ORIGINAL RESEARCH

Prognostic Impact of CCA Components in Combined Hepatocellular Carcinoma-Cholangiocarcinoma

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Purpose: To investigate the differences of combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) patients with a cholangiocarcinoma (CCA) component ≥ 30% or < 30% versus intrahepatic cholangiocarcinoma (iCCA) patients in recurrence-free survival (RFS) and overall survival (OS) prognoses.

Methods: Patients with cHCC-CCA and iCCA after surgery were recruited. All cHCC-CCA patients were divided into two subgroups (CCA components ≥ 30% and < 30%). Then, Kaplan-Meier survival analysis and Cox regression analysis were used to investigate and compare the differences of cHCC-CCAs with a CCA component ≥ 30% or < 30% versus iCCAs in RFS and OS prognoses, respectively. The differences of MRI features between cHCC-CCAs with a CCA component ≥ 30% and < 30% were also compared.

Results: One hundred sixty-four cHCC-CCAs and 146 iCCAs were enrolled. Compared with iCCAs, cHCC-CCAs with a CCA component < 30% had better OS prognosis (HR: 2.888, p = 0.045). However, Cox regression analysis revealed that cHCC-CCAs with a CCA component ≥ 30% had poorer RFS (HR: 0.503, p < 0.001) and OS (HR: 0.58, p = 0.033) prognoses than iCCAs. In addition, rim APHE (OR = 0.286, p < 0.001), targetoid diffusion restriction (OR = 0.316, p = 0.019), corona enhancement (OR = 0.481, p = 0.033), delayed enhancement (OR = 0.251, p = 0.001), and LR-M (OR = 1.586, p < 0.001) were significant factors associated with cHCC-CCAs with a CCA component ≥ 30%. Multivariable regression analyses showed that only LR-M (OR = 1.522, p = 0.042) was a significantly independent predictor for cHCC-CCAs with a CCA component ≥ 30%.

Conclusion: cHCC-CCAs with a CCA component ≥ 30% had worse prognoses than iCCAs. Therefore, we suggest that the postoperative treatment of cHCC-CCAs with a CCA component ≥ 30% can be based on the treatment strategy for iCCAs.

Keywords: liver neoplasms, prognosis, magnetic resonance imaging

Introduction

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) is a primary liver carcinoma with pathologic differentiation of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) within the same tumor.[1–4] Immunohistochemical markers may be applied for further specification but have limited value for diagnosis. The difficulty in the diagnosis, treatment, and prognosis of cHCC-CCA is mainly due to the different proportions of two components.[5–9]

The prognosis of cHCC-CCA patients is generally believed to be significantly worse than that of HCC patients, but whether it is better than intrahepatic cholangiocarcinoma (iCCA) patients is still controversial.[10–15] The reason for inconsistent prognosis may be that cHCC-CCA was treated as a whole, without considering the influence of its component ratios. Recent studies have shown that the proportion of cHCC-CCA components has a significant impact on recurrence-free survival (RFS) and overall survival (OS) prognoses.[16,17] In addition, our preliminary study also found that cHCC-CCAs with a CCA component < 30% had a significantly better prognosis than those with a CCA component ≥ 30%.[18] Therefore, we speculate whether cHCC-CCAs with a CCA component ≥ 30% have worse prognoses than iCCA, while cHCC-CCAs with a CCA component < 30% have better prognoses than iCCA.

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Therefore, the purpose of this study is to investigate the differences of cHCC-CCAs with a CCA component ≥ 30% or < 30% versus iCCAs in RFS and OS prognoses.

Materials and Methods

Our institutional review board of Zhongshan Hospital, Fudan University (Approval No.: B2021-325R) approved the study, and written informed consent for this retrospective review was obtained from each patient before enrolment.

Participants Sample

Patients with malignant liver neoplasms from Zhongshan Hospital, Fudan University were consecutively enrolled between January 2019 and December 2021. The inclusion criteria were as follows: (1) pathologically confirmed cHCC-CCAs and iCCAs after surgery according to the 2019 WHO classification system, and (2) preoperative contrast-enhanced MR imaging within 2 weeks of surgery. Some patients were excluded due to (1) a lack of clinical and histopathological data; (2) insufficient MR image quality; (3) preoperative treatment, or (4) lost follow-up.

Clinical and Pathological Data Evaluation

All clinical information of cHCC-CCA and iCCA patients contained the following: age, sex, hepatitis B virus infection status, and biomarker levels. Biomarker levels consisted of serum alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19–9 (CA19-9) within the 7 days before curative resection. The cutoff values for AFP, CEA, and CA19-9 were 20 ng/mL, 5 ng/mL, and 37 U/mL, respectively. The pathological features of the lesions included microvascular invasion (MVI) and tumor size.

Histopathological Analysis

Histopathologic diagnoses of tumors were determined according to updated 2019 WHO classification, based on hematoxylin-eosin–stained morphology with the assistance of immunohistochemistry analysis (arginase-1, AFP, cytokeratin-19, polyclonal carcinoembryonic antigen, etc). The CCA components and their proportions of cHCC-CCAs were analyzed and recorded in detail.

Follow-Up for RFS and OS

Follow-up data were obtained by a review of medical records or telephone interviews every 6 months after surgical resection. The primary end point was recurrence-free-survival, defined as the time from the date of surgery to the date of the first detected recurrence or death. Recurrence was determined as the presence of intrahepatic or extrahepatic neoplasms observed by ultrasound, CT/MRI, positron emission tomography (PET)-CT or pathological confirmation. All cHCC-CCA patients were divided into two subgroups according to whether the ratio of the histopathological CCA components was less than 30%. Then, the differences of cHCC-CCAs with a CCA components ≥ 30% or < 30% versus iCCAs in RFS and OS prognoses were compared, respectively.

Liver MRI

All patients underwent MRI with a 24-channel 1.5 T MR scanner (uMR 560, United Imaging Healthcare, China). Noncontrast liver protocols consisted of transverse diffusion-weighted imaging (DWI, b value = 0, 50, and 500 s/mm2), in-phase and out-phase imaging, T2-weighted imaging (T2WI), and T1WI sequences. Dynamic contrast-enhanced MR imaging was performed with a T1-weighted fat-suppressed sequence.

Image Features Interpretation

Two abdominal radiologists (C.W.Z. and C.Y., with 13 and 15 years of experience in abdominal imaging, respectively), who were blinded to the clinical data, tumor markers, pathological results, and clinical outcome, independently analyzed all MR images. The interval between readout sessions was 1 month. A consensus was reached after a disagreement arose between the two observers.

The following imaging characteristics of cHCC-CCAs and iCCAs were investigated on precontrast MR images: (a) intratumoral hemorrhage, (b) targetoid diffusion restriction (defined as the target sign with peripheral hyperintensity and central hypointensity on diffusion-weighted imaging), (c) peritumoral bile duct dilatation, and (d) hepatic capsule retraction. Moreover, the following dynamic enhancement features were evaluated: arterial phase: (e) rim arterial phase hyperenhancement (APHE); portal venous phase: (f) peripheral washout, and (g) corona enhancement (defined as enhancement adjacent to the tumor border); delayed phase: (h) delayed enhancement, and (i) enhancing capsule; and other imaging features: (j) nodule-in-nodule architecture, and (k) mosaic architecture. In addition, the Liver Imaging Reporting and Data System (LI-RADS ver. 2018) categorization (LR-4/5, LR-M, and LR-TIV) was also assessed in this study. The differences in MRI features of cHCC-CCAs with a CCA component ≥ 30% versus < 30% were also compared. The kappa values of inter-observer agreement were from 0.841 (95% CI: 0.746–0.918, p < 0.001) for mosaic architecture to 0.959 (95% CI: 0.915–0.99, p < 0.001) for intratumoral hemorrhage.

Statistical Analysis

Statistical analyses were performed by using SPSS 26.0 (SPSS, Inc., Chicago, IL, USA). Data with a normal distribution are presented as the mean ± standard deviation, and differences between the two groups were compared using an independent-sample t test. Moreover, categorical variables are shown as the number of cases and the percentages, and comparisons were performed by using the chi-square test or Fisher's exact test. Kaplan–Meier survival curves, Log rank tests, and Cox regression analyses were utilized to compare differences in RFS and OS between cHCC-CCAs (with a CCA component ≥ 30% or < 30%) and iCCAs, and the results of Cox regression analyses were presented as hazard ratios (HR) with 95% confidence intervals (95% CI). In addition, univariable and multivariable logistic regression analyses were performed to identify which of the clinicopathological features and MRI characteristics were independent risk factors for cHCC-CCAs with a CCA component ≥ 30% versus iCCAs, with the odds ratio (OR) and 95% confidence interval (CI). Differences with a p value < 0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 1742 patients with malignant liver neoplasms were initially enrolled. Of these, 1412 were excluded according to the inclusion and exclusion criteria, and 20 were removed due to the loss of follow-up. Finally, 164 cHCC-CCA (97 CCA components ≥ 30% and 67 CCA components < 30%) and 146 iCCA patients were recruited. The detailed reasons are presented in Figure 1.

The clinicopathological features of 164 cHCC-CCA (mean age: 54.8 ± 11.7 years old) and 146 iCCA (mean age: 61.3 ± 11.1 years old) patients are summarized in Table 1. The incidence of HBV infection (82.3% vs 46.6%, p < 0.001) and AFP > 20 ng/mL (53.7% vs 11.6%, p < 0.001) were significantly higher in cHCC-CCAs than that of iCCAs, while the prevalence of CA19-9 > 37 U/mL (21.3% vs 41.8%, p < 0.001) was significantly lower in cHCC-CCAs, and tumor size (4.0 ± 2.8 cm vs 5.2 ± 2.6 cm, p < 0.001) was significantly smaller in cHCC-CCAs.

The Differences of RFS and OS in cHCC-CCAs with CCA Components < 30% versus iCCAs

Of the 164 cHCC-CCAs and 146 iCCAs who were followed up for a median of 37 months (interquartile range, 27–41 months), 73 (44.5%) cHCC-CCAs (49 (67.1%) CCA components ≥ 30% and 24 (32.9%) CCA components < 30%) and 57 (39.0%) iCCAs experienced recurrences after curative treatment, respectively.

The survival analysis showed that there was no significant difference in time-to-recurrence (TTR) between cHCC-CCAs with a CCA component < 30% and iCCAs (log rank p = 0.452) (Figure 2). Furthermore, univariable Cox regression analysis also revealed that cHCC-CCAs with a CCA component < 30% had no better RFS prognoses than did the iCCAs (HR: 0.831, p = 0.458).

However, there was a significant difference in OS time between cHCC-CCAs with a CCA component < 30% and iCCAs (log rank p = 0.035) (Figure 3). Moreover, univariable Cox regression analysis also revealed that cHCC-CCAs with a CCA component < 30% had better OS prognoses than did the iCCAs (HR: 2.888, p = 0.045).
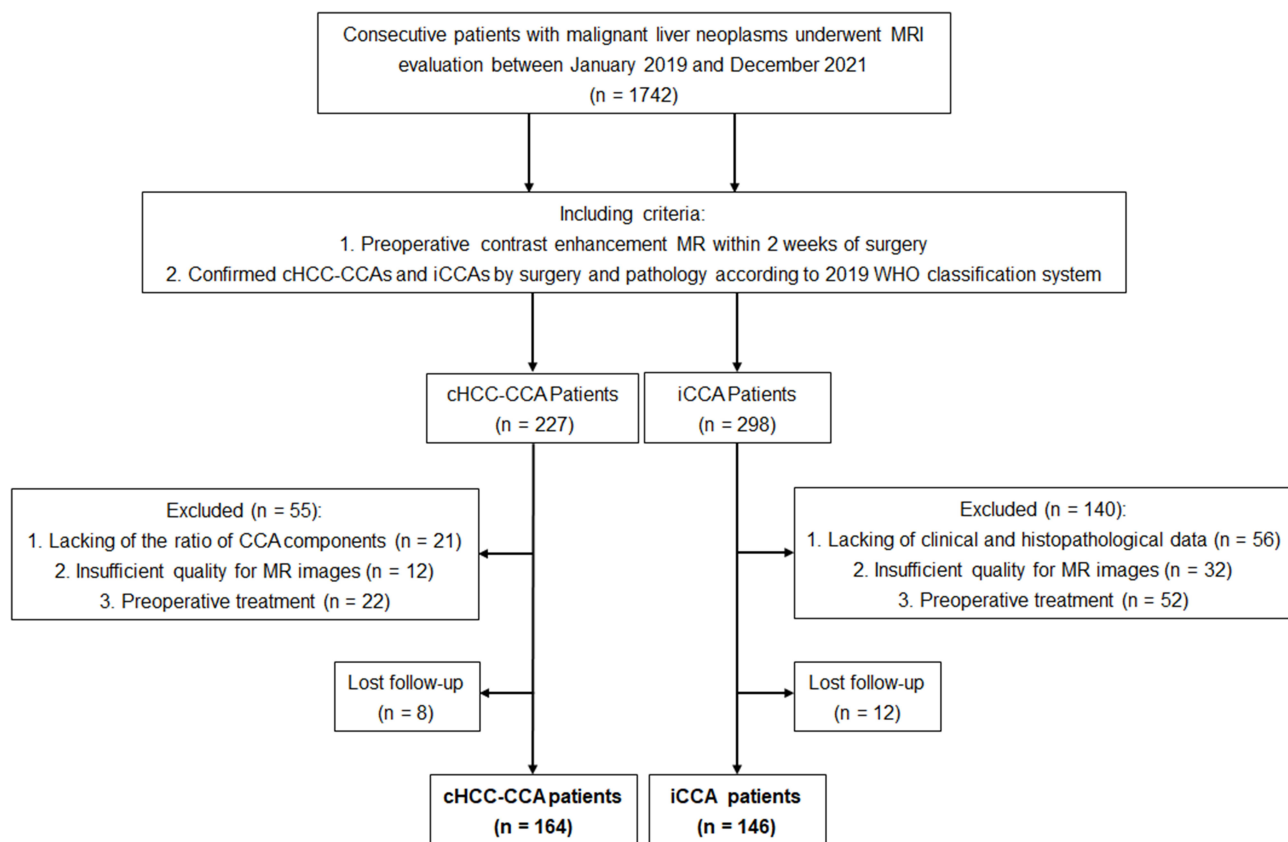
Figure 1 Flowchart of this study cohort. cHCC-CCA = combined hepatocellular carcinoma-cholangiocarcinoma.
Abbreviations: iCCA, intrahepatic cholangiocarcinoma; CCA, cholangiocarcinoma.

The Differences of RFS and OS in cHCC-CCAs with CCA Components ≥ 30% versus iCCAs

The survival analysis showed that cHCC-CCAs with a CCA component ≥ 30% had significantly shorter TTR than did the iCCAs (log rank P < 0.001) (Figure 4). Furthermore, univariable Cox regression analysis also revealed that cHCC-CCAs with a CCA component ≥ 30% had poorer RFS prognoses than iCCAs (HR: 0.503, p < 0.001).

Table 1 Clinicopathological Findings of cHCC-CCAs versus iCCAs

Variables	cHCC-CCAs (n = 164)	iCCAs (n = 146)	p value
Age (years)*	54.8 ± 11.7	61.3 ± 11.1	< 0.001
Sex (male)	131 (79.9%)	100 (68.5%)	0.026
HBV infection	135 (82.3%)	68 (46.6%)	< 0.001
AFP>20 ng/mL	88 (53.7%)	17 (11.6%)	< 0.001
CEA>5 ng/mL	23 (14.0%)	26 (17.8%)	0.436
CA19-9>37 U/mL	35 (21.3%)	61 (41.8%)	< 0.001
MVI	61 (37.2%)	59 (40.4%)	0.640
Tumor size (cm)	4.0 ± 2.8	5.2 ± 2.6	< 0.001

Notes: *Data are mean ± standard deviation. Except where labeled, data are numbers of patients, with percentages in parentheses.
Abbreviations: cHCC-CCA, combined hepatocellular carcinoma-cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; HBV, Hepatitis B virus; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; MVI, microvascular invasion.
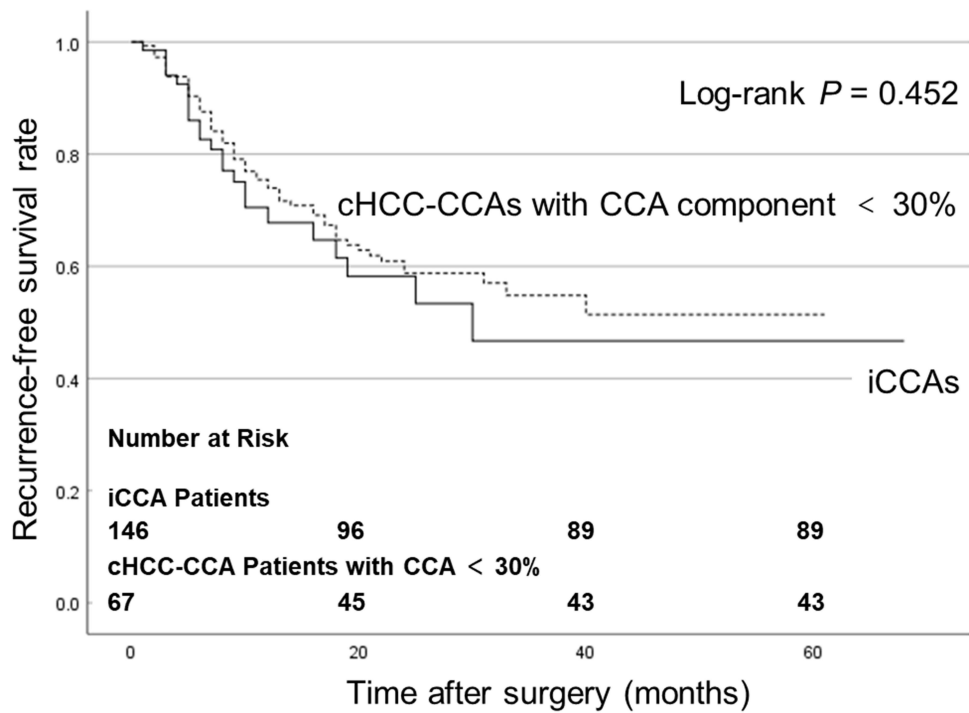
Figure 2 Kaplan-Meier survival curve shows that there is no significant difference in recurrence-free survival prognosis between cHCC-CCAs with a CCA component < 30% and iCCAs.
Abbreviations: cHCC-CCA, combined hepatocellular carcinoma-cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; CCA, cholangiocarcinoma.
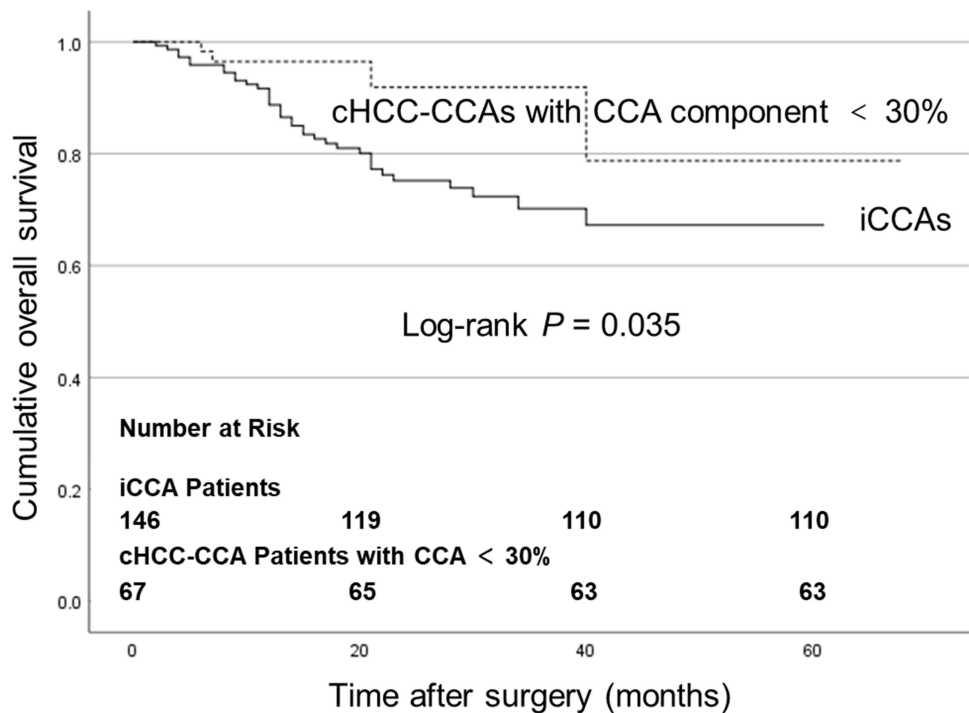

Figure 3 Kaplan-Meier survival curve shows that the recurrence-free survival prognosis of cHCC-CCAs with a CCA component < 30% is significantly better than that of iCCAs.
Abbreviations: cHCC-CCA, combined hepatocellular carcinoma-cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; CCA, cholangiocarcinoma.
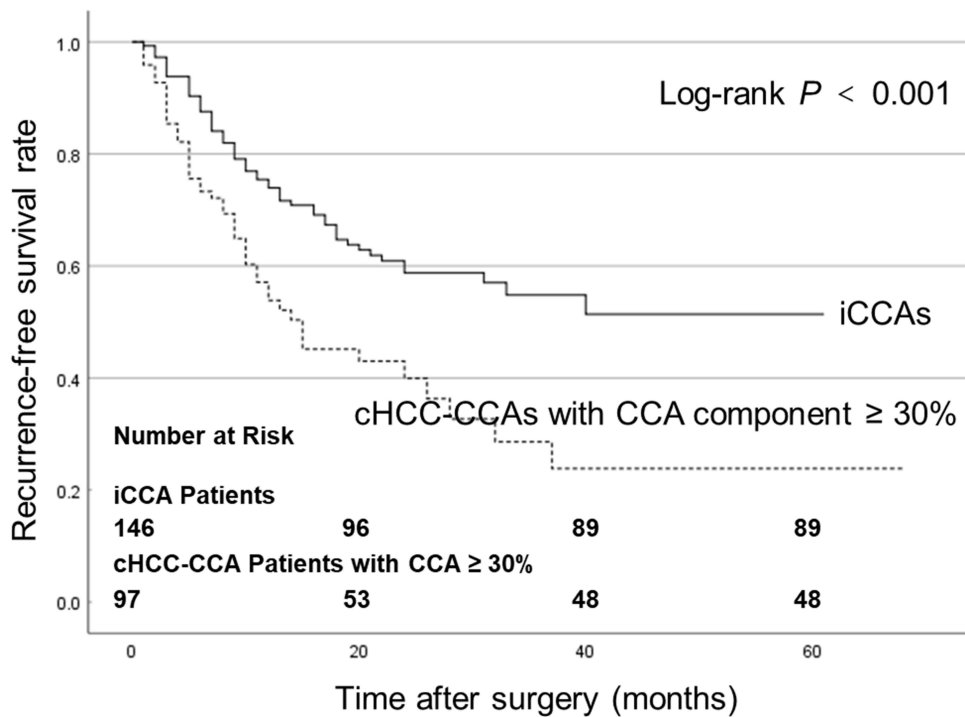
Figure 4 Kaplan-Meier survival curve shows that the recurrence-free survival prognosis of cHCC-CCAs with a CCA component ≥ 30% is significantly poorer than that of iCCAs.
Abbreviations: cHCC-CCA, combined hepatocellular carcinoma-cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; CCA, cholangiocarcinoma.

In addition, there was significant shorter OS time in cHCC-CCAs with a CCA component ≥ 30% versus iCCAs (log rank P = 0.03) (Figure 5). Moreover, univariable Cox regression analysis also revealed that cHCC-CCAs with a CCA component ≥ 30% had worse OS prognoses than iCCAs (HR: 0.58, p = 0.033).
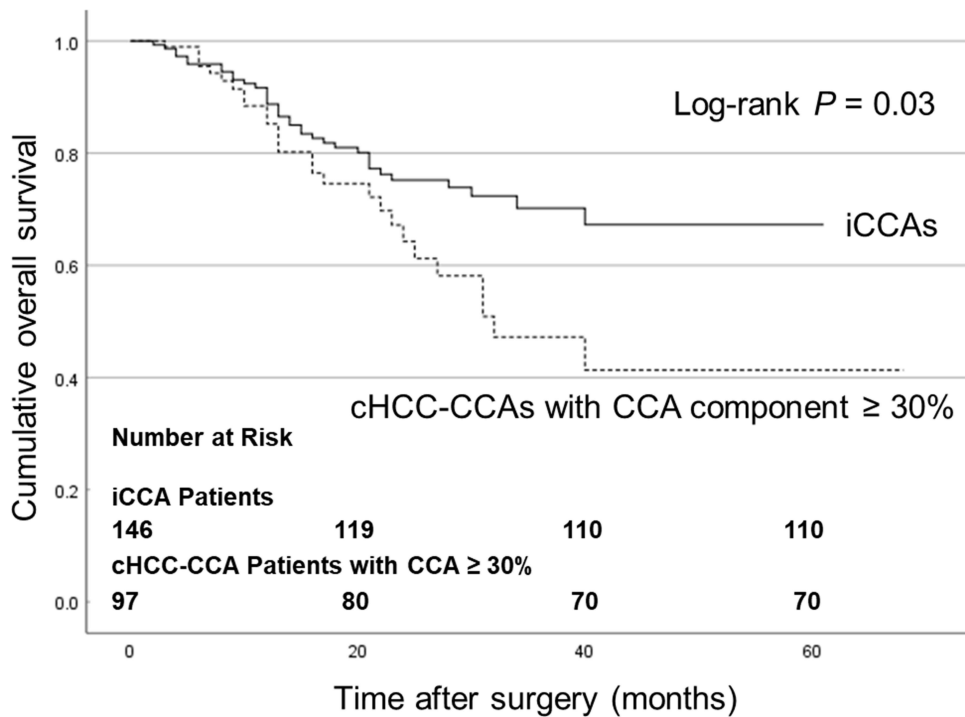

Figure 5 Kaplan-Meier survival curve shows that the overall survival prognosis of cHCC-CCAs with a CCA component ≥ 30% is significantly worse than that of iCCAs.

The Differences in Clinicopathological Findings and MRI Features of cHCC-CCAs with CCA Components ≥ 30% versus < 30%

Of 164 cHCC-CCAs, 97 had a CCA component of ≥ 30%. AFP > 20 ng/mL was less prevalent in cHCC-CCAs with a CCA component ≥ 30% (46.4% vs 64.2%, p = 0.027). Furthermore, the univariable and multivariable regression analyses (OR: 2.689, p = 0.017) also indicated that AFP > 20 ng/mL was an independent factor for cHCC-CCAs with a CCA component < 30%. However, there were no significant differences in age, sex, HBV infection, other biomarkers, tumor size, and microvascular invasion between cHCC-CCAs with a CCA component ≥ 30% and < 30% (Tables 2 and 3).

In addition, the incidence of rim APHE (59.8% vs 29.9%, p < 0.001), targetoid diffusion restriction (23.7% vs 9.0%, p = 0.021), corona enhancement (43.3% vs 26.9%, p = 0.034), delayed enhancement (35.1% vs 11.9%, p = 0.001), and LR-M (57.7% vs 28.4%, p < 0.001) was significantly higher in the cHCC-CCAs with a CCA component ≥ 30% than that of < 30%. Moreover, the univariable regression analysis revealed that rim APHE (OR = 0.286, p < 0.001), targetoid diffusion restriction (OR = 0.316, p = 0.019), corona enhancement (OR = 0.481, p = 0.033), delayed enhancement (OR = 0.251, p = 0.001), and LR-M (OR = 1.586, p < 0.001) were significant factors associated with cHCC-CCAs with a CCA component ≥ 30%. Multivariable regression analyses showed that only LR-M (OR = 1.522, p = 0.042) was a significantly independent predictor for cHCC-CCAs with a CCA component ≥ 30% (Tables 2 and 3).

Table 2 MRI Features of cHCC-CCAs with CCA Components ≥ 30% versus < 30%

Variables	CCA Components ≥ 30% (n = 97)	CCA Components < 30% (n = 67)	p value
Age (years)*	55.3 ± 11.7	54.2 ± 11.7	0.571
Sex (male)	80 (82.5%)	51 (76.1%)	0.329
HBV infection	77 (79.4%)	58 (86.6%)	0.299
AFP>20 ng/mL	45 (46.4%)	43 (64.2%)	0.027
CEA>5 ng/mL	18 (18.6%)	5 (7.5%)	0.066
CA19-9>37 U/mL	24 (24.7%)	11 (16.4%)	0.246
MVI	33 (34.0%)	28 (41.8%)	0.328
Tumor size (cm)	4.1 ± 2.7	3.7 ± 2.9	0.323
Intratumoral hemorrhage	13 (13.4%)	10 (14.9%)	0.821
Targetoid diffusion restriction	23 (23.7%)	6 (9.0%)	0.021
Rim APHE	58 (59.8%)	20 (29.9%)	< 0.001
Peripheral washout	3 (3.1%)	3 (4.5%)	0.689
Corona enhancement	42 (43.3%)	18 26.9%)	0.034
Delayed enhancement	34 (35.1%)	8 (11.9%)	0.001
Enhancing capsule	62 (63.9%)	44 (65.7%)	0.869
Peritumoral bile duct dilatation	19 (19.6%)	16 (23.9%)	0.563
Hepatic capsule retraction	19 (19.6%)	12 (17.9%)	0.841
Nodule-in-nodule architecture	6 (6.2%)	8 (11.9%)	0.257
Mosaic architecture	29 (29.9%)	22 (32.8%)	0.733
LI-RADS categorization			< 0.001
LR-4/5	21 (21.6%)	40 (59.7%)	
LR-M	56 (57.7%)	19 (28.4%)	
LR-TIV	20 (20.6%)	8 (11.9%)	

Notes: *Data are mean ± standard deviation. Except where labeled, data are numbers of patients, with percentages in parentheses.
Abbreviations: cHCC-CCA, combined hepatocellular carcinoma-cholangiocarcinoma; CCA, cholangiocarcinoma; HBV, Hepatitis B virus; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; MVI, micro-vascular invasion; APHE, arterial phase hyperenhancement; LR, LI-RADS, Liver Imaging Reporting and Data System; LR-M, LI-RADS category-malignancy.

Table 3 Regression Analysis of Risk Factors for cHCC-CCAs with CCA Components ≥ 30%

Variables	Univariable Analysis			Multivariable Analysis		
	p value	OR	95% CI	p value	OR	95% CI
Age (years)	0.569	0.992	0.966–1.019			
Sex (male)	0.320	0.677	0.314–1.460			
HBV infection	0.239	1.674	0.710–3.945			
AFP>20 ng/mL	0.026	2.070	1.093–3.932	0.017	2.689	1.193–6.064
CEA>5 ng/mL	0.051	0.354	0.124–1.007			
CA19-9>37 U/mL	0.204	0.597	0.270–1.322			
MVI	0.312	1.392	0.733–2.646			
Tumor size (cm)	0.323	0.943	0.838–1.060			
Intratumoral hemorrhage	0.783	1.134	0.465–2.762			
Targetoid diffusion restriction	0.019	0.316	0.121–0.827	0.256	0.440	0.107–1.815
Rim APHE	< 0.001	0.286	0.148–0.555	0.820	0.866	0.251–2.988
Peripheral washout	0.644	1.469	0.287–7.508			
Corona enhancement	0.033	0.481	0.245–0.943	0.168	0.526	0.211–1.312
Delayed enhancement	0.001	0.251	0.108–0.587	0.190	0.466	0.149–1.458
Enhancing capsule	0.817	1.080	0.562–2.074			
Peritumoral bile duct dilatation	0.510	1.288	0.607–2.734			
Hepatic capsule retraction	0.787	0.896	0.402–1.995			
Nodule-in-nodule architecture	0.202	2.056	0.679–6.228			
Mosaic architecture	0.689	1.146	0.587–2.240			
LR-M	< 0.001	1.586	1.313–1.916	0.042	1.522	1.015–2.282

Abbreviations: cHCC-CCA, combined hepatocellular carcinoma-cholangiocarcinoma; CCA, cholangiocarcinoma; OR, Odds Ratio; 95% CI, 95% Confidence interval; HBV, Hepatitis B virus; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; MVI, microvascular invasion; APHE, arterial phase hyperenhancement; LR-M, LI-RADS category-malignancy; iCCA, intrahepatic cholangiocarcinoma.

Discussion

Our study showed that cHCC-CCAs with a CCA component < 30% had significantly better OS prognosis than iCCAs. Furthermore, we also found that cHCC-CCAs with a CCA component ≥ 30% had significantly worse RFS and OS prognoses than iCCAs. In addition, LR-M was a significantly independent predictor for cHCC-CCAs with a CCA component ≥ 30%.

Prominent desmoplastic and hypovascularized tumor stroma are risk factors for the poor prognosis of tumors containing CCA components.[19] The prognosis of cHCC-CCAs and iCCAs is poorer than that of HCCs, but there is great controversy over who has a worse prognosis between them. He et al[16] found that cHCC-CCA with a predominant CCA component had a poorer prognosis, but the proportion of CCA components was not specified. Xiao et al[17] suggested that cHCC-CCAs with CCA components less than 35% tend to exhibit better overall survival. Our previous study also revealed that cHCC-CCAs with a CCA component < 30% had a significantly better prognosis than those with a CCA component ≥ 30%.[18] Therefore, we set 30% CCA components as a critical value and compared their prognostic differences with iCCAs, respectively. We found that cHCC-CCAs with a CCA component < 30% had significantly better OS prognosis than iCCAs, while cHCC-CCAs with a CCA component ≥ 30% had significantly worse RFS and OS prognoses than iCCAs. The reason for these findings is likely due to the fact that cHCC-CCA is a unique tumor type and not a simple combination of two components. In addition, a recent study constructed MRI-based habitat imaging model to predict component percentage, promoting the visualization of components in iCCAs.[20]

Some favoring-iCCA MRI features (rim APHE, targetoid diffusion restriction, corona enhancement, and delayed enhancement) were more prevalent in the cHCC-CCAs with a CCA component ≥ 30%. These features suggest the invasion of malignant tumor to surrounding tissues and complex components in tumor, indicating poor prognoses.[21–23] Jeon and Choi et al[24,25] also reported that cHCC-CCAs showing CCA-like imaging features had worse survival outcomes with regard to early recurrence.

The LR-4/5 category of cHCC-CCAs was correlated with a small ratio of CCA components (17.5% ± 22.2%).[26] Similarly, the LR-4/5 of cHCC-CCAs with a CCA component of < 30% accounted for 59.7%, while 57.7% cHCC-CCAs with a CCA component of ≥ 30% was classified as LR-M in this study. LR-M is defined as probably malignant lesions with targetoid mass appearances, including rim APHE, peripheral washout, delayed central enhancement, or targetoid diffusion restriction, reflecting the presence of tumor tissue in the periphery and fibrous stroma in the center, indicating a poor prognosis.[27,28] In the present study, LR-M was a significantly independent predictor for cHCC-CCAs with a CCA component ≥ 30%, suggesting that cHCC-CCAs classified as LR-M are likely to have a CCA component ≥ 30% and worse prognoses than iCCA.

Our study had several limitations. First, some cHCC-CCAs and iCCAs with pathological results obtained by puncture biopsy are excluded because it cannot obtain complete specimens and lead to the lack of pathological information, which inevitably leads to selection bias. Second, the ratio of histopathological components and their degree of differentiation might have a certain impact on the prognosis of cHCC-CCA. However, we only analyzed the proportion of CCA components and did not investigate their degree of differentiation in this study. Therefore, we will further explore the prognostic differences according to different ratios of CCA components with the assistance of their degree of differentiation. Finally, our setting of 30% as the critical value is only a preliminary reference and not an accurate cutoff value. Therefore, more prospective multicenter studies on the components of cHCC-CCAs are needed to validate and expand our findings.

Conclusion

In conclusion, cHCC-CCAs with a CCA component ≥ 30% had significantly poorer RFS and OS prognoses than iCCAs. Therefore, we suggest that the postoperative treatment of cHCC-CCAs with a CCA component ≥ 30% can be based on the treatment strategy for iCCAs.

Funding

Disclosure

All authors report no conflicts of interest in this work. All participants are informed about the purpose of the study, in accordance with the Declaration of Helsinki.

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