The Predictive Value of Staging Systems and Inflammation Scores for Patients with Combined Hepatocellular Cholangiocarcinoma After Surgical Resection: a Retrospective Study

Chaobin He, MD¹ · Yize Mao, MD¹ · Jun Wang, MD¹ · Yunda Song, MD¹ · Xin Huang, MD¹ · Xiaojun Lin, MD¹ · Shengping Li, MD, PhD¹

Received: 20 November 2017 / Accepted: 21 March 2018 / Published online: 17 April 2018

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Abstract

Background Combined hepatocellular cholangiocarcinoma (cHCC-CC) is a rare form of primary liver tumor. A specific staging system for predicting survival in patients with cHCC-CC is not available. The aim of the present study was to evaluate the ability of staging systems and inflammation-based scores to predict overall survival (OS) and progression-free survival (PFS) of patients with cHCC-CC after surgical resection.

Methods The data from 99 patients with cHCC-CC after surgical resection from June 2000 and January 2017 were retrospectively collected. Patients were allocated into HCC (hepatocellular carcinoma)—dominant (IHD) group and ICC (intrahepatic cholangiocarcinoma)—dominant (IID) group based on radiological characteristics. Similarly, patients were also divided into HCC-dominant (PHD) group and ICC-dominant (PID) group based on pathological characteristics. Univariate and multivariate analyses were performed to identify variables associated with OS and PFS. The prognostic value of staging systems and inflammation-based scores were analyzed and compared using receiver operating characteristic (ROC) curves.

Results The 1-, 2-, and 3-year OS rates were 82.6, 66.3, and 59.6%, respectively. The 1-, 2-, and 3-year PFS rates were 52.2, 38.1, and 31.5%, respectively. Independent prognostic factors identified by multivariate analyses included HCC-TNM staging system and tumor diameter both for OS and PFS analyses. HCC-TNM staging system displayed higher area under ROC curve (AUC) values than the other staging systems or inflammation-based scores.

Conclusions HCC-TNM staging system was able to adequately predict prognosis of patients with cHCC-CC after surgical resection, especially for patients with HCC-dominant characteristics in clinical practice.

Keywords Combined hepatocellular cholangiocarcinoma · Staging system · Predict · Prognosis

Introduction

Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC), which contains elements of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) within the same tumor,¹ is a rare subtype that constitutes

0.4–14.2% of primary liver cancer cases.² Surgical resection provides the best chance for long-term survival with a 5-year overall survival (OS) rate of 23.1–54.1%³ and 5-year progression-free survival (PFS) rate of 10.7%.⁴ Although cHCC-CC is similar to HCC or CC in some clinical factors,² the biological behavior and prognosis of cHCC-CC are completely different from those of HCC or ICC. Some prognostic factors, such as vascular invasion, lymph node metastasis, tumor size, tumor number, and carbohydrate antigen 19–9 (CA19-9), have been reported to be prognostic factors for cHCC-CC.^{5,6} However, due to the rarity of cHCC-CC, the predictors of survival for cHCC-CC have not been well investigated and the staging system for cHCC-CC is ambiguous.

Clinical staging is used to predict survival outcomes and determine the optimal therapeutic options for patients with

Chaobin He and Yize Mao contributed equally to this work.

✉ Shengping Li, MD, PhD
lishp@sysucc.org.cn

¹ Department of Hepatobiliary and Pancreatic Surgery, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-Sen University Cancer Center, Guangzhou 510060, Guangdong, People's Republic of China

cancer. Numerous staging systems, such as the Barcelona Clinic Liver Cancer (BCLC) staging score, Cancer of the Liver Italian Program (CLIP) score, and Okuda staging system, have been developed for HCC.^{7–10} Moreover, there are specific tumor-node-metastasis (TNM) staging systems for HCC (HCC-TNM) and ICC (ICC-TNM) according to the 2010 World Health Organization (WHO) classification,¹ while the staging system for cHCC-CC is undefined and controversial. The characteristics of patients with cHCC-CC might substantially differ from those of patients with HCC or ICC. Existing data provides limited information regarding whether the current staging systems are suitable candidates to accurately predict the prognosis of patients with cHCC-CC.

There is increasing interest in the role of inflammation in the development and progression of many malignancies by participating in the neoplastic process, proliferation, and migration.¹¹ Systemic inflammation is a complex process, and its response is assessed using inflammation indices. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and Glasgow prognostic score (GPS) are all useful inflammation scores for patients with cancers.^{12–15} In addition, according to Ke et al.,¹⁶ the prognostic nutritional index (PNI) is significantly associated with the prognosis of patients with HCC. However, which inflammation-based prognostic score is more suitable for predicting prognosis in cHCC-CC patients has not been fully elucidated.

Notably, cHCC-CC, which has mixed components, can be clinically diagnosed by imaging examination and pathologically diagnosed by histopathological examination. In addition, the proportion of HCC and ICC components can be assessed by both imaging and pathological examination. Previous studies have revealed that cHCC-CC can be divided into an HCC- or ICC-like pattern according to the imaging and pathological characteristics.^{17–20} Recent studies^{21,17} have shown that HCC- or ICC-like imaging or pathological patterns may be associated with the prognoses of patients with cHCC-CC; however, studies have not yet evaluated the prognostic power of the staging systems and inflammation-based prognostic scores in cHCC-CC patients with HCC- or ICC-like patterns.

In the present study, patients with cHCC-CC were divided into HCC-dominant and ICC-dominant groups based on both imaging and pathological characteristics. The prognostic value of the staging systems, including TNM, BCLC, CLIP, and the Okuda staging system, and inflammation-based prognostic scores, including the NLR, PLR, mGPS, and PNI, were evaluated and compared in all patients, patients of the HCC-dominant group and patients of the ICC-dominant group, to ascertain which prognostic score was a feasible prognostic indicator for patients with cHCC-CC after surgical resection.

Patients and Methods

Patients

Consecutive patients with pathologically confirmed cHCC-CC after surgical resection performed between June 2000 and January 2017 at the Department of Hepatobiliary and Pancreatic Surgery of Sun Yat-Sen University Cancer Center were enrolled in the present study. The following exclusion criteria were considered: (1) other treatments, including transarterial chemoembolization, radiofrequency treatment, and liver transplantation for patients with cHCC-CC prior to surgical resection; (2) inadequate renal function (serum creatinine and blood urea nitrogen levels higher than the upper limits of normal); (3) severe coagulopathy (prothrombin activity < 40% or platelet count < 40,000/mm³); (4) Child–Pugh C liver function or evidence of hepatocellular decompensation, including refractory ascites, esophageal or gastric variceal bleeding, and hepatic encephalopathy; (5) obstructive jaundice; (6) other concurrent primary tumors; (7) pathological confirmed subtype of cHCC-CC with stem cell features; or (8) lost to follow-up.

A total of 99 patients were included in the present study. For each patient, a computed tomography (CT) or magnetic resonance imaging (MRI) examination was reviewed by two independent radiologists with more than 10 years of experience. The imaging examination was performed using a previously reported procedure.¹⁷ Patients were allocated into imaging HCC-dominant (IHD) and imaging ICC-dominant (IID) groups based on their radiological characteristics. IHD tumors showed high attention in the arterial phase and declining attention in the portal and delayed phase,^{22,23} while IID tumors showed delayed enhancement in both the portal and delayed phases. The following characteristics were also present in IID tumors: rim enhancement capsular retraction and focal dilatation of the intrahepatic ducts around the tumor.^{24,25} Similarly, the pathological examination was reviewed by two professional pathologists separately. Patients were also divided into pathological HCC-dominant (PHD) and pathological ICC-dominant (PID) groups based on pathological performance and immunohistochemistry (IHC). The pathological features of HCC included trabecular growth pattern, bile production, and intercellular bile canaliculi, while classical gland formation or mucin production was considered to be features of ICC. Further IHC studies were conducted when there were difficulties of making pathological diagnoses. Tumor cells with Heppar1, GPC-3, CK8/18, CD10, and alpha-fetoprotein (AFP) positivity were classified to be HCC, while tumor cells with CK7, CK19, and carcinoembryonic antigen (CEA) positivity were considered to be ICC. In the present study, 50% was adopted as the practical and user-friendly cutoff value to divide patients into PHD group and PID group, which was similar with previous studies.^{17,25} The PHD or PID group

included patients for whom the proportion of HCC or ICC cells was over 50%, respectively.

Clinical Data Collection

All clinical and pathological data for diagnosis were retrieved from medical records archived at Sun Yat-Sen University Cancer Center. The following clinical and pathological data were collected and analyzed: age, gender, white blood cell (WBC) count, neutrophil count, lymphocyte count, hemoglobin (HGB), platelet (PLT) count, alanine transaminase (ALT), aspartate aminotransferase (AST), albumin (ALB), total bilirubin (TBIL), indirect bilirubin (IBIL), hepatitis B surface antigen (HBsAg), serum levels of AFP, CEA, carbohydrate antigen 19-9 (CA19-9), lymph node (LN) metastasis, microvascular invasion, nerve tract invasion, macrovascular invasion, satellite nodule, and tumor diameter. Macrovascular invasion was defined as the presence of a thrombus adjacent to the tumor in the portal system or the hepatic vein system with a vague boundary confirmed by at least two imaging modalities.²⁶ The inflammation-based prognostic scores were determined as described in Table 1. All the prognostic value of staging systems and inflammation-based prognostic scores were entered in the present study.

Follow-up

Patients were followed-up at least every 2 months during the first year and every 3 months thereafter. The AFP test, CEA test, CA19-9 test, liver ultrasonography, CT, and MRI were selectively performed as needed. OS was defined as the duration from the date of operation until death or the last follow-up. PFS was defined as the duration from the date of operation

until the date when tumor progression was diagnosed or the last follow-up. The last follow-up was completed on October 1, 2017. The median follow-up period was 537 days for the study cohort.

Statistical Analysis

SPSS version 22 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The optimal cutoff values for NLR and PLR were determined using time-dependent receiver operating characteristic (ROC) curve analysis, which was performed using the package “survivalROC” in R version 3.2.5 (The R Foundation for Statistical Computing, Vienna, Austria. <http://www.r-project.org>). The laboratory threshold was used as the cutoff value for other clinical data. Categorical variables were compared using the chi-square test and Fisher’s exact test. Continuous variables were compared using the two-tailed unpaired *t* test or Mann–Whitney U-test.

Survival times were estimated using the Kaplan–Meier method and compared using the log-rank test. Analyses for survival curves were performed using MedCalc software version 11.4.2.0 (MedCalc, Ostend, Belgium). Univariate analysis was performed to assess the significance of clinical and pathological characteristics. Multivariate analysis was performed using the Cox regression model for variables that were significantly associated with OS or PFS in the univariate analysis, and the corresponding 95% confidence intervals (CI) were calculated. Two-tailed *P* values less than 0.05 were considered statistically significant.

Analysis of the time-dependent ROC curves and comparisons were performed using R software with the “survivalROC” package and “survivalROC.C” package.

Results

Patient Characteristics

Over a 17-year period, between 2000 and 2017, 99 patients who were newly diagnosed with cHCC-CC and received surgical operation as the initial therapy in our hospital were included in the present study. The median age of all patients was 50 years (range 25–76 years). Most of the patients in the entire study cohort (73 patients, 73.7%) were men. All patients had a good reserve liver function with Child–Pugh A. Approximately, 80.8% of the enrolled patients were positive for HBsAg. Most of the patients were absent of LN metastasis and satellite nodules. The proportions of patients in the study cohort with microvascular invasion, perineural and lymphatic invasion, and macrovascular invasion were 74.7, 93.9, and 91.9%, respectively. The NLR and PLR scores were divided into two groups: <2.75 and ≥2.75, and <68.95 and ≥68.95, respectively. The baseline characteristics of patients are shown

Table 1 Inflammation-based prognostic scores

Scoring systems	Score
NLR	
Neutrophil count: lymphocyte count < 2.75	0
Neutrophil count: lymphocyte count ≥ 2.75	1
PLR	
Platelet count: lymphocyte count < 68.95	0
Platelet count: lymphocyte count ≥ 68.95	1
Modified Glasgow prognostic score (mGPS)	
CRP (≤ 10 mg/L) and ALB (≥ 35 g/L)	0
CRP (≤ 10 mg/L) and ALB (< 35 g/L)	0
CRP (> 10 mg/L) and ALB (≥ 35 g/L)	1
CRP (> 10 mg/L) and ALB (< 35 g/L)	2
PNI	
ALB (g/L) × total lymphocyte count × 10 ⁹ /L ≥ 45	0
ALB (g/L) × total lymphocyte count × 10 ⁹ /L < 45	1

WBC white blood cell counts, CRP C-reactive protein, ALB albumin

in Table 2. There were 72 (72.7%) patients in the IHD group and 27 (27.3%) patients in the IID group, whereas 61 (61.6%) patients were sorted into the PHD group and 38 (38.4%) patients were sorted into the PID group. The discrepancy between imaging and pathological examination was 35.4% (35/99).

OS Analysis

The median OS time was 1680 days, and the 1-, 2-, and 3-year OS rates were 82.6, 66.3, and 59.6%, respectively. The correlations between the staging systems and OS are shown in Fig. 1. A higher HCC-TNM stage ($P=0.008$, Fig. 1a) and BCLC stage ($P=0.048$, Fig. 1b) were associated with a reduced OS, while there were no significant differences of OS

stratified by ICC-TNM ($P=0.096$, Fig. 1c), CLIP scores ($P=0.375$, Fig. 1d), and Okuda staging ($P=0.943$, Fig. 1e). Furthermore, the elevated NLR ($P=0.014$, Fig. 1f) was associated with a reduced OS, while the differences of OS stratified by PLR ($P=0.149$, Fig. 1g), mGPS ($P=0.694$, Fig. 1h), and PNI ($P=0.214$, Fig. 1i) were not significant.

In univariate analysis, age, gender, WBC, neutrophil, lymphocyte, HGB, PLT, ALT, AST, ALB, TBIL, IBIL, AFP, CEA, CA19-9, satellite nodule, microvascular invasion, nerve tract invasion, PLR, mGPS, PNI, CLIP score, and Okuda staging were not related to OS ($P>0.05$). However, tumor diameter, LN metastasis, macrovascular invasion, NLR, and the HCC-TNM, ICC, and BCLC staging systems were significantly associated with OS (Table 3). These seven risk factors

Table 2 Clinical and radiological characteristics on the study cohort

Characteristics		N	Median (range)
Age (years)	< 60/≥ 60	80/19	50 (25–76)
Gender	Male/female	73/26	–
WBC (× 10 ⁹ /L)	< 10/≥ 10	87/12	6.9 (3.57–14.6)
Neutrophil count (× 10 ⁹ /L)	< 7/≥ 7	90/9	3.9 (1.6–12.4)
Lymphocyte count (× 10 ⁹ /L)	< 4/≥ 4	98/1	1.7 (0.6–4.2)
HGB (g/L)	< 100/≥ 100	0/99	143 (105–186)
PLT (× 10 ⁹ /L)	< 300/≥ 300	84/15	196 (59–462)
ALT (U/L)	< 40/≥ 40	65/34	30 (8.1–311)
AST (U/L)	< 45/≥ 45	78/21	30 (13.5–236.1)
ALB (g/L)	< 35/≥ 35	5/94	42.7 (24.53–51.4)
TBIL (mmol/L)	< 20.5/≥ 20.5	89/10	12.6 (5.8–29.3)
IBIL (mmol/L)	< 15/≥ 15	92/7	8.5 (3.4–23.4)
HbsAg	Absent/present	19/80	–
AFP (ng/mL)	< 25/≥ 25	44/55	39.7 (1.52–121,000)
CA19-9 (IU/mL)	< 35/≥ 35	58/41	25.85 (0.1–12,776)
Tumor diameter (cm)	< 5/≥ 5	41/58	5.75 (1.5–18)
LN metastasis	Absent/present	87/12	–
Satellite nodule	Absent/present	66/33	–
Microvascular invasion	Absent/present	74/25	–
Nerve tract invasion	Absent/present	93/6	–
Macrovascular invasion	Absent/present	91/8	–
NLR	< 2.75/≥ 2.75	68/31	–
PLR	< 68.95/≥ 68.95	11/88	–
mGPS	0/1/2	84/12/3	–
PNI	1/2	10/89	–
HCC-TNM	I/II/IIIa/IIIb/IIIc/IV	43/22/13/6/5/10	–
ICC-TNM	I/II/III/IV	40/41/7/11	–
BCLC	A/B/C	61/28/10	–
CLIP	0/1/2/3/4	45/34/12/6/2	–
Okuda	1/2/3	2/86/11	–

WBC white blood cell count, HGB hemoglobin; PLT platelets, ALT alanine aminotransferase, AST aspartate aminotransferase, ALB albumin, TBIL total serum bilirubin, IBIL indirect serum bilirubin, AFP alpha-fetoprotein, CA19-9 carbohydrate antigen 19-9, NLR neutrophil-lymphocyte ratio, PLR platelet-lymphocyte ratio, mGPS modified Glasgow prognostic score, PNI prognostic nutritional index, TNM tumor-node-metastasis, BCLC Barcelona clinic liver cancer, CLIP Cancer of the Liver Italian Program

Fig. 1 Kaplan–Meier curves for OS in patients with cHCC-CC after surgical resection were stratified by the staging systems and inflammation-based scores. **a** HCC-TNM, $P=0.008$; **b** BCLC, $P=$

0.049; **c** ICC-TNM, $P=0.096$; **d** CLIP, $P=0.375$; **e** Okuda, $P=0.943$; **f** NLR, $P=0.014$; **g** PLR, $P=0.149$; **h** mGPS, $P=0.694$; and **i** PNI, $P=0.214$

were entered into multivariate Cox regression analysis. After the stepwise removal of variables, HCC-TNM (hazard ratio (HR) = 1.224, 95%CI = 1.022–1.464, $P=0.028$) and tumor diameter (HR = 1.122, 95%CI = 1.015–1.240, $P=0.024$) remained significant predictors for OS (Table 4).

PFS Analysis

The median PFS time was 292 days. The 1-, 2-, and 3-year PFS rates were 52.2, 38.1, and 31.5%, respectively. The correlations between the staging systems and PFS are shown in Fig. 2. Univariate analysis revealed that tumor diameter, LN metastasis, microvascular invasion, macrovascular invasion, and the HCC-TNM, ICC, BCLC, CLIP, and Okuda staging systems were all associated with PFS ($P<0.05$, Table 3). After the stepwise removal of variables, multivariate analysis revealed that HCC-TNM (HR = 1.247, 95%CI = 1.084–1.434, $P=0.002$) and tumor diameter (HR = 1.117, 95%CI = 1.057–1.203, $P=0.003$) remained significant predictors for PFS (Table 4).

Comparison between Staging Systems and Inflammation-Based Scores

The prognostic value of the staging systems and inflammation-based scores was compared by analyzing the area under ROC curves (AUC) at the 1-, 2-, and 3-year follow-up (Fig. 3). As shown in Table 5, the HCC-TNM staging system had a higher AUC value at the 1-, 2-, and 3-year follow-up for both the OS and PFS predictions compared with other staging systems or inflammation-based scores. In addition, an evaluation and comparison of the predictive power were also performed in subgroup analyses for all of the staging systems and inflammation-based scores. The results showed that the HCC-TNM staging system had good predictive power for OS and PFS with relatively high values of AUC in patients of all subgroups, including the IHD, IID, PHD, and PID groups. Moreover, a higher HCC-TNM stage was associated with a reduced OS and PFS in patients in the HCC-dominant groups ($P<0.050$, Fig. 4a–g). However, in OS and PFS analyses of patients of the ICC-dominant groups, significant differences of OS stratified by the HCC-TNM stage were only

Table 3 Univariate of OS and PFS in the study cohort

Characteristic		OS		PFS	
		HR (95% CI)	P	HR (95% CI)	P
Age	< 60/≥ 60	0.981 (0.954–1.009)	0.187	0.990 (0.969–1.011)	0.341
Gender	Male/female	1.083 (0.554–2.120)	0.815	1.363 (0.789–2.354)	0.267
WBC ($\times 10^9/L$)	< 10/≥ 10	1.339 (0.524–3.422)	0.542	1.624 (0.798–3.303)	0.181
Neutrophil ($\times 10^9/L$)	3.9 (1.6–12.4)	1.098 (0.948–1.272)	0.212	1.084 (0.966–1.216)	0.170
Lymphocyte ($\times 10^9/L$)	1.7 (0.6–4.2)	0.734 (0.451–1.197)	0.215	0.983 (0.710–1.361)	0.916
HGB (g/L)	143 (105–186)	0.999 (0.979–1.018)	0.883	1.009 (0.995–1.023)	0.217
PLT ($\times 10^9/L$)	< 300/≥ 300	1.416 (0.628–3.193)	0.402	1.589 (0.870–2.903)	0.132
ALT (U/L)	< 40/≥ 40	1.640 (0.896–3.000)	0.109	1.308 (0.817–2.095)	0.269
AST (U/L)	< 45/≥ 45	1.505 (0.756–2.995)	0.244	1.494 (0.885–2.524)	0.402
ALB (g/L)	< 35/≥ 35	0.637 (0.225–1.803)	0.396	0.653 (0.262–1.626)	0.360
TBIL (mmol/L)	< 20.5/≥ 20.5	1.758 (0.776–3.981)	0.176	1.097 (0.545–2.211)	0.795
IBIL (mmol/L)	< 15/≥ 15	1.198 (0.469–3.057)	0.705	0.573 (0.230–1.426)	0.231
AFP (ng/mL)	< 25/≥ 25	1.409 (0.762–2.004)	0.274	1.079 (0.681–1.711)	0.745
CA19-9 (U/mL)	< 35/≥ 35	1.251 (0.684–2.290)	0.467	1.350 (0.855–2.131)	0.198
Tumor diameter (cm)	< 5/≥ 5	1.149 (1.047–1.260)	0.003	2.019 (1.241–3.285)	0.005
Satellite nodule	Absent/present	1.415 (0.768–2.606)	0.266	1.315 (0.826–2.093)	0.248
LN metastasis	Absent/present	2.787 (1.271–6.113)	0.011	2.202 (1.149–4.222)	0.017
Microvascular invasion	Absent/present	1.319 (0.621–2.801)	0.472	2.117 (1.257–3.566)	0.005
Macrovascular invasion	Absent/present	2.963 (1.041–8.433)	0.042	3.179 (1.503–6.726)	0.002
Nerve tract invasion	Absent/present	1.248 (0.382–4.075)	0.714	0.858 (0.312–2.358)	0.766
NLR	< 2.75/≥ 2.75	2.098 (1.145–3.846)	0.017	1.295 (0.787–2.132)	0.309
PLR	< 68.95/≥ 68.95	2.729 (0.658–11.321)	0.167	2.086 (0.840–5.181)	0.113
mGPS	0/1/2	1.238 (0.709–2.161)	0.453	1.527 (0.984–2.368)	0.059
PNI	1/2	0.577 (0.240–1.389)	0.220	1.179 (0.538–2.582)	0.681
HCC-TNM	I/II/IIIa/IIIb/IIIc/IV	1.265 (1.075–1.487)	0.005	1.257 (1.107–1.427)	< 0.001
ICC-TNM	I/II/III/IV	1.386 (1.037–1.854)	0.028	1.298 (1.033–1.631)	0.025
BCLC	A/B/C	1.713 (1.101–2.665)	0.017	1.476 (1.057–2.062)	0.022
CLIP	0/1/2/3/4	0.307 (0.858–1.627)	0.307	1.317 (1.048–1.655)	0.018
Okuda	1/2/3	1.055 (0.360–3.095)	0.922	2.093 (1.056–4.149)	0.034

HR hazard ratio, CI confidence interval

observed in patients of the IID group ($P < 0.001$, Fig. 4b). There were no significant association between the HCC-TNM stage and PFS in patients of the IID group ($P = 0.210$, Fig. 4f) and PID group ($P = 0.281$, Fig. 4h).

Discussion

According to the WHO classification,¹ cHCC-CC is a mixed carcinoma that comprises two distinct tumor elements in which both HCC and CC intimately coexist in the same tumor rather than in the same liver. Patients with cHCC-CC are mostly diagnosed by pathology, especially after surgery. Due to the lack of unified pathological criteria, the pathological diagnosis may be a conundrum. Different pathological criteria may lead to inconsistent results for patients with respect to the

cHCC-CC criteria and outcomes.² Moreover, whether cHCC-CC stems from bile duct or hepatic cells has been the subject of dispute and remains to be clarified.²⁷ Although cHCC-CC has been considered to be a subtype of the carcinoma of the intrahepatic bile ducts according to the 7th AJCC manual,¹ the staging systems for patients with cHCC-CC remain controversial and should be clarified.

In the present study, the OS rates of patients with higher stages were significantly lower than those of patients with lower stages in the HCC-TNM staging system. However, there were no differences in the OS rates between the lower and higher stages according to the ICC-TNM staging system. This finding was consistent with that of Chu et al.⁶ Moreover, clear different prognostic strata for PFS analysis was observed for patients stratified by the HCC-TNM staging system. The comparison of the AUC indicated that the HCC-TNM staging

Table 4 Multivariate of OS and PFS in the study cohort

Characteristic		OS		PFS	
		HR (95% CI)	P	HR (95% CI)	P
Tumor diameter (cm)	< 5/≥ 5	1.122 (1.015–1.240)	0.024	1.117 (1.057–1.203)	0.003
LN metastasis	Absent/present	1.105 (0.714–1.246)	0.143	0.977 (0.319–2.992)	0.269
Microvascular invasion	Absent/present		NI	0.952 (0.812–1.199)	0.177
Macrovascular invasion	Absent/present	0.867 (0.755–1.040)	0.842	1.079 (1.003–3.246)	0.169
NLR	< 2.75/≥ 2.75	1.104 (0.812–1.846)	0.065		NI
HCC-TNM	I/II/IIIa/IIIb/IIIc/IV	1.224 (1.022–1.464)	0.028	1.247 (1.084–1.434)	0.002
ICC-TNM	I/II/III/IV	0.879 (0.557–1.386)	0.279	0.801 (0.549–1.170)	0.251
BCLC	A/B/C	0.902 (0.701–1.665)	0.152	0.907 (0.502–1.639)	0.348
CLIP	0/1/2/3/4		NI	1.008 (0.679–1.527)	0.130
Okuda	1/2/3		NI	1.031 (0.562–2.168)	0.105

NI not included

system consistently exhibited a higher AUC value at the 1-, 2-, and 3-year follow-ups compared with the ICC-TNM staging system or other staging systems and inflammation-based

scores. Additionally, the HCC-TNM staging system showed *relatively good* discriminatory performance for patients in both the HCC- and ICC-dominant groups stratified by

Fig. 2 Kaplan–Meier curves for PFS in patients with cHCC-CC after surgical resection were stratified by the staging systems and inflammation-based scores. **a** HCC-TNM, $P < 0.001$; **b** BCLC, $P =$

0.056; **c** ICC-TNM, $P = 0.008$; **d** CLIP, $P = 0.003$; **e** Okuda, $P = 0.024$; **f** NLR, $P = 0.307$; **g** PLR, $P = 0.105$; **h** mGPS, $P = 0.122$; and **i** PNI, $P = 0.680$

Fig. 3 Comparisons of the AUC values between the staging systems and the inflammation-based scores for OS analysis at 1- (a), 2- (b), and 3-year (c) and PFS analysis at 1- (d), 2- (e), and 3-year (f)

imaging and pathological examinations in the present study. Thus, cHCC-CC resembled HCC more than ICC with respect to the long-term clinical behavior.

Previous studies have reported that cHCC-CC is similar to HCC in terms of some clinicopathological features, such as mean age, gender ratio, hepatitis B virus (HBV)-positive rate, and AFP level.² In the present study, HBV infection was the main etiological factor. Most of the enrolled patients were positive for HBsAg. The HBV-positive rate of patients in the present study was similar to that of patients with HCC.¹⁰ It is likely that the high prevalence of HBV in the entire population contributed to the strikingly high rate of HBV-positive patients with cHCC-CC. In addition, imaging or pathological analysis showed that most patients were allocated into the IHD or PHD group in the present study, suggesting that there were more similarities shared by both cHCC-CC and HCC. This finding might partly explain why stratification by the HCC-TNM staging system rather than the ICC-TNM staging system resulted in a notable prognostic stratification of the OS and PFS rates.

Further, some studies conducted at Asian institutions have speculated that cHCC-CC represents a variant of ordinary HCC that exhibits cholangiocellular metaplasia, rather than a

true intermediate disease entity between HCC and ICC.²⁴ Additionally, LN metastasis was more frequently associated with ICC than HCC, suggesting a poor prognosis for these patients.^{28,29} By contrast, in the present study, an enlarged LN was present in only 29.3% of patients with cHCC-CC during surgery, and only 12.1% of patients has LN metastasis. This finding was similar to that of a previous study of patients with HCC.⁶ It is likely that diagnoses of LN metastasis based on a surgical examination rather than an imaging scan contributed to the lower rate of lymphatic metastasis. It was similar in terms of LN metastasis between HCC and cHCC-CC. Moreover, the effectiveness of lymphadenectomy in improving the prognosis of patients with cHCC-CC remains controversial. Similar to a previous study of HCC,³⁰ the present study failed to show that LN metastasis had a negative impact on OS or PFS. However, other tumor-related factors, such as tumor diameter, remained associated with the prognosis of cHCC-CC patients. It was shown that LN metastasis was not classified as an advanced stage disease and did not indicate a poor survival in patients with cHCC-CC.^{31,32} This finding may be the reason why the ICC-TNM staging did not show good monotonicity of the gradient for advanced stages of HBV-related cHCC-CC. Similarly, the present study showed

Table 5 Comparison of the AUC values between the inflammation-based scores and the staging systems

Patient			Score/staging system								
			HCC-TNM	ICC-TNM	CLIP	Okuda	BCLC	PNI	mGPS	NLR	PLR
All	OS	1 year	0.705	0.632	0.559	0.449	0.667	0.454	0.487	0.596	0.533
		2 years	0.707	0.636	0.534	0.472	0.649	0.491	0.483	0.600	0.558
		3 years	0.673	0.574	0.579	0.548	0.611	0.596	0.463	0.587	0.569
	PFS	1 year	0.676	0.669	0.620	0.573	0.608	0.537	0.557	0.483	0.525
		2 years	0.658	0.605	0.573	0.551	0.578	0.525	0.541	0.540	0.555
		3 years	0.642	0.609	0.588	0.562	0.570	0.513	0.522	0.535	0.576
IHD	OS	1 year	0.654	0.577	0.503	0.395	0.697	0.465	0.425	0.552	0.527
		2 years	0.650	0.571	0.485	0.402	0.640	0.516	0.493	0.578	0.549
		3 years	0.582	0.498	0.565	0.531	0.589	0.494	0.469	0.573	0.569
	PFS	1 year	0.708	0.656	0.659	0.576	0.620	0.547	0.553	0.495	0.532
		2 years	0.639	0.570	0.592	0.551	0.571	0.553	0.561	0.572	0.571
		3 years	0.635	0.557	0.637	0.568	0.580	0.536	0.547	0.534	0.598
IID	OS	1 year	0.798	0.725	0.687	0.575	0.679	0.425	0.614	0.612	0.547
		2 years	0.693	0.653	0.608	0.572	0.670	0.421	0.426	0.601	0.554
		3 years	0.693	0.653	0.608	0.572	0.670	0.421	0.426	0.601	0.554
	PFS	1 year	0.712	0.670	0.529	0.570	0.563	0.505	0.557	0.442	0.500
		2 years	0.717	0.657	0.530	0.556	0.551	0.435	0.495	0.474	0.500
		3 years	0.653	0.713	0.466	0.551	0.500	0.440	0.463	0.537	0.500
PHD	OS	1 year	0.707	0.652	0.521	0.460	0.688	0.485	0.470	0.585	0.568
		2 years	0.694	0.623	0.497	0.461	0.663	0.485	0.416	0.603	0.565
		3 years	0.689	0.602	0.577	0.577	0.652	0.494	0.399	0.565	0.570
	PFS	1 year	0.778	0.703	0.688	0.628	0.688	0.533	0.584	0.502	0.533
		2 years	0.684	0.601	0.603	0.591	0.624	0.517	0.548	0.626	0.550
		3 years	0.664	0.560	0.633	0.607	0.607	0.472	0.529	0.597	0.565
PID	OS	1 year	0.703	0.597	0.623	0.414	0.686	0.397	0.515	0.561	0.477
		2 years	0.700	0.677	0.608	0.447	0.679	0.478	0.579	0.666	0.527
		3 years	0.591	0.563	0.591	0.458	0.606	0.433	0.543	0.648	0.552
	PFS	1 year	0.614	0.623	0.491	0.471	0.465	0.538	0.516	0.460	0.511
		2 years	0.624	0.594	0.515	0.478	0.469	0.533	0.519	0.459	0.562
		3 years	0.601	0.650	0.514	0.480	0.479	0.563	0.499	0.468	0.589

IHD imaging HCC-dominant, *IID* imaging ICC-dominant *PHD* pathological HCC-dominant, *PID* pathological ICC-dominant

that HCC-TNM performed well in predicting the risk stratification of prognosis for patients with cHCC-CC.

Cancer-related inflammation responses affect the proliferation, angiogenesis, and metastasis of tumors, showing that cancer and inflammation are closely associated.³³ However, although the NLR score stratified patients into distinct risk categories for OS, NLR was not a significant predictor of survival in multivariate analysis in the present study. Moreover, the differences of OS and PFS in patients stratified by other inflammation-based scores were also not significant. The inflammation-based scores exhibited significant lower AUC values than those of the HCC-TNM staging system, indicating that inflammation-based scores may not be the best prognostic stratifications

for these patients. The inflammation process in cHCC-CC, in which the HCC and CC components exist together, may be more complicated than that of HCC. The underlying mechanisms remain to be elucidated and await further investigation.

Patients with cHCC-CC represent a heterogeneous cohort. It is difficult to construct a standard staging system that can precisely predict survival or prognosis. We analyzed and compared the prognostic values of several staging systems and inflammation-based scores for patients with cHCC-CC. The HCC-TNM staging system exhibited higher ROC values for predicting OS and PFS. Additionally, both OS and PFS could be predicted well by HCC-TNM staging system in patients of the imaging

Fig. 4 Kaplan–Meier curves stratified by HCC-TNM staging system for OS in patients of IHD group (**a** $P = 0.023$), IID group (**b** $P < 0.001$), PHD group (**c** $P = 0.015$) and PID group (**d** $P = 0.398$) and PFS in patients of

IHD group (**e** $P < 0.001$), IID group (**f** $P = 0.210$), PHD group (**g** $P < 0.001$), and PID group (**h** $P = 0.281$)

or pathological HCC- and ICC-dominant groups. The relatively high predictive power for OS and PFS prediction of the HCC-TNM stage may not be greatly influenced by the differences in the proportions of HCC or ICC components in the whole tumor. Indeed, the HCC-TNM stage may be a practical tool for predicting the prognosis of patients with cHCC-CC after surgical resection in clinical practice. However, although the AUC values of the HCC-TNM stage for predicting survival were relatively high in both HCC- and ICC-dominant groups, there was no significant association between the HCC-TNM stage and PFS in patients of the ICC-dominant groups. Perhaps, the HCC-TNM stage is not an ideal stratification for these patients. Some modifications of the HCC-TNM stage are needed when this indicator is applied to cHCC-CC patients with ICC-dominant characteristics.

There were several limitations in the present study. First, the present study was a retrospective study that relied on a single-institutional dataset. The geographic and institutional heterogeneity of patients may affect these results. Second, all patients included in the present study received surgical resection. The predictive value of staging systems or inflammation-based scores for patients with cHCC-CC receiving other treatments have not been evaluated and compared. Third, the AUC values of all of the staging systems and inflammation-based scores were not extraordinarily high for OS and PFS predictions. Moreover, the HCC-TNM stage was only suitable for the prediction of prognosis after operation, suggesting that the existing staging systems or inflammation-based scores are not the ideal stratification for patients with cHCC-CC, particularly patients with ICC-dominant characteristics. Novel preoperative variables or specific staging systems should be further

investigated to more accurately predict the survival of patients with cHCC-CC.

Conclusion

In conclusion, evaluation and comparison of the predictive power of staging systems and inflammation-based prognostic scores for OS and PFS were conducted in patients with cHCC-CC. The HCC-TNM staging system showed good predictive power for OS and PFS in patients with cHCC-CC, indicating that the HCC-TNM stage is a feasible prognostic indicator for patients with cHCC-CC after surgical resection, but should be validated and improved as a daily clinical practice in future studies.

Author Contribution Chaobin He, Yize Mao, and Shengping Li designed the research; Jun Wang, Yunda Song, Xin Huang, and Xiaojun Lin collected the data; Chaobin He, Yize Mao, and Shengping Li were responsible for data analysis; Chaobin He and Yize Mao contributed to the writing; Shengping Li was responsible for the supervision.

Funding This work was supported by grants from the National Natural Science Foundation of China (81171890; 81672390) and the Major National Scientific Research Projects of China (No. 2013CB910304).

Compliance with Ethical Standards

This study was approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center. All procedures performed in the present study involving human participants were in accordance with the ethical standards of institutional and/or national research committees and the 1964 Helsinki Declaration and its later amendments or similar ethical standards.

Conflict of Interest The authors declare that they have no conflicts of interest.

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