



The combination of preoperative D-dimer and CA19-9 predicts lymph node metastasis and survival in intrahepatic cholangiocarcinoma patients after curative resection

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Background: To investigate the predictive role of D-dimer and its combination of preoperative CA19-9 for lymph node metastasis (LNM) and prognosis in intrahepatic cholangiocarcinoma (ICC) patients who underwent curative-intent resection.

Methods: One hundred and seventy-three patients admitted to our hospital between April 2012 and December 2018 were included. The combination of preoperative D-dimer and CA19-9 (CPDC) was scored as 0 (decreased D-dimer levels with decreased CA19-9 levels), 2 (elevated D-dimer levels with elevated CA19-9 levels), or 1 (all other combinations). Multivariate logistic regression analysis was performed to identify independent factors. Cox proportional hazard regression was adopted for the multivariate survival analysis.

Results: The CPDC score was an independent predictor of LNM and overall survival (OS) in the multivariate analyses. For the prediction of LNM, the area under the curve (AUC) for the CPDC score was 0.722 (95% CI: 0.613–0.831, $P < 0.001$), and for the prediction of survival, the AUC for the CPDC score was 0.756 (95% CI: 0.658–0.854, $P < 0.001$). The predictive capacity of the CPDC score was higher than that of D-dimer or CA19-9. Kaplan-Meier curve analysis revealed that a CPDC =2 was significantly associated with a worse OS ($P < 0.001$, median OS: 8.00 versus 19.00 months versus not reached) and shorter progression-free survival (PFS) ($P < 0.001$, median PFS: 4.00 versus 11.00 versus 15.00 months) than a CPDC =1 or CPDC =0 in ICC patients. There were significant differences in the OS comparisons between any two groups. Decreased preoperative CPDC was associated with worse OS and PFS in all subgroups except in the HBsAg (+) group. In the cirrhosis, HBsAg (–) and tumour size ≥ 5 cm subgroups, there were significant differences in the OS and PFS comparisons between any two groups.

Conclusions: The preoperative CPDC score is a convenient and powerful prognostic biomarker to predict LNM and OS for ICC patients after curative resection. Especially for radiologically-negative metastatic lymph node in ICC patients, CPDC could be helpful to assess the extent of lymph node dissection and make follow-up plans.

Keywords: Intrahepatic cholangiocarcinoma (ICC); liver resection; D-dimer; CA19-9; prognosis; lymph node metastasis (LNM)

Submitted Sep 13, 2019. Accepted for publication Sep 26, 2019.

doi: 10.21037/atm.2020.01.72

View this article at: <http://dx.doi.org/10.21037/atm.2020.01.72>

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary malignant tumor in the liver, which is originated from hepatobiliary tract and have worse prognosis than hepatocellular carcinoma (1). Surgical resection, hepatic resection and lymph node dissection, is the only potentially curative treatment for ICC patients (2,3). However, a 5-year survival rate after resection merely increased 15–40% and up to 50–70% of patients still have tumour recurrence after radical resection (1,4). Different from hepatocellular carcinoma, lymph node metastasis (LNM) is common in ICC, which is reported to be one of the most important poor prognostic factors for ICC patients following curative resection (5,6). The ability to preoperatively predict lymph node status would aid clinical decisions regarding therapeutic strategies for ICC patients. Therefore, useful preoperative biomarkers for prediction of LNM and to predict the prognosis of ICC patients after resection are urgently needed.

D-dimer is an important marker in clinic for thromboembolism, such as deep venous thromboembolism (DVT), and recently it has been found to be associated with progression and recurrence of several malignant diseases including colorectal liver metastasis (7-9). However, no studies have investigated the relationship between serum D-dimer levels and LNM and the prognosis of ICC. Carbohydrate antigen 19-9 (CA19-9) is frequently used as a tumour biomarker for detection and prediction of adenocarcinomas, while it was also reported as an independent prognostic factor of ICC (10,11). Therefore, we established a new parameter, the combination of preoperative D-dimer and CA19-9 (CPDC), and hypothesized that CPDC might have better prediction value for LNM and prognosis in ICC patients after curative liver resection, which might be helpful to make surgical strategies and follow-up plans.

Methods

Patients

Clinical and pathological data were collected retrospectively from 173 patients admitted to our hospital between April

2012 and December 2018. The eligibility criteria were as follows: (I) complete resection of liver tumours with a gross-negative surgical margin and histopathological diagnosis of ICC; (II) no history of other previous malignancies. The exclusion criteria included: (I) the presence of clinical or pathological distant metastases; (II) perioperative mortality; (III) loss of follow-up data and (IV) patients with preoperatively acute and chronic infection [joint infection, chronic obstructive pulmonary disease (COPD) *et al.*], inflammation, HIV-infected and diseases of blood system associated with D-dimer levels (deep venous thrombosis, pulmonary embolism or disseminated intravascular coagulation *et al.*). Flow diagram for the selection of ICC patients included in the final analyses was showed in *Figure 1*. The Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences approved the study (ID: LC2018A15), and the necessity for informed consent was waived.

Hematologic examinations including the serum tumour markers carcinoembryonic antigen (CEA) and CA19-9, routine blood tests and liver function tests, were performed within 1 week before operation. An electrochemiluminescence immunoassay (ECLI) method was established to detect serum CA19-9 and CEA. An enzyme-linked fluorescent immunoassay was used to evaluate serum D-dimer concentrations. We mainly take the following measures to ensure the accuracy of the laboratory detection: (I) in clinical laboratory detection, the examiners carry on the check and maintenance to the detection instruments every day to ensure the normal operation of the detection instruments; (II) every sample is tested for at least three times and the results are averaged; (III) after clinical laboratory detection, the examiners shall repeatedly check the test results by two persons and record the test results in detail. In our hospital, the normal reference range of the serum D-dimer levels was 0 to 0.55 mg/L, and the normal reference range of the CA19-9 levels was between 0 and 27 U/mL. The combination of the preoperative D-dimer with CA19-9 levels (CPDC) was established to analyse the prognostic value of LNM and survival. The CPDC was scored as 0 (decreased D-dimer levels with decreased CA19-9 levels), 2 (elevated D-dimer levels with elevated CA19-9 levels), or 1 (all other combinations).

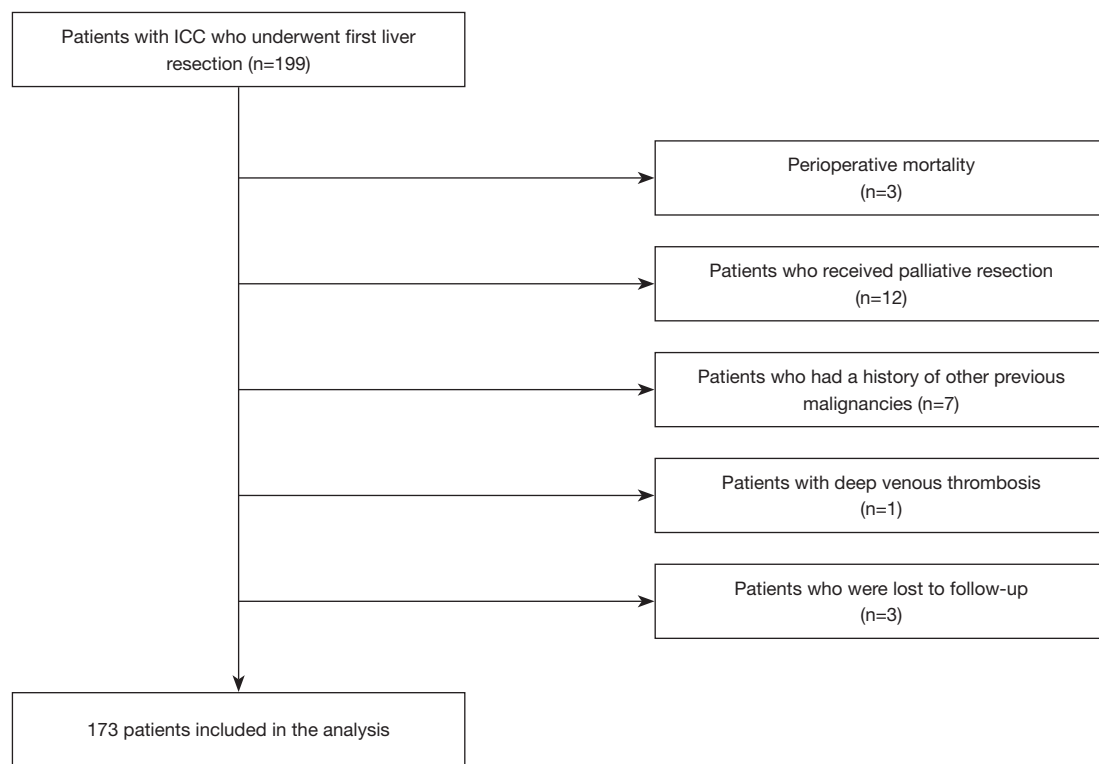


Figure 1 Flow diagram for the selection of ICC patients included in the final analyses. ICC, intrahepatic cholangiocarcinoma.

Treatment and follow-up

Decisions about the treatment strategy have been described previously (12). Treatment-related factors included preoperative chemotherapy and radiotherapy, extent of hepatic resection, lymph node dissection, duration of inpatient hospital stay, postoperative complications, and postoperative chemotherapy and radiotherapy. Chemotherapy, radiation therapy, transhepatic arterial chemotherapy and embolization (TACE), percutaneous ablation and repeated surgery were applied for recurrent patients. All postoperative complications were graded according to the Clavien-Dindo classification system (13). Progression-free survival (PFS) and overall survival (OS) were used to estimate the survival of ICC patients after resection. The first endpoint of survival was the date of recurrence and the second endpoint of survival was the date of death. PFS was calculated from the date of the operation to the date of recurrence or the last follow-up time. OS was defined as the length of time from the date of hepatic resection to the last follow-up or death. Patients underwent first postoperative CT or MRI examination and hematological examination 1 month after surgery. After this,

they were required to visit the clinics every 3 months during the first 2 postoperative years, every 6 months thereafter for 3 years, and yearly after 5 years. This study followed up the patients by telephone and searching for patient check data in hospital medical record system after each check. The deadline of follow-up was the date of death or the last follow-up date. The last follow-up date of this study was May 2019. During the follow-up, three patients were lost to follow-up.

Statistical analysis

The frequency distribution of categorical variables was compared with the chi-square test or Fisher's exact test when appropriate and that of continuous variables was compared with the Mann-Whitney U test. A receiver operating characteristic curve (ROC) analysis was used to select the best cut-off value and the highest Youden index was used to investigate the optimal cut-off value. According to the optimal cut-off point, the pre-operative D-dimer levels and CA19-9 levels were classified into the high and low subgroups. The area under the ROC curve was used to evaluate the prediction accuracy. Clinicopathological factors

with a $P < 0.1$ for significance in univariate analysis were included in multivariate analysis. A multivariate logistic regression analysis for LNM was performed to identify independent factors. The OS and PFS were compared using the Kaplan-Meier method; comparisons were performed with the log-rank test. Multivariate analyses of survival were conducted by cox regression models. Forward: likelihood ratio (LR) was used in multivariate analysis. $P < 0.05$ was considered statistically significant. SPSS, version 21 software (Armonk, NV, USA) was used to perform the statistical analyses.

Results

Clinicopathological characteristics

Among all 173 patients, 75 patients (43.35%) were female, and the median age [interquartile range (IQR)] was 58.00 (51.50–64.00) years. Thirty-six patients (20.81%) had positive serum hepatitis B surface antigen (HBsAg), and 63 patients (36.42%) had cirrhosis. Preoperative therapy was administered to 11 patients (6.36%), and postoperative therapy was administered to 69 patients (39.88%) (adjuvant chemotherapy: 34 cases; adjuvant radiotherapy: 23 cases; adjuvant chemotherapy combined with adjuvant radiotherapy: 9 cases; other: 3 cases). Seventy-three patients (42.20%) had lesions in left liver lobe. The median diameter of the largest lesion was 5.10 (IQR, 3.70–7.00) cm, and 53.18% of patients had a lesion larger than 5 cm. Nineteen-point-six-five percent of patients had multiple tumours and 56.07% of patients had tumours in poor differentiation. Twenty-three-point-one-two percent of the patients had LNM. Sixty-four patients (36.99%) underwent hemi-hepatectomy. In this study, 58.96% (102/173) of the patients experienced postoperative complications, including 37 major complications (37/102, 36.27%) and 65 minor complications (65/102, 63.73%). The clinicopathological characteristics of the patients are listed in *Table 1*.

Prognostic value of D-dimer levels and CA19-9 levels for survival

The median follow-up period was 35.00 months. A total of 112 patients (64.74%) experienced recurrence, and 79 patients (45.66%) died. The median OS was 25.00 months [95% confidence interval (CI): 9.96–40.04], and the median PFS was 10.00 months (95% CI: 7.21–12.79). The 1-, 3- and 5-year survival rates were 70.99%,

45.51% and 38.58%, respectively. The 1-, 3- and 5-year PFS rates were 41.45%, 29.46%, and 21.46%, respectively.

The median survival time (25.00 months) was considered an endpoint. The best cut-off value of the preoperative D-dimer levels and CA19-9 levels for predicting survival was determined by the ROC curves (*Figure 2*). The optimal cut-off level for D-dimer was 0.365 mg/L, and the area under the curve (AUC) was 0.704 (95% CI: 0.610–0.798, $P < 0.001$). This value was associated with a sensitivity of 0.686 and a specificity of 0.694. Ninety patients (52.02%) had a D-dimer < 0.365 mg/L. For CA19-9 levels, the optimal cut-off level was 871.65 U/mL, and the AUC was 0.661 (95% CI: 0.552–0.769, $P = 0.007$). This value was associated with a sensitivity of 0.358 and a specificity of 0.950. Twenty-six patients (15.03%) had a CA19-9 ≥ 871.65 U/mL.

Patients with a D-dimer level ≥ 0.365 mg/L had significantly worse OS and PFS than patients with a D-dimer level < 0.365 mg/L ($P < 0.001$, median OS: 14.00 months versus not reached; $P = 0.005$, median PFS: 7.00 versus 13.00 months) (*Figure 3*). Patients with a CA19-9 level ≥ 871.65 U/mL had a significantly worse OS and PFS than patients with a CA19-9 level < 871.65 U/mL ($P < 0.001$, median OS: 9.00 versus 58.00 months; $P < 0.001$, median PFS: 4.00 versus 13.00 months) (*Figure 4*).

The univariate analysis revealed D-dimer levels ≥ 0.365 mg/L ($P < 0.001$), CA19-9 ≥ 871.65 U/mL ($P < 0.001$), microvascular invasion ($P = 0.046$), T3–T4 stage ($P = 0.001$), LNM ($P < 0.001$), operation time ≥ 230 min ($P = 0.016$), blood loss ≥ 300 mL ($P = 0.025$), tumour location (central tumour) ($P = 0.032$), preoperative CEA ≥ 2.53 ng/mL ($P = 0.001$) and preoperative fibrinogen (FIB) ≥ 3.67 g/L ($P = 0.013$) were all associated with shorter OS (*Table 2*). These factors were included in the multivariate analysis. In the multivariate analysis, elevated preoperative D-dimer levels [hazard ratio (HR) = 5.009, 95% CI: 1.732–14.486, $P = 0.003$], T3–T4 stage (HR = 3.426, 95% CI: 1.385–8.472, $P = 0.008$) and microvascular invasion (HR = 3.232, 95% CI: 1.281–8.156, $P = 0.013$) remained independently associated with shorter OS (*Table 2*). In the univariate analysis of the PFS, D-dimer levels ≥ 0.365 mg/L ($P = 0.005$), CA19-9 ≥ 871.65 U/mL ($P < 0.001$), T3–T4 stage ($P = 0.015$), LNM ($P < 0.001$), multiple metastases ($P = 0.014$) and preoperative CEA ≥ 2.53 ng/mL ($P = 0.002$) significantly decreased PFS. These factors were included in the multivariate analysis. In the multivariate analysis, the elevated preoperative D-dimer levels and elevated preoperative CA19-9 levels were not independent factors associated with this reduction in PFS (*Table 3*).

Table 1 Patient and tumour characteristics

Item	All patients (n=173) (%)	P value		
		CA19-9 <871.65 U/mL vs. CA19-9 ≥871.65 U/mL	D-dimer <0.365 U/mL vs. D-dimer ≥0.365 U/mL	CPDC =0 vs. CPDC =1 vs. CPDC =2
Age ≥60 years	76 (43.93)	0.416	0.021	0.166
Female	75 (43.35)	0.066	0.217	0.110
BMI ≥24 kg/m ²	106 (61.27)	0.570	0.371	0.037
Comorbidity	75 (43.35)	0.741	0.763	0.510
ASA score 1–2	158 (91.33)	0.381	0.518	0.921
Preoperative therapy	11 (6.36)	0.112	0.652	0.249
Adjuvant therapy	69 (39.88)	0.243	0.737	0.162
Adjuvant chemotherapy	34 (19.65)	–	–	–
Adjuvant radiotherapy	23 (13.29)	–	–	–
Cirrhosis	63 (36.42)	0.022	0.011	0.004
HBsAg (+)	36 (20.81)	0.002	0.036	0.004
Microvascular invasion	47 (27.17)	0.485	0.749	0.605
T3–T4 stage	35 (20.23)	0.241	0.114	0.078
Complication	102 (58.96)	0.498	0.984	0.717
Lymph node metastasis	40 (23.12)	<0.001	0.153	<0.001
Tumor size ≥5 cm	92 (53.18)	0.738	0.017	0.077
Multiple tumors	34 (19.65)	0.956	0.301	0.954
Tumor location (left liver lobe)	73 (42.20)	0.053	0.766	0.497
Operation time ≥230 min	88 (50.87)	0.029	0.484	0.101
Blood loss ≥300 mL	84 (48.55)	0.002	0.018	0.007
Tumor location (central tumor)	86 (49.71)	0.898	0.321	0.497
Poorly differentiation	97 (56.07)	0.888	0.267	0.486
Hemi-hepatectomy	64 (36.99)	<0.001	0.001	0.001
TBIL ≥21 μmol/L	19 (10.98)	0.993	0.955	0.812
AST ≥40 U/L	17 (9.83)	0.329	0.346	0.450
ALT ≥50 U/L	17 (9.83)	0.794	0.049	0.488
GGT ≥60 U/L	67 (38.73)	0.022	0.084	0.053
D-dimer ≥0.365 mg/L	83 (47.98)	<0.001	–	–
Preoperative CA19-9 ≥871.65 U/mL	26 (15.03)	–	<0.001	–
Preoperative CEA ≥2.53 ng/mL	88 (50.87)	<0.001	0.103	0.005
Preoperative FIB ≥3.67 g/L	42 (24.28)	0.050	<0.001	0.002

CPDC, combination of preoperative D-dimer and CA19-9; BMI, body mass index; ASA, American Society of Anesthesiologists; HBsAg, serum hepatitis B surface antigen; TBIL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; FIB, fibrinogen.

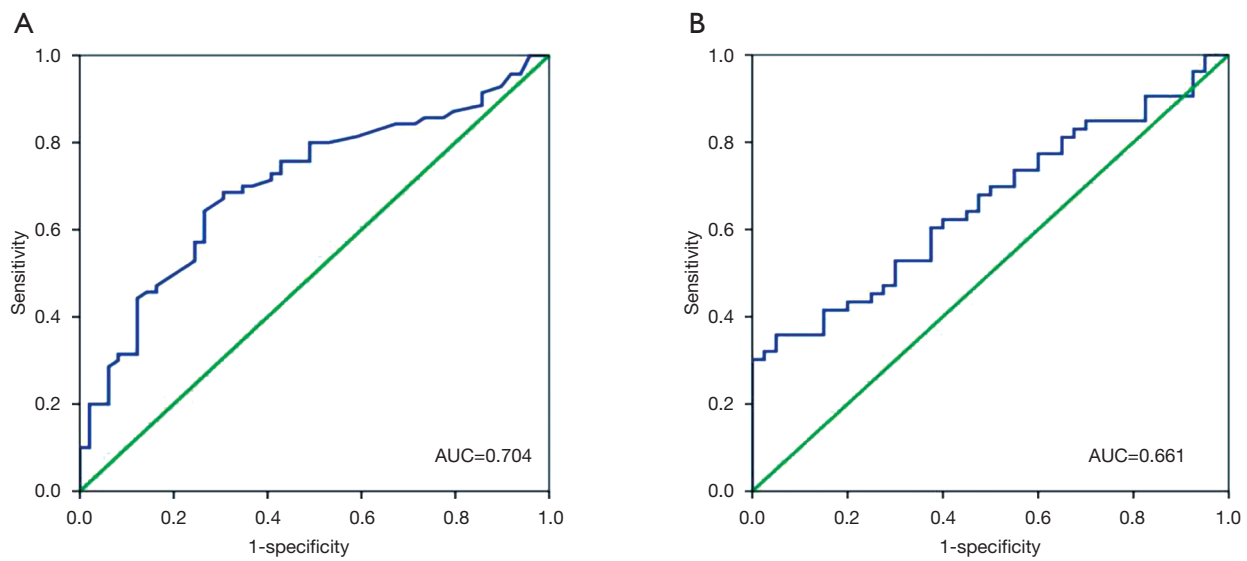


Figure 2 ROC analysis for survival status was performed to determine the optimal cut-off value of D-dimer and CA19-9 in ICC patients after hepatectomy. (A) The optimal cut-off level for D-dimer was 0.365 mg/L, and the AUC was 0.704 (95% CI: 0.610–0.798, $P < 0.001$); (B) for CA19-9 levels, the optimal cut-off level was 871.65 U/mL, and the AUC was 0.661 (95% CI: 0.552–0.769, $P = 0.007$). ROC, receiver operating characteristic curve; ICC, intrahepatic cholangiocarcinoma; AUC, area under the curve; CI, confidence interval.

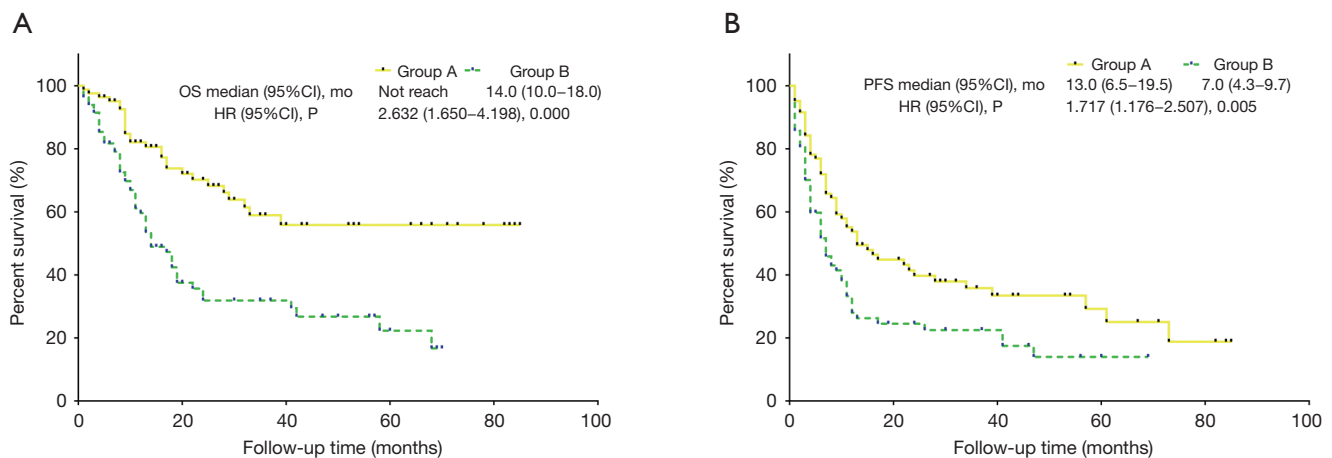


Figure 3 Survival analysis of D-dimer < 0.365 mg/L versus D-dimer ≥ 0.365 mg/L. (A) OS analysis of D-dimer < 0.365 mg/L versus D-dimer ≥ 0.365 mg/L; (B) PFS analysis of D-dimer < 0.365 mg/L versus D-dimer ≥ 0.365 mg/L. Group A: D-dimer < 0.365 mg/L; Group B: D-dimer ≥ 0.365 mg/L. OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

Prognostic value of CPDC for survival

The CPDC score had an AUC of 0.756 (95% CI: 0.658–0.854, $P < 0.001$) with a sensitivity of 0.778 and a specificity of 0.659. For predicting survival, the AUC for the CPDC score was stronger than the D-dimer levels ($P = 0.009$, AUC: 0.756 versus 0.707) and CA19-9 levels ($P = 0.010$, AUC: 0.756

versus 0.661). Because the CPDC score was based on the D-dimer levels and CA19-9 levels, the multivariate analysis of prognostic value of CPDC score included factors with a $P < 0.1$ in the univariate analysis exclude of the D-dimer levels and CA19-9 levels. In the multivariate analysis, the CPDC score was an independent prognostic factor for OS and was not an independent factor for PFS (Tables 2,3).

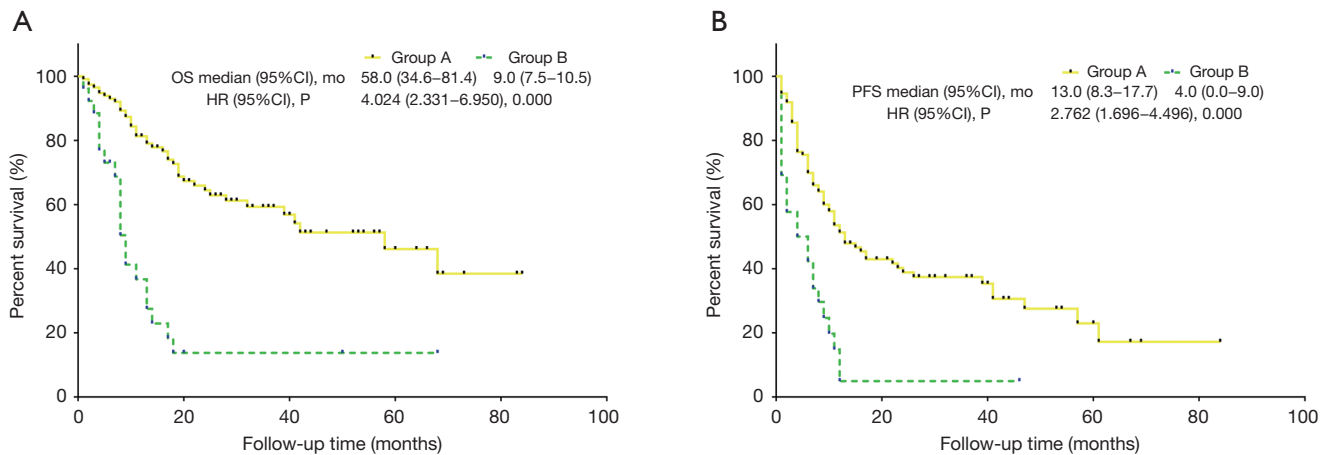


Figure 4 Survival analysis of CA19-9 <871.65 U/mL versus CA19-9 ≥871.65 U/mL. (A) OS analysis of CA19-9 <871.65 U/mL versus CA19-9 ≥871.65 U/mL; (B) PFS analysis of CA19-9 <871.65 U/mL versus CA19-9 ≥871.65 U/mL. Group A: CA19-9 <871.65 U/mL; Group B: CA19-9 ≥871.65 U/mL. OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

Table 2 Prognostic factors for OS for ICC patients after surgery

Factor	Univariate analysis		Multivariate analysis ^c	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥60 years	0.811 (0.513–1.282)	0.369	–	–
Female	0.689 (0.439–1.084)	0.107	–	–
BMI ≥24 kg/m ²	1.441 (0.908–2.286)	0.121	–	–
Comorbidity	0.781 (0.494–1.235)	0.291	–	–
ASA score 3–4	1.227 (0.590–2.552)	0.584	–	–
Preoperative therapy	0.611 (0.193–1.941)	0.404	–	–
Adjuvant therapy	0.659 (0.406–1.070)	0.092	–	–
Cirrhosis	0.961 (0.605–1.527)	0.866	–	–
HBsAg (+)	0.729 (0.408–1.301)	0.285	–	–
Microvascular invasion	2.050 (1.014–4.146)	0.046	3.232 (1.281–8.156)	0.013
T3–T4 stage	2.360 (1.438–3.872)	0.001	3.426 (1.385–8.472)	0.008
Complication	1.013 (0.642–1.599)	0.954	–	–
Lymph node metastasis		<0.001	–	–
Undissected lymph node	Reference			
Negative lymph node	0.717 (0.413–1.246)	0.238		
Positive lymph node	2.592 (1.475–4.556)	0.001		
Tumor size ≥5 cm	1.491 (0.950–2.339)	0.082	–	–
Multiple metastases	1.633 (0.958–2.785)	0.072	–	–

Table 2 (continued)

Table 2 (continued)

Factor	Univariate analysis		Multivariate analysis ^c	
	HR (95% CI)	P value	HR (95% CI)	P value
Tumor location		0.796	–	–
Left liver lobe	Reference			
Right liver lobe	1.118 (0.703–1.778)	0.638		
Other	1.311 (0.545–3.154)	0.546		
Operation time \geq 230 min ^a	1.738 (1.110–2.722)	0.016	–	–
Blood loss \geq 300 mL ^a	1.710 (1.069–2.736)	0.025	–	–
Tumor location			–	–
Central tumor	Reference	–		
Edged tumor	1.638 (1.042–2.573)	0.032		
Poorly differentiation	1.542 (0.961–2.474)	0.073	–	–
Hemi-hepatectomy	1.109 (0.698–1.761)	0.661	–	–
TBIL \geq 21 μ mol/L	0.878 (0.422–1.824)	0.726	–	–
AST \geq 40 U/L	1.647 (0.848–3.200)	0.141	–	–
ALT \geq 50 U/L	1.604 (0.825–3.120)	0.164	–	–
GGT \geq 60 U/L	1.390 (0.889–2.174)	0.148	–	–
Preoperative CA19-9 \geq 871.65 U/mL ^a	4.024 (2.331–6.950)	<0.001	2.639 (0.983–7.088)	0.054
Preoperative D-dimer \geq 0.365 mg/L ^a	2.632 (1.650–4.198)	<0.001	5.009 (1.732–14.486)	0.003
Preoperative CEA \geq 2.53 ng/mL ^a	2.217 (1.382–3.557)	0.001	–	–
Preoperative FIB \geq 3.67 g/L ^a	1.857 (1.141–3.022)	0.013	–	–
The prognostic value on CPDC score ^b				
CPDC =0	Reference	<0.001	Reference	<0.001
CPDC =1	2.924 (1.559–5.482)	0.001	4.969 (1.711–14.436)	0.003
CPDC =2	6.579 (3.286–13.171)	<0.001	13.225 (4.124–42.414)	<0.001

^a, ROC curves were constructed to estimate the optimal cutoff value; ^b, because the CPDC score was based on the D-dimer levels and CA19-9 levels, the multivariate analysis of prognostic value of CPDC score included factors with a P<0.1 in univariate analysis exclude of the D-dimer levels and CA19-9 levels; ^c, clinicopathological factors with a P<0.1 in univariate analysis were included in multivariate analysis. Multivariable analysis was performed using Cox regression models. Forward: LR was used in multivariate analysis. OS, overall survival; ICC, intrahepatic cholangiocarcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; HBsAg, serum hepatitis B surface antigen; TBIL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; CEA, carcinoembryonic antigen; FIB, fibrinogen; CPDC, combination of preoperative D-dimer and CA19-9; ROC, receiver operating characteristic curve; LR, likelihood ratio.

Kaplan-Meier curve analysis showed that compared with a CPDC =1 or CPDC =0, CPDC =2 was significantly associated with worse OS (P<0.001, median OS: 8.00 versus 19.00 months versus not reached, respectively) and worse PFS (P<0.001, median PFS: 4.00 versus 11.00 versus

15.00 months, respectively) in patients (Figure 5). The differences between any two groups were significant for the OS comparisons (CPDC =0 versus CPDC =1, P<0.001; CPDC =0 versus CPDC =2, P<0.001; CPDC =1 versus CPDC =2, P=0.008).

Table 3 Prognostic factors for PFS for ICC patients after surgery

Factor	Univariate analysis		Multivariate analysis ^c	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥60 years	0.848 (0.579–1.240)	0.395	–	–
Female	0.841 (0.576–1.227)	0.365	–	–
BMI ≥24 kg/m ²	1.057 (0.722–1.548)	0.775	–	–
Comorbidity	0.819 (0.559–1.200)	0.306	–	–
ASA score 3–4	1.347 (0.701–2.587)	0.371	–	–
Preoperative therapy	0.989 (0.666–1.469)	0.956	–	–
Adjuvant therapy	1.203 (0.585–2.473)	0.616	–	–
Cirrhosis	1.170 (0.794–1.725)	0.427	–	–
HBsAg (+)	1.188 (0.764–1.848)	0.444	–	–
Microvascular invasion	1.441 (0.851–2.439)	0.174	–	–
T3–T4 stage	1.717 (1.111–2.652)	0.015	–	–
Complication	1.004 (0.680–1.481)	0.985	–	–
Lymph node metastasis		<0.001		0.006
Undissected lymph node	Reference		Reference	
Negative lymph node	1.168 (0.725–1.883)	0.523	1.521 (0.786–2.945)	0.213
Positive lymph node	2.821 (1.668–4.771)	<0.001	2.945 (1.426–6.084)	0.004
Tumor size ≥5 cm	1.308 (0.898–1.905)	0.162	–	–
Multiple metastases	1.757 (1.120–2.757)	0.014	2.177 (1.266–3.744)	0.005
Poorly differentiation	1.409 (0.949–2.091)	0.089	1.657 (1.039–2.643)	0.034
Hemi-hepatectomy	1.245 (0.850–1.824)	0.260	–	–
Tumor location			–	–
Left liver lobe	Reference	–		
Right liver lobe	0.876 (0.645–1.188)	0.394		
Other	0.879 (0.653–1.184)	0.397		
Operation time ≥230 min ^a	1.420 (0.973–2.071)	0.069	–	–
Blood loss ≥300 mL	1.759 (1.186–2.608)	0.005	1.842 (1.145–2.962)	0.012
Tumor location			–	–
Central tumor	Reference	–		
Edged tumor	1.338 (0.920–1.946)	0.127		
TBIL ≥21 μmol/L	0.901 (0.483–1.682)	0.744	–	–
AST ≥40 U/L	1.571 (0.879–2.808)	0.127	–	–
ALT ≥50U/L	1.952 (1.085–3.510)	0.026	–	–
GGT ≥60 U/L	1.246 (0.850–1.825)	0.260	–	–
Preoperative CA19-9 ≥871.65 U/mL ^a	2.762 (1.696–4.496)	<0.001	–	–

Table 3 (continued)

Table 3 (continued)

Factor	Univariate analysis		Multivariate analysis ^c	
	HR (95% CI)	P value	HR (95% CI)	P value
Preoperative D-dimer ≥ 0.365 mg/L ^a	1.717 (1.176–2.507)	0.005	–	–
Preoperative CEA ≥ 2.53 ng/mL ^a	1.876 (1.271–2.770)	0.002	–	–
Preoperative FIB ≥ 3.67 g/L ^a	2.069 (1.361–3.146)	0.001	–	–
The prognostic value on CPDC score ^b		<0.001	–	–
CPDC =0	Reference			
CPDC =1	1.348 (0.843–2.154)	0.213		
CPDC =2	3.117 (1.808–5.374)	<0.001		

^a, ROC curves were constructed to estimate the optimal cutoff value; ^b, because the CPDC score was based on the D-dimer levels and CA19-9 levels, the multivariate analysis of prognostic value of CPDC score included factors with a P<0.1 in univariate analysis exclude of the D-dimer levels and CA19-9 levels; ^c, clinicopathological factors with a P<0.1 in univariate analysis were included in multivariate analysis. Multivariable analysis was performed using Cox regression models. Forward: LR was used in multivariate analysis. PFS, progression-free survival; ICC, intrahepatic cholangiocarcinoma; OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; HBsAg, serum hepatitis B surface antigen; TBIL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; CEA, carcinoembryonic antigen; FIB, fibrinogen; CPDC, combination of preoperative D-dimer and CA19-9; BMI, body mass index; LR, likelihood ratio.

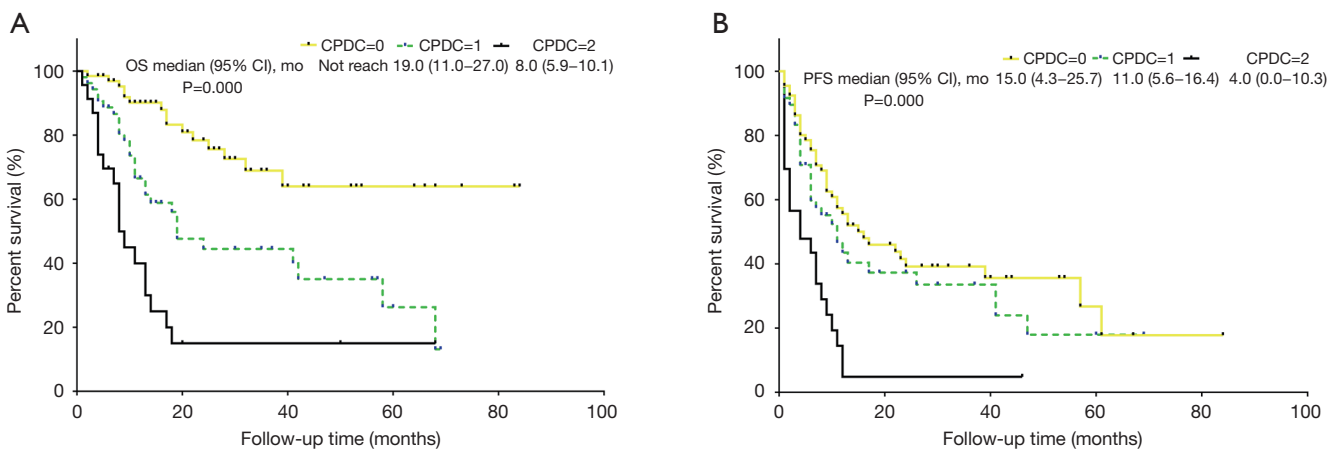


Figure 5 Survival analysis of CPDC =0 versus CPDC =1 versus CPDC =2. (A) OS analysis of CPDC =0 versus CPDC =1 versus CPDC =2; (B) PFS analysis of CPDC =0 versus CPDC =1 versus CPDC =2. OS, overall survival; PFS, progression-free survival; CI, confidence interval; CPDC, combination of preoperative D-dimer and CA19-9.

Prognostic value of CPDC in various subgroups of ICC

Prognostic significance of preoperative CPDC was evaluated in various subgroups of ICC patients then (Table 4). As seen in the Table 4, the predictive value of increased preoperative CPDC for a poorer OS or PFS in almost all subgroups except the HBsAg (+) group, aspartate aminotransferase (AST) ≥ 40 U/L group and alanine

aminotransferase (ALT) ≥ 50 U/L group.

Predictors for LNM

ROC curves were generated to illustrate the ability of preoperative D-dimer and CA19-9 levels to predict LNM. For D-dimer, the optimal cut-off level was 0.575 mg/L, and the AUC was 0.620 (95% CI: 0.509–0.730, P=0.034) with

Table 4 Prognostic values of CPDC in various subgroups of ICC

Item	P value	
	OS	PFS
Age, years		
≥60	<0.001	0.002
<60	<0.001	0.015
Gender		
Male	<0.001	0.010
Female	<0.001	0.003
BMI, kg/m ²		
≥24	<0.001	0.003
<24	<0.001	0.027
Cirrhosis		
Yes	<0.001	0.029
No	<0.001	<0.001
HBsAg		
(+)	0.655	0.827
(-)	<0.001	<0.001
Stage		
T1–T2	<0.001	0.029
T3–T4	0.017	0.005
Tumor size, cm		
≥5	<0.001	0.001
<5	0.002	0.008
Number of ICC		
Multiple tumors	<0.001	0.050
Solitary tumors	<0.001	0.001
Tumor location		
Left liver lobe	<0.001	0.013
None left liver lobe	0.003	0.001
Central tumor	<0.001	0.005
None central tumor	0.009	0.008
Histological grading		
Poorly differentiation	<0.001	0.001
Well differentiation	<0.001	0.096

Table 4 (continued)**Table 4** (continued)

Item	P value	
	OS	PFS
TBIL, μmol/L		
≥21	0.080	0.044
<21	<0.001	0.001
AST, U/L		
≥40	0.386	0.085
<40	<0.001	<0.001
ALT, U/L		
≥50	0.311	0.690
<50	<0.001	<0.001
GGT, U/L		
≥60	<0.001	0.001
<60	0.022	0.031
Preoperative CEA, ng/mL		
≥2.53	<0.001	0.001
<2.53	0.007	0.384
Preoperative FIB, g/L		
≥3.67	0.030	0.301
<3.67	<0.001	0.001

CPDC, combination of preoperative D-dimer and CA19-9; BMI, body mass index; ICC, intrahepatic cholangiocarcinoma; OS, overall survival; PFS, progression-free survival; BMI, body mass index; HBsAg, serum hepatitis B surface antigen; TBIL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; CEA, carcinoembryonic antigen; FIB, fibrinogen.

a sensitivity of 0.450 and a specificity of 0.789 (Figure 6). Eighty-two patients had a D-dimer level <0.575 mg/L. For CA19-9, the optimal cut-off level was 997.80 U/mL, and the AUC was 0.692 (95% CI: 0.576–0.808, P=0.001) with a sensitivity of 0.441 and a specificity of 0.924. Eighty-three patients had a CA19-9 level <997.80 U/mL.

The predictors for LNM were analysed. In the univariate analysis, multiple metastases (P=0.045), preoperative CA19-9 ≥997.80 (P<0.001), preoperative D-dimer ≥0.575 (P=0.007), preoperative CEA ≥2.53 ng/mL (P<0.001)

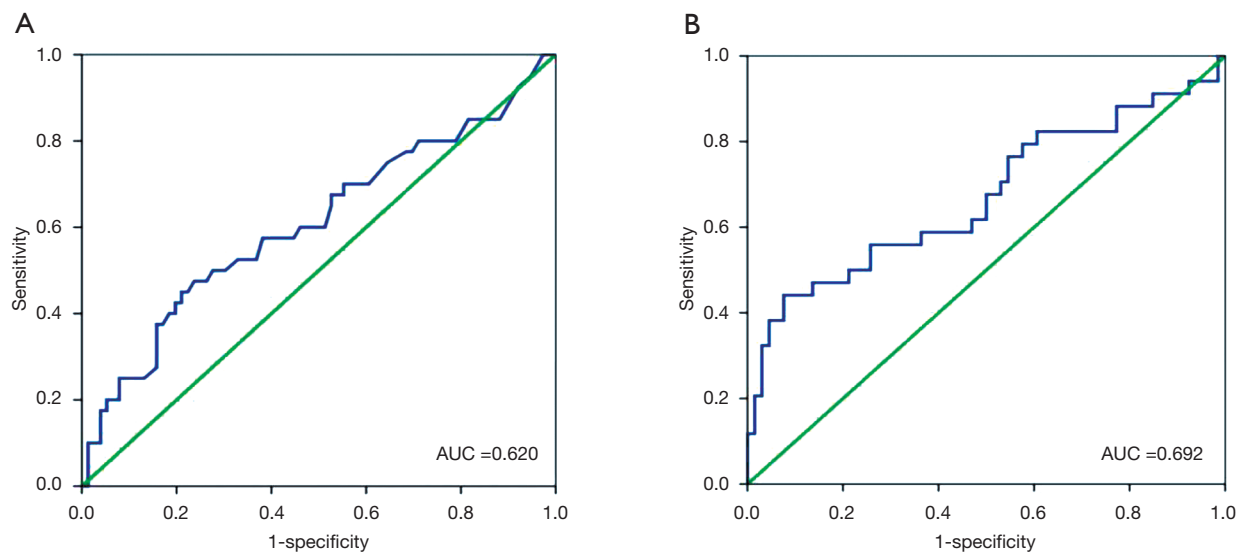


Figure 6 ROC analysis for lymph node metastasis status was performed to determine the optimal cut-off value of D-dimer and CA19-9 in ICC patients after hepatectomy. (A) For D-dimer, the optimal cut-off level was 0.575 mg/L, and the AUC was 0.620 (95% CI: 0.509–0.730, $P=0.034$); (B) for CA19-9, the optimal cut-off level was 997.80 U/mL, and the AUC was 0.692 (95% CI: 0.576–0.808, $P=0.001$). AUC, area under the curve; ICC, intrahepatic cholangiocarcinoma; CI, confidence interval.

and preoperative FIB ≥ 3.67 ($P=0.016$) were statistically significant with LNM. These statistically significant parameters in the univariate analysis were retained in the multivariate model. In the multivariate analysis, elevated preoperative CA19-9 levels [odds ratio (OR) =8.720, 95% CI: 2.439–31.174, $P=0.001$], multiple metastases (OR =6.159, 95% CI: 1.304–29.104, $P=0.022$) and elevated preoperative CEA levels (OR =3.144, 95% CI: 1.116–8.861, $P=0.030$) significantly predicted LNM (Table 5).

Because the CPDC score was based on the D-dimer levels and CA19-9 levels, the multivariate analysis of the predictive value of CPDC score for lymph node metastasis included factors with a $P<0.1$ in univariate analysis exclude of the D-dimer levels and CA19-9 levels. In the multivariate logistic regression analysis, the CPDC score independently predicted LNM (Table 5). The AUC for the CPDC score was 0.722 (95% CI: 0.613–0.831, $P<0.001$). This value was associated with a sensitivity of 0.657 and a specificity of 0.739.

Relationships among D-dimer, CA19-9, CPDC and clinicopathological characteristics

The clinicopathologic factors of patients with different D-dimer, CA19-9 and CPDC statuses are summarized in Table 1. Age ≥ 60 years ($P=0.021$), cirrhosis ($P=0.011$),

HBsAg (+) ($P=0.036$) and tumour size ≥ 5 cm ($P=0.017$) were observed in the elevated D-dimer level group. Elevated CA19-9 levels were significantly associated with cirrhosis ($P=0.022$) and HBsAg positivity ($P=0.002$). The increased CPDC was associated with body mass index (BMI) ≥ 24 kg/m² ($P=0.037$), cirrhosis ($P=0.004$) and HBsAg positivity ($P=0.004$).

Discussion

Among current researches about ICC, this study seems to be the first to describe the relationships between preoperative D-dimer levels, CPDC and survival and LNM in ICC patients. We found that increased preoperative D-dimer levels, CA19-9 levels and CPDC were associated with worse survival and LNM in ICC patients after hepatic resection, and CPDC score had stronger predictive ability than that of D-dimer or CA19-9 levels alone, indicating that CPDC could be used as a useful prognostic marker for ICC patients in clinics preoperatively.

This study revealed that a poor prognosis of ICC patients was associated with high D-dimer levels. Furthermore, elevated D-dimer levels were correlated with worse prognosis in lung cancer, ovarian cancer, colorectal liver metastases and renal cancer patients in several studies (7-9,14). These findings are consistent with the results of

Table 5 Prognostic factors for lymph node metastasis for ICC patients after Surgery

Factor	Univariate analysis	Multivariate analysis ^b	
	P value	OR (95% CI)	P value
Age ≥60 years	0.235	–	–
Female	0.914	–	–
BMI ≥24 kg/m ²	0.169	–	–
Comorbidity	0.418	–	–
ASA score 3–4	0.580	–	–
Cirrhosis	0.551	–	–
HBsAg (+)	0.223	–	–
Tumor size ≥5 cm	0.453	–	–
Multiple metastases	0.045	6.159 (1.304–29.104)	0.022
Tumor location			
Left liver lobe	0.372	–	–
Central tumor	0.624	–	–
TBIL ≥21 umol/L	0.930	–	–
AST ≥40 U/L	0.280	–	–
ALT ≥50 U/L	0.701	–	–
GGT ≥60 U/L	0.376	–	–
Preoperative CA19-9 ≥997.80 U/mL	<0.001	8.720 (2.439–31.174)	0.001
Preoperative D-dimer ≥0.575 mg/L	0.007	–	–
Preoperative CEA ≥2.53 ng/mL	<0.001	3.144 (1.116–8.861)	0.030
Preoperative FIB ≥3.67 g/L	0.016	–	–
The prognostic value on CPDC score ^a	<0.001		0.006
CPDC =0		Reference	
CPDC =1		2.942 (1.068–8.105)	0.037
CPDC =2		13.850 (2.337–82.095)	0.004

^a, because the CPDC score was based on the D-dimer levels and CA19-9 levels, the multivariate analysis of the predictive value of CPDC score for lymph node metastasis included factors with a P<0.1 in univariate analysis exclude of the D-dimer levels and CA19-9 levels. ^b, clinicopathological factors with a P<0.1 in univariate analysis were included in multivariate analysis. Multivariable analysis was performed using logistic regression analysis. Forward: LR was used in multivariate analysis. ICC, intrahepatic cholangiocarcinoma; OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; HBsAg, serum hepatitis B surface antigen; TBIL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; CEA, carcinoembryonic antigen; FIB, fibrinogen; CPDC, combination of preoperative D-dimer and CA19-9; LR, likelihood ratio.

the current study. The reasons of the association between elevated D-dimer levels and poor prognoses are as follows: malignant tumour cells can express a large amount of procoagulant molecules and promote the coagulation system and fibrinolysis (15,16). Serum D-dimer levels, a sign of abnormal fibrinolysis, increase with fibrin degradation.

D-dimer promotes proliferation and induces angiogenesis by modulating cellular signalling (17). Moreover, some researches have revealed that serum D-dimer levels are positively related to the presence of circulating tumour cells (CTCs) or micro-metastases, which are associated with poor survival (18,19). Our study also indicated that

increased serum CA19-9 levels were an independent prognostic factor for poor prognosis. This finding parallels those of previous studies indicating that serum CA19-9 is significantly correlated with inferior survival in ICC patients who underwent surgery (10,11). The preoperative serum CA19-9 level was identified as having a significant relationship with the CTC count in cholangiocarcinoma, and the CTC count was associated with a significantly shorter survival (20).

To increase the predictive value, we combined the preoperative D-dimer with CA19-9 to establish a new parameter, CPDC. Our results suggest that the predictive capacity of the CPDC score was stronger than any one parameter alone. Moreover, patients with a CPDC score =2 had a poorer OS and PFS than patients with a CPDC score =1 or CPDC score =0. Further, there were significant differences between any two groups in the OS comparisons. Particularly in the subgroup analysis, the predictive value of an increased preoperative CPDC for worsened OS and PFS existed in almost all subgroups. These results indicate that preoperative CPDC was an accurate marker to predict the survival of ICC patients after resection, especially in various subgroups of ICC patients whose prognoses are difficult to estimate.

LNM is an important prognostic factor for ICC patients following resection (5,6). The results of this study suggested that the preoperative level of D-dimer and CA19-9 have potential as predictors of LNM in ICC patients. Some studies have revealed that serum D-dimer levels are a potential marker for predicting distant metastasis in various cancer types (21,22). Our study first found a relationship between D-dimer levels and LNM in ICC patients. The underlying mechanism may be the following: Metastasis signifies the escape of tumour cells from the primary tumour site their entry into the peripheral blood or lymph system (tumours in the lymph system can enter peripheral blood through lymphatic circulation). During migration, micrometastatic tumour cells express tissue factors to activate coagulation and fibrinolysis (23,24). Serum D-dimer levels are widely used biomarkers for the activation of coagulation and fibrinolysis. In addition, elevated D-dimer levels can induce the growth and spread of tumour cells through many mechanisms (24-26). Several reports have indicated that elevated CA19-9 levels are associated with a high ratio of LNM (11,27), which suggests that high CA19-9 levels could signify the presence of metastatic tumour cells (11,20). Interestingly, the results of our study indicated that CPDC had a strong predictive value for LNM with high sensitivity and specificity and was an independent predictive factor for LNM. Early, accurate detection of LNM is

important for patient prognosis and treatment (either lymph node resection or the timing of chemotherapy and radiotherapy). Imaging techniques such as CT and MRI are commonly used for diagnosing LNM. By comparison, blood tests are relatively non-invasive, rapid, economical, and repeatable, and ionizing radiation is not used. Blood tests for D-dimer and CA19-9 could become common indicators to determine whether further detailed imaging examination is warranted. In addition, serum biomarkers are more suitable for long-term follow-up. In the future, we will investigate the predictive value of imaging techniques combined with this indicator for LNM.

The CPDC score is not only accurate but also clinically meaningful. Prior to resection, the predictive value of the CPDC score can help clinicians identify patients at high risk for LNM and a poor prognosis and guide decisions regarding individual treatment strategies according to the patient's CPDC score. ICC patients with a CPDC score =2 were more prone to LNM and a poor prognosis after liver resection, and these patients should be provided with closer surveillance and even targeted adjuvant therapy.

According to previous studies, elevated D-dimer levels were significantly associated with larger tumours, multiple metastases and elevated CEA levels in several malignancies (7,28). Elevated CA19-9 levels were demonstrated to be significantly correlated with a high Child-Pugh score, large tumour size, and high TNM stage for ICC patients (10). Notably, our study found that elevated D-dimer levels and elevated CA19-9 levels were correlated with cirrhosis, HBsAg positivity, and LNM in ICC patients.

It is worth noting that the results of our study showed that LNM was an independent prognostic factor of PFS but not for OS. However, some studies have shown that LNM is predictive for the PFS and OS of ICC patients (10,29). The reason may be that the samples in this study included both patients with and those without lymph node resection, which were divided into three categories: no lymph node resection, positive LNM and negative LNM. Whether positive LNM is an independent risk factor for prognosis under this classification is not very clear. The samples in other studies included only patients with lymph node resection, which were divided into two categories: positive LNM and negative LNM. The difference between the samples and the classification variables leads to differences in the results. In addition, multivariate analysis in this study showed that positive LNM was an independent prognostic factor in patients with lymph node resection, which was consistent with other studies (10,29). For ICC patients,

lymph node resection is recommended (30-32), which was always followed in this study. However, the diagnostic criteria of preoperative ICC depend on the imaging characteristics and tumour markers of the patients. In this study, some patients did not receive lymph node resection because the preoperative clinical features were not typical.

The present study does have some limitations. First, this was a single-centre retrospective study and the sample size was relatively small. Small sample size might affect the identified power. In addition, some biases exist, such as a lack of random assignment and patient selection bias. Second, there was no validation setting to validate the results because of the small sample size. In the future, we will further expand the sample size to construct a validation setting and verify our results. We look forward to conducting prospective cohort studies to improve the limitations in this study.

In conclusion, our study revealed that preoperative CPDC is a novel independent factor for poor prognosis and LNM in ICC patients. The measurement of CPDC is based on standard laboratory measurements of D-dimer and serum tumour marker CA19-9, which is in clinical routine. Therefore, CPDC is a convenient and meaningful prognostic biomarker for ICC prognosis, which has reference significance for operation strategies about lymph node dissection and early therapeutic intervention according to different clinicopathological characteristics.

Acknowledgments

Funding: This work was supported by the State Key Project on Infection Diseases of China (Grant No. 2017ZX10201021-007-003), the National Capital Health Research and Development of Special (No. 2018-1-4021), the Beijing Hope Run Special Fund of Cancer Foundation of China (No. LC2018A15) and the National Natural Science Foundation of China (No. 81672461).

Footnote

Conflicts of Interest: HZ serves as an unpaid Associate Editors-in-Chief of Annals of Translational Medicine from Jun 2019 to May 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The research was

in compliance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of the Cancer Hospital, Chinese Academy of Medical Sciences (ID: LC2018A15), and the necessity for informed consent was waived.

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Cite this article as: Chen Q, Zheng Y, Zhao H, Cai J, Wang L, Zhao J, Bi X, Li Z, Huang Z, Zhang Y, Zhou J, Wu J. The combination of preoperative D-dimer and CA19-9 predicts lymph node metastasis and survival in intrahepatic cholangiocarcinoma patients after curative resection. *Ann Transl Med* 2020;8(5):192. doi: 10.21037/atm.2020.01.72