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ORIGINAL ARTICLE

Clinical Value of Inflammation-Based Prognostic Scores to Predict the Resectability of Hyperbilirubinemia Patients with Potentially Resectable Hilar Cholangiocarcinoma

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Abstract

Background We aimed to examine whether inflammation-based prognostic scores could predict tumor resectability in a cohort of hilar cholangiocarcinoma patients with preoperative hyperbilirubinemia. We also sought to investigate the prognostic factors associated with overall survival in the subgroup of patients with an R0 resection.

Methods A total of 173 patients with potentially resectable hilar cholangiocarcinoma, as judged by radiological examinations, were included. The potential relationship of the Glasgow prognostic score (GPS), modified GPS, platelet lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), prognostic nutritional index (PNI), and prognostic index (PI) with tumor resectability were investigated using univariate and multivariate analysis.

Results Among the 173 patients, 134 had R0 resection margins. Univariate analysis identified that patients with PLR ≥ 150, NLR ≥ 3, PNI ≥ 45, GPS (0.1/2), modified GPS (0.1/2), preoperative CA 125 > 35 U/mL, and a tumor size ≥ 3 cm were more likely to have unresectable tumors. Multivariate analysis indicated that tumor size ≥ 3 cm (OR = 2.422, 95% CI: 1.053–5.573; $P = 0.037$), PLR ≥ 150 (OR = 3.324, 95% CI: 1.143–9.667; $P = 0.027$), preoperative CA 125 > 35 U/mL (OR = 3.184, 95% CI: 1.316–7.704; $P = 0.010$), and GPS (0.1/2) (OR = 2.440, 95% CI: 1.450–4.107; $P = 0.001$) were independent factors associated with tumor resectability. In selected patients with an R0 resection in this cohort, nodal status ($P = 0.010$) and tumor differentiation ($P = 0.025$) were predictive of poor survival outcome.

Conclusion Patients with higher GPS, CA 125, and PLR levels, and a larger tumor size, tend to have unresectable tumors even if they were judged as potentially resectable using preoperative radiological examinations.

Keywords Hilar cholangiocarcinoma · Inflammation-based prognostic score · Tumor resectability · Prognosis

Introduction

Hilar cholangiocarcinoma (HCCA) is a devastating disease, accounting for 60% of all bile duct cancers.[1–3] Removing the entire tumor without any additional residual disease is mandatory to guarantee a good long-term survival outcome.[4,5] Unfortunately, HCCA has the characteristics of early lymph node and caudate lobe metastasis and early vascular and perineural involvement.[6,7] Only 25% of patients are judged to have potentially resectable tumors preoperatively and have the opportunity of radical surgery.[8,9] In fact, the predictive value of preoperative computed tomography or magnetic resonance imaging to judge unresectability is approaching 100%;[10] however, for potentially resectable tumors, the reported predictive value of preoperative radiological examinations for tumor resectability is only 71.4%, which is not satisfactory.[11] The failure of precise preoperative assessment of tumor resectability can ultimately lead to needless surgical risk, delayed systematic palliative care, and increased financial burden.[12]

Our previous study identified carbohydrate antigen (CA) 19-9 as a good supplementary marker for the preoperative imaging in patients with normal bilirubin levels.[13] The combination of CA 19-9 levels and preoperative imaging could further help surgeons estimate whether a potentially resectable tumor is really resectable or unresectable.[13] However, as

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HCCA is characterized as obstructive jaundice, patients with hyperbilirubinemia may have even higher CA 19-9 levels.[14,15] Hence, the actual CA19-9 levels to predict survival or tumor resectability should be measured after complete biliary decompression; however, most resections tend to be performed before bilirubin level normalization.[16,17] Thus, for patients with HCCA with hyperbilirubinemia, potential biomarkers to predict tumor resectability should be identified to help surgeons devise proper surgical plans.

Increased inflammatory cytokines, such as tumor necrosis factor and interleukin-6, have been observed in both animal models and patients with obstructive jaundice.[18,19] Jaundiced individuals may manifest an anti-inflammatory immune response that possibly regulates the body's defense mechanism. Meanwhile, a systemic inflammatory response has also been identified as a valuable predictor for various cancers, including HCCA.[20–24] Subsequently, measurement of the systemic inflammatory response was refined using a selection of inflammation-based prognostic scores. However, the utility of inflammation-based prognostic scores on resectability for jaundiced patients with HCCA has not been well characterized. Thus, the current study aimed to examine whether inflammation-based prognostic scores [such as the Glasgow prognostic score (GPS), the modified GPS, the platelet lymphocyte ratio (PLR), the neutrophil lymphocyte ratio (NLR), the prognostic nutritional index (PNI), and the prognostic index (PI)] could predict tumor resectability in a cohort of jaundiced patients with HCCA judged as having potentially resectable disease using preoperative radiological examinations. We also sought to investigate prognostic factors associated with overall survival in a subgroup of patients with an R0 resection.

Materials and Methods

A total of 173 patients with potentially resectable HCCA, as assessed radiographically, at West China Hospital of Sichuan University from 2009 to 2014 were included. Patients with intrahepatic cholangiocarcinoma involving the hepatic portal, distal cholangiocarcinoma, ampullary carcinomas, and gallbladder cancer were excluded. Histologically, adenocarcinoma was identified in all selected patients. The study was approved by the Institutional Review Board of West China Hospital.

Before surgery, laboratory tests, ultrasonography, computed tomography, and magnetic resonance imaging were conducted regularly to help assess the general physical conditions of the patients and the tumor classification. The blood tests were usually performed 1–3 days before the surgery. All patients in this cohort had preoperative hyperbilirubinemia, with a mean bilirubin level of 14.01 ± 5.56 mg/dl. The patients were then operated on with preoperative biliary drainage, which was consistent with previous studies.[25] After drainage, the mean bilirubin level was 7.05 ± 1.52 mg/dl. Surgical exploration was conducted in all patients. Patients with negative margins (an R0 resection) were deemed as resectable, while those with R1 resection, R2 resection, or palliative surgery were classified as unresectable. The inflammation-based prognostic scores GPS, mGPS, NLR, PLR, PI, and PNI were analyzed. The definition of the scoring systems was in accordance with previous studies (Table 1).[23,24,26]

All patients in this cohort were rigorously monitored and followed up in the outpatient department. Patients were assessed every 1–2 months with the basic measurement of tumor markers, liver functions, and ultrasonography in the first year after surgical exploration, and then at 3–6 months annually thereafter. For those who underwent curative surgery and had R0 margins, if recurrence was suspected, computed tomography or magnetic resonance imaging was further conducted.

Patient characteristics were expressed using frequencies or descriptive analyses. Univariate and multivariate logistic regression models were performed to assess the independent factors that correlated with resectability of these patients. The Kaplan–Meier method was used to estimate survival, and differences were compared using the log-rank test. Univariate and multivariate Cox proportional hazard models were also used to select independent factors associated with survival in the subgroup of patients with an R0 resection margin. A P value < 0.05 was deemed significant. The statistical analysis was presented using the SPSS version16.0 (SPSS Inc. Chicago, IL, USA).

Results

Demographic and Clinical Characteristics

One hundred and seventy-three patients were included in the current study and their baseline data are presented in Table 2. The mean age of all patients was 59.72 ± 10.58 years, and the majority of patients were male (63.01%). According to the Bismuth-Corlette classification, 93 patients were classified as types I and II, while the other 80 patients were labeled as types III and IV. According to the preoperative imaging examinations, all 173 patients appeared to have potentially resectable tumors. One hundred and thirty-four patients had R0 resection margins, which included hilar bile duct resection (12 cases), left hemihepatectomy (60 cases), right hemihepatectomy (39 cases), left trisegmentectomy (13 cases), right trisegmentectomy (7 cases), and mesohepatectectomy (3 cases). The caudate lobe was removed conventionally in 103 patients. The remaining 39 patients were identified as unresectable because of wide bilateral intrahepatic bile duct involvement ($n = 9$), bilateral portal vein involvement ($n = 8$),

Table 1 Definition of inflammation-based prognostic scores

Inflammation-based prognostic scoring system	Score
GPS	
CRP (≤ 10 mg/L) and albumin (≥ 35 g/L)	0
CRP (≤ 10 mg/L) and albumin (< 35 g/L)	1
CRP (> 10 mg/L) and albumin (≥ 35 g/L)	1
CRP (> 10 mg/L) and albumin (< 35 g/L)	2
Modified GPS	
CRP (≤ 10 mg/L) and albumin (≥ 35 g/L)	0
CRP (≤ 10 mg/L) and albumin (< 35 g/L)	0
CRP (> 10 mg/L) and albumin (≥ 35 g/L)	1
CRP (> 10 mg/L) and albumin (< 35 g/L)	2
PLR	
Platelet count: lymphocyte count < 150	Low
Platelet count: lymphocyte count ≥ 150	High
NLR	
Neutrophil count: lymphocyte count < 3	Low
Neutrophil count: lymphocyte count ≥ 3	High
PI	
CRP (≤ 10 mg/L) and white cell count ($\leq 10 \times 10^9$)	0
CRP (≤ 10 mg/L) and white cell count ($> 10 \times 10^9$)	1
CRP (> 10 mg/L) and white cell count ($\leq 10 \times 10^9$)	1
CRP (> 10 mg/L) and white cell count ($> 10 \times 10^9$)	2
PNI	
Albumin (g/L) + 5 × total lymphocyte count ≥ 45	0
Albumin (g/L) + 5 × total lymphocyte count < 45	1

PLR platelet lymphocyte ratio, *NLR* neutrophil lymphocyte ratio, *PNI* prognostic nutritional index, *GPS* Glasgow prognostic score, *PI* prognostic nutritional index

distant lymph node metastases ($n = 3$), or peritoneal metastases ($n = 16$); the other three patients had an R1 resection because of a false negative of the intraoperative frozen-section examination.

Analysis of the Relationship of Preoperative Factors with Tumor Resectability

The relationship of various preoperative tumor factors with resectability is presented in Table 3. Patients with PLR ≥ 150 were more likely to have unresectable tumors (27.2%), while only 10.4% of patients had unresectable diseases in the cohort of PLR < 150 ($P = 0.018$). NLR also seemed to affect resectability; in patients with NLR < 3, 88.9% ($n = 48$) of patients had R0 resection margins, while only 72.3% patients achieved R0 resection margins in those with NLR ≥ 3 ($P = 0.015$). Simultaneously, PNI was also directly correlated with resectability: 9.8% of patients had unresectable tumors in the group of PNI ≥ 45, while 27.9% of patients had unresectable tumors in the group with a PNI < 45 ($P = 0.010$). The GPS and modified GPS were also associated with resectability; specifically,

Table 2 Baseline characters of 173 patients with potential resectable hilar cholangiocarcinoma

Variables	$n = 173$
Age, years	59.72 ± 10.58
Sex, male (%)	109 (63.01)
Preoperative TB level,mg/dl[a]	14.01 ± 5.56
Preoperative TB level,mg/dl[b]	7.05 ± 1.52
Preoperative ALT level, U/L	125.51 ± 101.71
Preoperative AST level, U/L	108.95 ± 76.73
Preoperative albumin level, g/L	36.46 ± 4.14
Preoperative CA 19-9 level, U/mL	350.87 ± 319.73
Preoperative CA 125 level,U/mL	28.32 ± 24.15
Preoperative CEA level, ng/mL	5.93 ± 9.08
Preoperative CRP level, mg/L	7.91 ± 2.76
Preoperative neutrophil level, 10^9/L	4.81 ± 2.39
Preoperative lymphocytes level, 10^9/L	1.23 ± 0.46
Preoperative platelet level, 10^9/L	229.71 ± 84.49
Preoperative WBC level, 10^9/L	6.84 ± 2.61
Total hospital stay	20.17 ± 8.47
Preoperative biliary drainage (%)	173 (100)
Portal vein embolization (%)	21 (12.14)
Bismuth-Corlette classification	
Types I and II	93 (53.76)
Types III and IV	80 (46.24)
Tumor size, cm	2.85 ± 1.08

TB total bilirubin, *ALT* alanine aminotransferase, *AST* aspartate transaminase, *CA19-9* carbohydrate antigenic determinant 19-9, *CA125* carbohydrate antigen 125, *CEA* carcino embryonie antigen, *CRP* C-reaction protein, *WBC* white blood cell

[a] Before preoperative biliary drainage

[b] 1–3 days before surgery

the likelihood of achieving an R0 resection margin decreased as the GPS and modified GPS scores increased [GPS (0:1:2): 87.5 vs. 70.7 vs. 59.3%; modified GPS (0:1:2): 82.0 vs. 75.0 vs. 59.3%; all $P < 0.05$]. Notably, CA 125 also affected resectability; higher CA 125 levels were associated with a lower rate of R0 resection, while lower CA 125 levels were more likely to have resectable disease (62.2 vs. 81.6%; $P = 0.012$). Preoperative tumor size was also noted to affect resectability, with a larger size more likely to be unresectable (30.1 vs. 13.8%; $P = 0.010$).

To estimate the independent contributing determinants to tumor resectability, a multivariate logistic regression model was carried out (Table 4). Multivariate analysis indicated the tumor size ≥ 3 cm (OR = 2.422, 95% CI: 1.053–5.573; $P = 0.037$), PLR ≥ 150 (OR = 3.324, 95% CI: 1.143–9.667; $P = 0.027$), preoperative CA 125 > 35 U/mL (OR = 3.184, 95% CI: 1.316–7.704; $P = 0.010$), and GPS (0.1/2) (OR = 2.440, 95% CI: 1.450–4.107; $P = 0.001$) were independent factors associated with tumor resectability.

Table 3 Analysis of the relationship of preoperative factors with the tumor resectability in patients with potentially resectable tumors judged by radiologic examination with hyperbilirubinemia

Variable	Resectable ($n = 134$)	Unresectable ($n = 39$)	P value
Age[a]			
≤ 60	68 (50.7)	14 (35.9)	0.102
> 60	66 (49.3)	25 (64.1)	
Gender			
Male	84 (62.7)	25 (64.1)	0.872
Female	50 (37.3)	14 (35.9)	
PLR ≥ 150[b]			
No	43 (32.1)	5 (12.8)	0.018
Yes	91 (67.9)	34 (87.2)	
NLR ≥ 3[b]			
No	48 (35.8)	6 (15.4)	0.015
Yes	86 (64.2)	33 (84.6)	
PNI ≥ 45[b]			
No	88 (65.7)	34 (87.2)	0.010
Yes	46 (34.3)	5 (12.8)	
Modified GPS			
0	100 (74.6)	22 (56.4)	0.036
1	18 (13.4)	6 (15.4)	
2	16 (11.9)	11 (28.2)	
GPS			
0	77 (57.5)	11 (28.2)	0.003
1	41 (30.6)	17 (43.6)	
2	16 (11.9)	11 (28.2)	
Preoperative CA 125 > 35 U/mL[c]			
No	111 (82.8)	25 (64.1)	0.012
Yes	23 (17.2)	14 (35.9)	
Preoperative CEA > 3.4 ng/mL[c]			
No	69 (51.5)	14 (35.9)	0.086
Yes	65 (48.5)	25 (64.1)	
Tumor size[d]			
< 3 cm	69 (51.5)	11 (28.2)	0.01
≥ 3 cm	65 (48.5)	28 (71.8)	
Bismuth-Corlett classification			
I and II	77 (57.5)	16 (41.0)	0.07
III and IV	57 (42.5)	23 (59.0)	

PLR platelet lymphocyte ratio, *NLR* neutrophil lymphocyte ratio, *PNI* prognostic nutritional index, *GPS* Glasgow prognostic score, *CA125* carbohydrate antigen 125, *CEA* carcino embryonie antigen

Factors not associated with resectability were PI, BMI, ALT, AST, et al.

[a] Using the median value

[b] Using the cut-off point recommended by other studies

[c] Using the lowing limit of the normal range

[d] Using the cut-off recommended in the DeOliveira staging system

Clinicopathological Factors Associated with Survival in Patients with an R0 Resection In the resected group, the median survival time was 30.87 months, with 1-, 3-, and 5-year survival rates of 88, 46, and 28%, respectively. By contrast, the median survival time for the unresected group was 14.97 months, with the 1-, 3-, and 5-year survival rates of 62, 8, and 0%, respectively (Fig. 1; $P < 0.001$). Further analysis focused on the risk factors associated with survival in patients with R0 resections. The univariate analysis suggested that tumor size, tumor differentiation, and lymph node status all had prognostic significance (Table 5). For example, positive lymph node status was associated with a decrease in median survival from 38.03 to 24.73 months (Fig. 2a; log-rank test, $P = 0.001$). Patients with well-differentiated tumors had a median survival of 50.33 months, while those with moderately or poorly differentiated tumors had a median survival of 35.20 and 20.87 months, respectively (Fig. 2b; log-rank test, $P = 0.003$). Furthermore, median survival was also inversely proportional to pathological tumor size; the median survival decreased from 38.03 to 28.57 months as the tumor size increased (log-rank test, $P = 0.023$).

Table 4 Variables associated with tumor resectability in multivariate logistic analysis in those with potentially resectable tumors judged by radiologic examination with hyperbilirubinemia

Variables	Odds ratio	95% CI	P value
Tumor size ≥ 3 cm	2.422	1.053–5.573	0.037
PLR ≥ 150	3.324	1.143–9.667	0.027
Preoperative CA 125 > 35 U/mL	3.184	1.316–7.704	0.010
GPS (0/1/2)	2.440	1.450–4.107	0.001

CI confidence interval, *PLR* platelet lymphocyte ratio, *CA125* carbohydrate antigen 125, *GPS* Glasgow prognostic score

We further used a multivariate analysis model. After controlling for competing risk factors, lymph node status (hazard ratio (HR) = 1.655, 95% CI: 1.128–2.429; $P = 0.010$) and tumor differentiation (HR = 1.356, 95% CI: 1.039–1.769; $P = 0.025$) remained as independent factors associated with overall survival in the subgroup of jaundiced patients with R0 resection margins.

Discussion

The existence of systemic inflammatory responses sustains the acknowledged relevance of poor prognosis and bad nutritional conditions in various cancers.[27] Inflammation-based prognostic scores have been widely used in the preoperative diagnosis and in short- and long-term prognosis prediction of these cancer patients.[28,29] Despite the improvement in radiological diagnosis in the preoperative examination of tumor status, tumor classification, and the tumor relationship with surrounding tissues, there still seems to be a distinct discrepancy between the preoperative judgment and intraoperative findings for patients with HCCA. In the current study, we

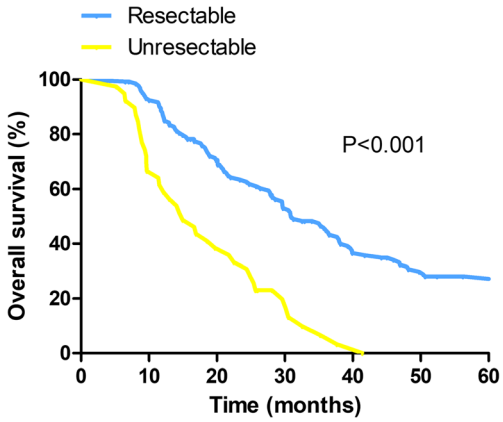

Fig. 1 Kaplan–Meier curves comparing survival status based on resectable and unresectable tumors in jaundiced patients hilar cholangiocarcinoma (HCCA) with potentially resectable disease as diagnosed by preoperative imaging examinations ($P < 0.001$)

examined the predictive value of inflammation-based prognostic scores on the resectability of jaundiced patients with HCCA and potential resectable disease. To the best of our knowledge, no previous study has analyzed the risk factors of tumor resectability for jaundiced patients with HCCA.

Among the inflammation-based prognostic scores we investigated, GPS and PLR were the two prognostic factors associated with tumor resectability. The GPS is the combination of C-reactive protein (CRP) and albumin. CRP is an acute-phase reactant generated by hepatocytes; its upregulation is regulated by several proinflammatory cytokines, such as interleukin-6, interleukin-8, and tumor necrosis factor-α.[27] An elevated CRP level is an indirect reflection of cytokine activation levels in the body. These cytokines could induce a systematic inflammatory response, breaking down the immune system and leading to rapid cancer progression. Albumin is the manifestation of nutrition status of individuals: lower albumin levels representing poor nutritional conditions. In the univariate analysis, the likelihood of achieving an R0 resection margin decreased as the GPS score increased. This was re-confirmed in the later multivariate analysis; the GPS score remained as an independent factor associated with tumor resectability. However, most studies only emphasized the prognostic effect of GPS on short- and long-term outcomes, totally ignoring its predictive value on resectability. Meanwhile, the PLR level also appeared to affect resectability. The cut-off value was acquired from many previous studies, showing that patients with PLR levels ≥ 150 had poor prognostic outcomes.[26,30,31] In our present series, PLR levels ≥ 150 conferred a decrease in resectability from 89.6 to 72.8%. This was also statistically significant in the multivariate analysis ($P = 0.027$). Considering that higher systematic inflammatory scores could predict poor survival in patients with HCCA, higher systematic inflammatory scores may also associate with advanced tumor stage, patients in this cohort have a higher chance of unresectability and are less likely to have R0 resections. Taken together, the GPS and PLR are two

Table 5 Univariate and multivariate analysis of tumor factors associated with overall survival after curative surgery in hyperbilirubinemia patients

	Univariate			Multivariate		
Tumor factors	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age > 60 years	1.227	0.848–1.777	0.278			
Male gender	1.352	0.923–1.980	0.122			
Tumor size ≥ 3 cm	1.533	1.059–2.219	0.024	1.447	0.990–2.114	0.056
Bismuth classification (III, IV)	1.107	0.764–1.605	0.591			
CA 125 > 35 U/mL	1.061	0.624–1.802	0.828			
CEA > 3.4 ng/mL	1.111	0.768–1.606	0.577			
NLR ≥ 3	1.132	0.776–1.652	0.520			
PLR ≥ 150	1.112	0.753–1.641	0.594			
Modified GPS (0/1/2)	1.205	0.939–1.547	0.143			
GPS (0/1/2)	1.181	0.916–1.524	0.200			
PI (0/1/2)	1.170	0.833–1.643	0.364			
PNI ≥ 45	1.378	0.941–2.018	0.100			
Caudate lobe resection	0.743	0.497–1.111	0.148			
AJCC T stage	1.259	0.871–1.819	0.220			
Positive nodal status	1.818	1.253–2.636	0.002	1.655	1.128–2.429	0.010
Tumor differentiation	1.529	1.182–1.979	0.001	1.356	1.039–1.769	0.025
Vascular invasion	1.379	0.735–2.588	0.317			
Perineural invasion	1.936	0.968–3.875	0.062			

CA125 carbohydrate antigen 125, *CEA* carcino embryonie antigen, *PLR* platelet lymphocyte ratio, *NLR* neutrophil lymphocyte ratio, *PNI* prognostic nutritional index, *GPS* Glasgow prognostic score, *PI* prognostic index, *AJCC* American Joint Committee on Cancer

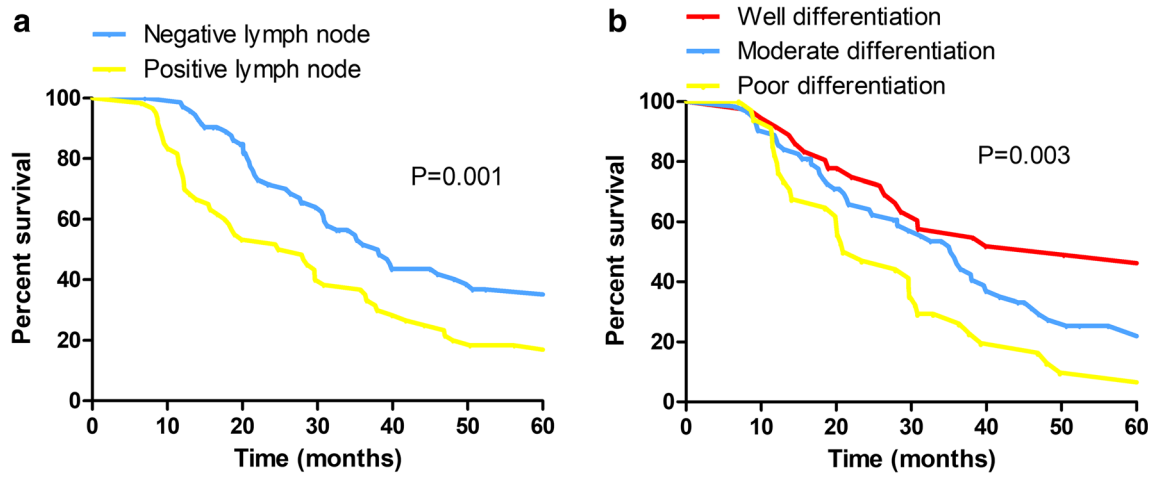

Fig. 2 **a** Kaplan–Meier curves comparing survival status based on lymph node status in jaundiced patients with an R0 resection of hilar cholangiocarcinoma (HCCA) ($P = 0.001$). **b** Kaplan–Meier curves comparing survival status based on tumor differentiations in jaundiced patients with an R0 resection of HCCA ($P = 0.003$)

inflammation-based prognostic scores that can predict tumor resectability in jaundiced HCCA patients with potentially resectable tumors. These indexes are only based on laboratory data; therefore, they can act as simple and complementary prognostic tools to traditional preoperative imaging to allow an accurate estimate of the resectability of HCCA.

Notably, CA 125 was also noted to affect tumor resectability. Encoded by a homonymic gene, CA 125 is a large mucin-like glycoprotein that is mostly overexpressed by epithelial ovarian cancer cells.[10,16,32,33] Our previous study also identified that CA 125 is a predictor of resectability, with an area under the curve (AUC) of 0.730 and an optimal cut-off value of 25.9 U/mL in patients with normal bilirubin levels.[13] In the current study, we confirmed that CA 125 levels greater than 35 U/mL were inversely associated with a decreased resectability rate, from 81.6 to 62.2% ($P = 0.012$). The CA 125 level also remained an independent factor in the subsequent multivariate study ($P = 0.010$). Thus, given that CA 125 levels are strongly associated with tumor resectability, preoperative CA 125 detection should be managed on a regular basis and the CA 125 level can be regarded as a reference for resectability in jaundiced patients with HCCA.

Importantly, tumor size was also predictive of tumor resectability in the cohort of jaundiced patients with HCCA. Tumor size is an important prognostic factor for HCCA. Regimbeau et al.[34] found that a tumor size > 3 cm could predict death in < 12 months ($P = 0.004$). In addition, those with tumors < 3 cm who underwent liver transplantations were associated with evident survival advantages compared with those with tumors > 3 cm.[35] Thus, tumors > 3 cm has been established as a contraindicant criterion for choosing patients with HCCA undergoing liver transplantation. The 3-cm cut-off point is also solely differentiated by a T2 or T3 tumor in the DeOliveira staging system.[36] In our previous study, the 3-cm cut-off point for tumor size was also noted to be associated with long-term survival and other prognostic factors related to tumor differentiation and lymph node metastasis.[6,25,37] In the present series, the resectability decreased from 86.2 to 69.9% as the tumor size increased ($P = 0.01$). Meanwhile, the postoperative tumor size was also examined as a prognostic factor in jaundiced patients with HCCA with an R0 resection margin: tumor size ≥ 3 cm conferred a median survival of 28.57 months compared with 38.03 months for those with smaller tumors ($P = 0.024$). Taken together, tumor size could not only predict survival, but also indicated resectability, with larger sized tumors more likely to be unresectable and ultimately have poor prognosis.

Another important finding in the present series was that tumor differentiation and lymph node metastasis remained predictive of long-term survival in jaundiced patients with HCCA patients with an R0 resection margins. Most of the previous studies reported that tumor differentiation and lymph node status are two main predictors of survival for patients with curative surgery for HCCA.[5] In our cohort of jaundiced patients with HCCA, positive lymph node status was associated with a decrease in median survival from 38.03 to 24.73 months ($P = 0.001$). Additionally, well-differentiated tumors conferred a median survival of 50.33 months, while those with moderately and poorly differentiated tumors had a decreased median survival of 35.20 and 20.87 months, respectively, even after R0 resection ($P = 0.003$). This was further reaffirmed in the multivariate analysis. These data suggested that tumor differentiation and lymph node metastasis remained predictive of long-term survival. Patients with poor differentiation and lymph node metastasis should be carefully monitored in the postoperative follow-up to detect any disease recurrence early.

In conclusion, jaundiced HCCA patients with higher GPS, CA 125, and PLR levels and larger preoperative tumor size tended to have unresectable tumors, even if judged as

potentially resectable by preoperative radiological examinations. These factors may support precise preoperative assessment of tumor resectability. Patients with poor tumor differentiation and lymph node metastasis may also have a worse prognosis, even after R0 resection.

Author's Contributions Hu HJ and Jin YW contributed equally to the study; Hu HJ and Jin YW contributed to data acquisition and drafted the manuscript. Ma WJ, Yang Q, Wang JK, and Liu F contributed to data acquisition and analysis of the manuscript. Zhou RX and Cheng NS were involved in the revision of the manuscript. Li FY contributed to the study design and revision of the manuscript. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

The study was approved by the Institutional Review Board of West China Hospital.

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

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