                 | < 0.001   |
| Low risk                   | Ref.             |           |
| High risk                  | 8.155 (4.498-14.785) |           |

CI: Confidence interval; HR: Hazard ratio; Ref.: Reference.

**Figure 2 Flow diagram of patient selection.** cHCC-CCA: Combined hepatocellular carcinoma and cholangiocarcinoma; LASSO: Least absolute shrinkage and selection operator; OS: Overall survival; ROC: Receiver operating characteristic.
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Figure 3 Radiomics feature selection. A: Random forest analysis. Least absolute shrinkage and selection operator regression selected nine radiomics features, of which three were chosen by random forest analysis; B: Weights of MeanValue, NGLDM Busyness, and GLZLM HGZE in each patient; C: Overall survival curves for the entire cohort of patients, stratified by low or high radiomics score.

Studies have suggested that anatomical hepatectomy can prolong survival in HCC but not ICC patients\cite{48,49}; however, we are unaware of studies that have examined this issue in cHCC-CCA patients. The impact of anatomical hepatectomy on OS of
Figure 4 Construction and validation of a radiomics nomogram to predict overall survival of combined hepatocellular carcinoma and cholangiocarcinoma patients after surgical resection. A: Radiomics nomogram to predict overall survival (OS) at 1 and 3 years; B and C: Receiver operating characteristic curves for predicting 1-year OS in the training or validation set. The area under the curve in both cases was > 0.85; D and E: Calibration curves for 1-year OS in the training and validation sets. The horizontal axis is the survival rate predicted by the nomogram, and the vertical axis is the actual survival rate. The black dashed line indicates the case of perfect agreement between the two rates.

cHCC-CCA patients after resection should be explored in large, prospective studies.
The present study has some limitations. First, its retrospective nature may be associated with a greater risk of selection bias and loss to follow-up, although only eight (6.8%) patients were lost to follow-up. Second, we validated the nomogram internally, not externally; nevertheless, AUCs were > 0.85 for both training and validation sets. Third, the study involved a small sample; thus, the nomogram described here should be validated and optimized using larger samples.

CONCLUSION

This study established a nomogram which combined the CT radiomics score with clinical risk factors to predict OS in patients with cHCC-CCA after resection with curative intent. The radiomics score was strongly associated with postoperative prognosis, and the integrative nomogram predicted OS well: High-risk patients showed a significantly shorter OS than low-risk patients. This integrative nomogram may aid in predicting the prognosis of cHCC-CCA patients after resection, and may support clinical decision-making.
Figure 6 Clinical usefulness of the radiomics nomogram. A and B: Decision curve analysis assessing the ability of the radiomics nomogram or a model based on four clinical factors to predict overall survival (OS) in the training and validation sets. The y-axis indicates “net benefit”; the red line, the radiomics nomogram; the blue dotted line, the model based on clinical factors; the gray dotted line, the result in the event that all patients died; and the black dotted line, the result in the event that no patient died. C-E: OS comparison between patients classified by the radiomics nomogram as at “low risk” or “high risk” of poor OS; C: All patients; D: The training set; and E: The validation set.
ARTICLE HIGHLIGHTS

Research background
Combined hepatocellular carcinoma (HCC) and cholangiocarcinoma (cHCC-CCA) arises in hepatic progenitor cells and are defined as a single nodule showing differentiation into HCC and intrahepatic cholangiocarcinoma (ICC) with 5-year postoperative overall survival (OS) rates ranging from 8% to 63%. There are different opinions in the literature on whether the prognosis of patients with cHCC-CCA is worse than that of patients with simple HCC or similar ICC.

Research motivation
Due to the poor prognosis of cHCC-CCA and absence of a promising way to predict prognosis of cHCC-CCA, the authors aimed to construct a radiomics nomogram for predicting postoperative survival of cHCC-CCA patients. This prognostic model may help guide treatment decisions for these patients.

Research objectives
The purpose of this study was to construct and validate a nomogram based on radiomics and clinical characteristics to predict the postoperative survival rate of patients with cHCC-CCA.

Research methods
We collected the clinical data and computed tomography (CT) imaging data of patients with cHCC-CCA. Radiomics features were extracted from portal venous phase CT images using the least absolute shrinkage and selection operator Cox regression and random forest analysis. A nomogram integrating radiomics score and clinical factors was developed using multivariate Cox regression and each patient got a risk score. And patients were categorized as being at “high” or “low” risk based on their risk scores.

Research results
A total of five factors, which were Radiomics score, vascular invasion, anatomical resection, total bilirubin level, and satellite lesions, were independent predictors of prognosis and the nomogram was associated with OS more strongly than a model based on radiomics score or only clinical factors. Patients stratified as being at high risk showed a significantly shorter median OS than those stratified as being at low risk (6.1 vs 81.6 mo, P < 0.001).

Research conclusions
This nomogram have potential usefulness in predicting postoperative survival of cHCC-CCA patients and may therefore help identify those more likely to benefit from it, which may facilitate clinical decision-making.

Research perspectives
Considering the high AUC of this radiomics nomogram in predicting prognosis of cHCC-CCA, this prognostic model may help guide treatment decisions for these patients.

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