Original Article

Perineural invasion confers poorer clinical outcomes in patients with T1/T2 intrahepatic cholangiocarcinoma: a single center, retrospective cohort study

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Background: Intrahepatic cholangiocarcinoma (ICC) poses a significant clinical challenge, demanding a thorough understanding of prognostic indicators for effective patient management. Despite reports suggesting the impact of perineural invasion (PNI) on the prognosis of early-stage ICC patients, there has been a dearth of comprehensive research specifically targeting this subgroup. This study seeks to investigate the influence of PNI on survival outcomes in early-stage ICC patients and aims to enhance the prognostic value of the American Joint Committee on Cancer (AJCC) T category.

Methods: A cohort of 268 early-stage (T1-T2N0M0) ICC patients, who underwent curative-intent resection (R0) between 2011 and 2015 at the Eastern Hepatobiliary Surgery Hospital, were enrolled in this study. Lasso and Cox regression analyses were employed to explore differences in clinical and prognostic data. Kaplan-Meier curves were generated to illustrate the clinical significance of the combination of PNI and T category.

Results: Among the 268 patients, 24.6% exhibited PNI. Patients with PNI demonstrated shorter recurrence-free survival (RFS) [median RFS: 16 months (interquartile range, 9.5–19 months)] and overall survival (OS) [median OS: 16.53 months (interquartile range, 10–25 months)]. PNI emerged as an independent risk factor for both RFS and OS in T1- and T2-stage patients (all $P<0.05$), whereas tumor size was only an independent risk factor for OS ($P=0.004$). PNI was associated with all prognostic markers for ICC patients, including gender, jaundice, cholangitis, hepatitis B virus (HBV) infection, cancer antigen 199 (CA199), preoperative serum albumin, and preoperative platelet count (all $P<0.05$). However, there was no significant difference in RFS ($P=0.270$) and OS ($P=0.360$) between T2 patients without PNI and T1 patients with PNI.

Conclusions: This study underscores PNI as a robust prognostic factor in early-stage ICC, emphasizing the necessity of incorporating PNI into the AJCC T category for precise risk stratification. Clinically,

understanding the impact of PNI on survival outcomes can guide tailored treatment strategies for early ICC patients.

Keywords: Intrahepatic cholangiocarcinoma (ICC); perineural invasion (PNI); prognosis; diseases category

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Introduction

Intrahepatic cholangiocarcinoma (ICC), the second most prevalent kind of malignant liver tumor after hepatocellular carcinoma, comes from grade II or higher bile duct epithelial cells in the liver (1). The incidence of ICC has been increasing over the past few decades, with a higher prevalence reported in certain regions of the world (2). ICC commonly presents in the early stages as an asymptomatic disease. Radical resection represents the sole curative option for ICC; nonetheless, a significant proportion of patients present with advanced disease at the time of diagnosis, limiting the feasibility of curative resection to a mere 30% of cases (3). Even when there is a potential for resection, the prognosis is disappointing, with a 5-year survival rate of 25–35% due to a lack of effective, comprehensive treatment (4).

Perineural invasion (PNI) is a pathologic finding characterized by the infiltration of cancer cells into the surrounding nerves. This phenomenon is frequently observed in pancreatic, head and neck, prostate, stomach, and colon cancers, among others (5-8). PNI is associated with a higher risk of cancer recurrence and a shorter patient survival time, and it can cause paralysis and agony (9). Although the prognostic importance of PNI is widely recognized, the etiological mechanisms driving their pathogenesis remain largely elusive, and no targeted therapies aimed at nerve invasion are presently available (3). Recent studies suggest that PNI may indicate a worse prognosis for ICC patients (10-12). Due to the varying prognoses within different subgroups of early ICC patients (13,14), despite the existing research on PNI in this population, the impact of PNI on the prognosis of early ICC patients still requires further exploration.

In this study, we investigated the effect of PNI on survival and recurrence in patients with early-stage ICC who underwent resection. We sought to elucidate the predictive influence of PNI in early-stage ICC and assess the value added for the T category of the eighth edition of the American Joint Committee on Cancer (AJCC). We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-950/rc).

Highlight box

Key findings

- Perineural invasion (PNI) emerges as a significant and independent risk factor impacting both recurrence-free survival (RFS) and overall survival (OS) in early-stage intrahepatic cholangiocarcinoma (ICC) patients undergoing resection.

What is known and what is new?

- PNI holds prognostic importance in ICC, extending to early-stage ICC (T1-T2N0M0).
- The exploration of PNI's impact on the prognosis of early-stage ICC patients remains insufficiently investigated.

What is the implication, and what should change now?

- Clinical reassessment of current staging criteria is warranted, and the potential role of PNI as a supplementary factor in treatment decisions for early ICC patients undergoing resection should be evaluated.

Methods

Study cohort and data collection

This study employs a retrospective cohort study design, with a primary emphasis on investigating the prognostic significance of PNI in individuals diagnosed with early-stage ICC. Patients with early-stage ICC (T1-T2N0M0), as classified by the 8th edition of the AJCC (15), who had R0 radical liver resection at the Eastern Hepatobiliary Surgery Hospital (EHBH) between January 2011 and November 2015 were eligible for inclusion. In the retrospective study, patients were selected on the basis of the following inclusion criteria: (I) pathological diagnosis of ICC; (II) absence of preoperative treatment; (III) Child-Pugh A and B; (IV) first R0 surgical resection; and (V) no adjuvant therapy following resection. The exclusion criteria were

as follows: (I) incomplete clinical or follow-up data; (II) other malignancies. In accordance with the inclusion and exclusion criteria, a total of 268 patients with early-stage ICC were enrolled in this study, and no patient was lost during follow-up.

The medical histories and pathology reports were reviewed for basic information, clinical data and tumor characteristics. In accordance with the postoperative diagnostic information provided by the pathologist, we extracted data regarding the patient's liver cirrhosis, tumor differentiation, tumor diameter, multifocality, vascular invasion, and PNI. Subsequently, based on the AJCC staging criteria, tumors were categorized into T1 and T2 stages depending on whether they were solitary or accompanied by vascular invasion. Further classification into T1a and T1b stages was performed based on whether the tumor diameter exceeded 5 cm. Pathologists certified PNI in 66 cases, but the remaining 202 cases did not.

Follow-up and outcomes

Regular abdominal computer tomography (CT), magnetic resonance imaging (MRI), or ultrasonography examinations (quarterly from years 0 to 3, and semiannually between years 3 and 5) were performed on patients after surgery. Overall survival (OS) was computed from the date of surgery until the date of death or the end of follow-up (November 2015). Recurrence-free survival (RFS) was defined as the time between surgery and recurrence of the tumor. Recurrences were categorized as intrahepatic or extrahepatic (lungs, peritoneum, bone, or other distant sites). The primary outcome of the trial was RFS, with OS and recurrence patterns serving as the secondary outcome (recurrence sites and timing).

Statistical analysis

Statistical analyses were conducted using Statistical Package for Social Sciences 22.0. The R package "glmnet" was utilized for performing Lasso regression analysis on the dataset. Continuous variables were presented as mean ± standard deviation or median value (range) and analyzed using independent-sample *t*-test or Mann-Whitney *U* test, as appropriate. Categorical variables were represented as frequency (percentage) and subjected to analysis using Chi-square or Fisher exact test, as appropriate. Survival analyses were carried out using Kaplan-Meier (K-M) curves, and differences between groups were assessed using the log-rank test. Univariate and multivariate Cox proportional hazard regression analyses were employed to identify significant risk factors for survival data. Variables with a significance level of $P<0.05$ in the univariate analysis were included in the multivariate analysis, utilizing the Listening-Reading method. All statistical evaluations were two-tailed, and a significance level of $P<0.05$ was considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Eastern Hepatobiliary Surgery Hospital (No. EHBHKY2016-01-018). Because of the retrospective nature of the study, the requirement for informed consent was waived.

Results

Baseline characteristics

In this study, the impact of various clinical factors on the prognosis of patients with RFS and OS was analyzed. A total of 268 patients were evaluated, and 29 clinical data points were analyzed using lasso regression analysis and validated through 10-fold cross-validation. The results showed that only seven clinical factors had a significant impact on RFS and only 6 had a significant impact on OS, with smoking, PNI, T2 stage, and tumor size identified as the only factors that negatively impacted both RFS and OS (Figure S1A,S1B). The optimal values for the LASSO models were determined to be a value of =0.0560506 with log (λ) =−2.8815 for the RFS model, and a value of 0.08170221 with log (λ) =−2.504674 for the OS model (Figure S1C,S1D).

Additionally, this study found that T1a and T1b staging had no significant impact on the prognosis of patients and therefore were considered for inclusion in follow-up analysis as T1 stage. The incidence of PNI was 24.6% (66 patients), and several variables, including gender, jaundice, cholangitis, hepatitis B virus (HBV) infection, cancer antigen 199 (CA199), serum albumin, and platelet count, were found to be associated with a poor prognosis for tumors and connected to PNI (all $P<0.05$). The frequencies of T1 and T2 patients, patients with different tumor sizes and numbers, as well as patients with varying degrees of tumor differentiation, were similar between the

Table 1 Characteristics of 268 early intrahepatic cholangiocarcinoma patients with/without perineural invasion

Variables	PNI (–) (n=202)	PNI (+) (n=66)	P value
Age, mean (SD)	56.59 (10.03)	57.06 (10.75)	0.747
Male gender, n (%)	138 (68.3)	26 (39.4)	<0.001*
Smoking, n (%)	63 (31.2)	20 (30.3)	>0.99
Drinking, n (%)	44 (21.8)	13 (19.7)	0.852
Hypertension, n (%)	45 (22.3)	11 (16.7)	0.424
Diabetes, n (%)	15 (7.4)	6 (9.1)	0.862
Jaundice, n (%)	3 (1.5)	6 (9.1)	0.01*
Cholangiolithiasis, n (%)	2 (1.0)	11 (16.7)	<0.001*
Schistosome, n (%)	12 (5.9)	2 (3.0)	0.546
Steatosis, n (%)	12 (5.9)	3 (4.5)	0.905
HBV, n (%)	101 (50.0)	22 (33.3)	0.027*
HCV, n (%)	11 (5.4)	4 (6.1)	>0.99
AFP (>400 ng/mL), n (%)	10 (5.0)	0 (0.0)	0.142
CA199 (>40 U/mL), n (%)	100 (49.5)	43 (65.2)	0.038*
CA125, (U/mL), median [IQR]	29.74 [12.85, 87.71]	30.70 [14.88, 71.63]	0.974
CA242 (U/mL), median [IQR]	21.52 [6.25, 87.47]	47.00 [13.20, 70.20]	0.174
CEA (ng/mL), median [IQR]	2.50 [1.60, 4.50]	3.00 [1.92, 5.77]	0.063
Preoperative albumin (g/L), median [IQR]	42.70 [40.30, 44.75]	41.10 [37.90, 43.27]	0.002*
Preoperative platelet ($\times10^9$/L), median [IQR]	176.50 [135.00, 234.75]	199.00 [153.50, 251.75]	0.022*
Tumor size (cm), median [IQR]	5.00 [3.73, 7.20]	5.00 [3.28, 7.00]	0.833
Multiple tumors, n (%)	63 (31.2)	15 (22.7)	0.247
Cirrhosis, n (%)	45 (22.3)	7 (10.6)	0.057
Poor differentiation, n (%)	22 (10.9)	4 (6.1)	0.379
AJCC-8th T stage, n (%)			0.120
I	117 (57.9)	46 (69.7)	
II	85 (42.1)	20 (30.3)	

*, P<0.05 was considered statistically significant. PNI, perineural invasion; SD, standard deviation; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha fetoprotein; IQR, interquartile range; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer.

PNI-positive and PNI-negative groups (all P>0.05) (*Table 1*).

PNI impairs the long-term survival prognosis in patients with early ICC

In this study, we categorized patients based on tumor T staging and the presence of PNI and analyzed the impact of these indicators on patient prognosis (*Figure 1*). The RFS of patients with stage T1 ICC or without PNI was found to be superior to that of patients with stage T2 ICC or PNI (P=0.011 and 0.001) (*Figure 1A*,*1B*). Further analysis of the impact of PNI on RFS showed that patients with PNI had a shorter RFS in both T1 and T2 stages compared to patients without PNI (P=0.001; P=0.022) (*Figure 2A*). The results showed that PNI, T2-stage, or a combination of both were independent risk factors for a worse RFS [hazard ratio (HR)

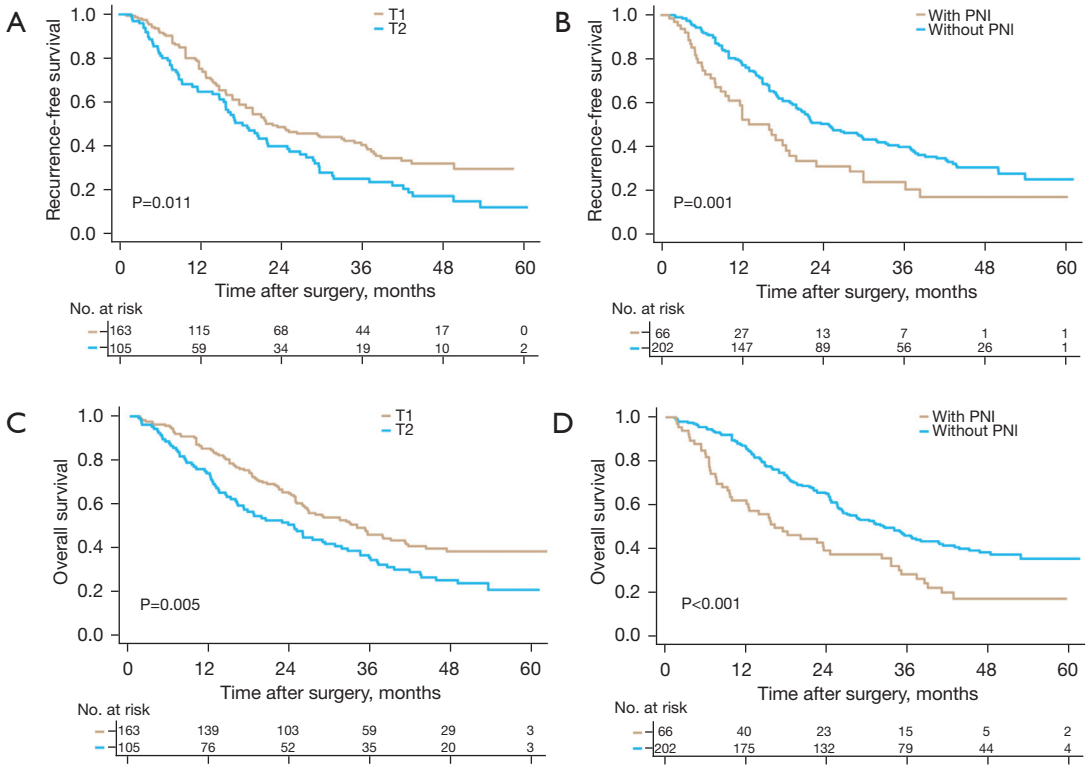


Figure 1 Comparison of RFS (A) and OS (C) for T1- and T2-patients. Comparison of RFS (B) and OS (D) for patients with or without PNI. RFS, recurrence-free survival; OS, overall survival; PNI, perineural invasion.

=1.86, 95% confidence interval (CI): 1.17–2.95, P=0.009; HR =1.44, 95% CI: 1.01–2.06, P=0.046; HR =2.78, 95% CI: 1.55–4.96, P=0.001] (*Table 2*).

The OS followed a similar pattern as RFS. Patients with T2-stage, PNI, or both exhibit a shorter OS compared to patients with T1-stage ICC, without PNI, or both (*Figures 1C*,*1D*,*2B*, *Table 3*). Tumor size was found to be an independent risk factor for OS (HR =1.07, 95% CI: 1.02–1.13, P=0.004) (*Table 3*). The presence or absence of multiple tumors did not have a significant impact on the prognosis of patients with early ICC (RFS: P=0.078; OS: P=0.100) (*Table 3*).

The prognosis of T1 patients with PNI is similar to T2 patients without PNI

The study exploring the relationship between PNI and T-stage in patients with early ICC found that PNI was associated with a worse prognosis, as mentioned previously. However, no statistically significant difference was observed in RFS and OS between T1-stage patients with PNI and T2-stage patients without PNI (RFS: P=0.270; OS: P=0.360), as demonstrated by the Kaplan-Meier curve. Further analysis that accounted for potential patient prognostic factors found that RFS and OS of T1-stage patients with PNI were not significantly different from those of T2-stage patients without PNI (RFS: HR =1.29, 95% CI: 0.80–2.07, P=0.303; OS: HR =1.36, 95% CI: 0.87–2.11, P=0.177). The results showed that tumor size had a significant impact on OS (HR =1.07, 95% CI: 1.02–1.13, P=0.004) but no effect on RFS (HR =1.04, 95% CI: 0.99–1.10, P=0.119). These findings were presented in *Figure 2A*,*2B* and Tables S1,S2.

Discussion

The study aimed to investigate the association of PNI with RFS and OS in patients with early-stage ICC. While the majority of patients with early cancers have a favorable prognosis, this is not the case for individuals with early ICC (10,16,17). The study found that PNI is a poor indicator of prognosis, regardless of whether patients were at T1 or

Table 2 Risk factors associated with recurrence-free survival of patients with/without PNI

Variables	Univariate			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.97–1.00	0.132			
Gender (male/female)	0.83	0.61–1.14	0.254			
Smoking	1.24	0.90–1.71	0.198			
Drinking	0.89	0.61–1.31	0.563			
Hypertension	0.95	0.65–1.38	0.783			
Diabetes	1.04	0.58–1.87	0.907			
Jaundice	0.51	0.13–2.07	0.347			
Cholangiolithiasis	1.03	0.46–2.33	0.942			
Schistosomal history	0.70	0.33–1.49	0.351			
Steatosis	0.91	0.48–1.73	0.782			
HBV	0.96	0.70–1.30	0.779			
HCV	1.08	0.57–2.05	0.809			
AFP (>400 ng/mL)	1.13	0.53–2.42	0.744			
CA199 (>40 U/mL)	1.18	0.87–1.60	0.294			
CA125 (U/mL)	1.00	1.00–1.00	0.223			
CA242 (U/mL)	1.00	1.00–1.00	0.685			
CEA (ng/mL)	1.00	1.00–1.01	0.039*	1.00	1.00–1.01	0.083
Preoperative albumin (g/L)	1.00	0.99–1.01	0.787			
Preoperative platelet ($\times10^9$/L)	1.00	1.00–1.00	0.878			
Tumor size (cm)	1.06	1.01–1.12	0.025*	1.04	0.99–1.10	0.119
Multiple tumors	1.34	0.97–1.86	0.078			
Cirrhosis	1.11	0.77–1.62	0.578			
Poor differentiation	1.22	0.73–2.05	0.447			
AJCC-8th T stage and PNI						
T1 stage without PNI	Reference			Reference		
T1 stage with PNI	1.81	1.14–2.87	0.011*	1.86	1.17–2.95	0.009*
T2 stage without PNI	1.51	1.06–2.15	0.021*	1.44	1.01–2.06	0.046*
T2 stage with PNI	3.08	1.75–5.42	<0.001*	2.78	1.55–4.96	0.001*

*, P<0.05 was considered statistically significant. PNI, perineural invasion; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha fetoprotein; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer.

T2 stages. However, the prognosis for T1-stage patients with PNI was found to be comparable to that of T2-stage patients without PNI. Thus, PNI may be a valuable prognostic factor that can stratify patients according to their long-term outcomes and may potentially play a supplementary function in AJCC staging.

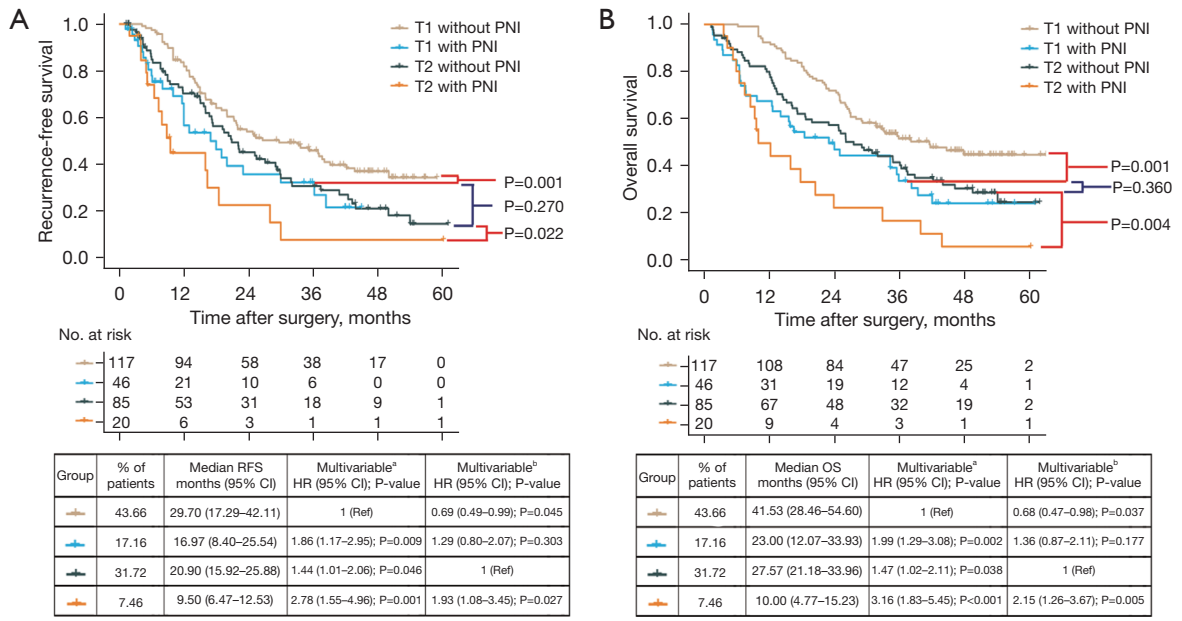
Multiple clinical investigations have demonstrated that PNI, a widespread pathological feature of digestive tract

Table 3 Risk factors associated with long-term overall survival of patients with/without PNI

Variables	Univariate			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.00	0.99–1.02	0.702			
Gender (male/female)	0.90	0.66–1.22	0.495			
Smoking	1.32	0.96–1.80	0.086			
Drinking	1.29	0.91–1.84	0.147			
Hypertension	0.97	0.67–1.41	0.892			
Diabetes	1.16	0.66–2.04	0.613			
Jaundice	2.47	1.21–5.03	0.013*	1.93	0.94–3.98	0.074
Cholangiolithiasis	1.71	0.87–3.35	0.118			
Schistosomal history	0.93	0.46–1.89	0.841			
Steatosis	0.71	0.35–1.45	0.351			
HBV	0.75	0.55–1.01	0.062			
HCV	1.25	0.68–2.30	0.476			
AFP (>400 ng/mL)	1.04	0.49–2.23	0.912			
CA199 (>40 U/mL)	1.33	0.98–1.81	0.063			
CA125 (U/mL)	1.00	1.00–1.00	0.371			
CA242 (U/mL)	1.00	1.00–1.00	0.136			
CEA (ng/mL)	1.00	1.00–1.01	0.448			
Preoperative albumin (g/L)	1.00	0.99–1.01	0.808			
Preoperative platelet ($\times10^9$/L)	1.00	1.00–1.00	0.453			
Tumor size (cm)	1.09	1.04–1.14	0.001*	1.07	1.02–1.13	0.004*
Multiple tumors	1.31	0.95–1.81	0.100			
Cirrhosis	1.02	0.71–1.49	0.901			
Poor differentiation	1.37	0.85–2.21	0.198			
AJCC-8th T stage and PNI						
T1 stage without PNI	Reference			Reference		
T1 stage with PNI	2.00	1.3–3.07	0.001*	1.99	1.29–3.08	0.002*
T2 stage without PNI	1.61	1.13–2.31	0.009*	1.47	1.02–2.11	0.038*
T2 stage with PNI	3.69	2.17–6.27	<0.001*	3.16	1.83–5.45	<0.001*

*, P<0.05 was considered statistically significant. PNI, perineural invasion; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha fetoprotein; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer.

cancer following resection, has a significant impact on the prognosis of ICC patients. Wei *et al.* analyzed 1,095 cases and concluded that PNI affects the prognosis of early ICC patients (11). Our study validated the above conclusion and revealed that PNI had predictive value for the prognosis of ICC patients at the T1 and T2 early stages. While our study focuses on early-stage ICC patients without further postoperative adjuvant therapy, existing literature has



Group	% of patients	Median RFS months (95% CI)	Multivariable[a] HR (95% CI); P-value	Multivariable[b] HR (95% CI); P-value
	43.66	29.70 (17.29–42.11)	1 (Ref)	0.69 (0.49–0.99); P=0.045
	17.16	16.97 (8.40–25.54)	1.86 (1.17–2.95); P=0.009	1.29 (0.80–2.07); P=0.303
	31.72	20.90 (15.92–25.88)	1.44 (1.01–2.06); P=0.046	1 (Ref)
	7.46	9.50 (6.47–12.53)	2.78 (1.55–4.96); P=0.001	1.93 (1.08–3.45); P=0.027

Group	% of patients	Median OS months (95% CI)	Multivariable[a] HR (95% CI); P-value	Multivariable[b] HR (95% CI); P-value
	43.66	41.53 (28.46–54.60)	1 (Ref)	0.68 (0.47–0.98); P=0.037
	17.16	23.00 (12.07–33.93)	1.99 (1.29–3.08); P=0.002	1.36 (0.87–2.11); P=0.177
	31.72	27.57 (21.18–33.96)	1.47 (1.02–2.11); P=0.038	1 (Ref)
	7.46	10.00 (4.77–15.23)	3.16 (1.83–5.45); P<0.001	2.15 (1.26–3.67); P=0.005

Figure 2 Comparison of recurrence-free survival (A) and overall survival (B) for T1- and T2-patients with/without PNI. [a], T1 without PNI group was set as a reference; [b], T2 without PNI group was set as a reference. PNI, perineural invasion; HR, hazard ratio; CI, confidence interval; RFS, recurrence-free survival; OS, overall survival.

reported that PNI-positive ICC patients exhibit insensitivity to postoperative chemotherapy (10). However, following combined immunotherapy, the prognosis of PNI-positive postoperative patients is superior to that of negative patients (18,19). ICC, characterized by a poor prognosis, despite numerous studies suggesting various approaches to improve outcomes (20-23), still lacks a standardized and effective treatment. This suggests that ICC may serve as a potential indicator for combined chemotherapy and immunotherapy.

Cytologically, any tumor cell that is present in all three layers of the neural membrane or surrounds more than one-third of the outer neural membrane is known as PNI (24). PNI is a unique disease entity distinguished by the lack of lymphatic or vascular invasion. Since tumor cells have the potential to active migration, PNI is the path with the least degree of resistance, and is regarded as the earliest step of malignant tumor metastasis (25,26). This study validated previous work that early ICC patients with PNI had higher rates of more severe jaundice, cholangitis, HBV infection, CA199, serum albumin, and platelet count, all of which were believed to be closely connected with ICC patients' prognosis (27-32). Moreover, PNI is closely associated with the pathological malignancy phenotype of ICC, with patients exhibiting PNI often accompanied by large duct-type and lymph node metastasis (19). Furthermore, PNI may serve as a substitute for biological markers of invasive disorders that reflect tumor or stage-specific characteristics substantially. In PNI-positive ICC patients, molecules associated with a poorer prognosis for ICC, such as *NPY1R*, *A1ATD*, *GPX4*, and *KRAS* mutations, exhibit elevated levels (33-36). Future research should focus on elucidating the molecular mechanism behind tumor-nerve interactions and PNI-related carcinogenesis.

Currently, the standard clinical staging of patients with early ICC only considers tumor size and vascular penetration (15). The 8th edition's T category changes for ICC remain controversial, particularly in regard to the T staging of early ICC patients (37-39). Some researchers indicate that modifying the tumor size and the threshold for vascular invasion may be more feasible to predict the prognosis of early ICC patients (13). Nonetheless, this study revealed that tumor size only accurately predicted patients' OS, not their RFS. As the prognosis of T1 patients with PNI follows the same trend as that of T2 patients without PNI, the addition of PNI to the T category may provide more specific prognostic guidance for early ICC patients.

The study has limitations, including the retrospective design and the use of data from a single Chinese institution,

which could result in inherent patient selection bias. Therefore, conducting a multicenter prospective study is imperative to advance and elucidate the outcomes.

Conclusions

The addition of PNI as a prognostic indicator improves the ability to predict the prognosis of patients with early ICC and may enhance its prognostic value when paired with the most recent AJCC T category recommendations.

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Footnote

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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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Eastern Hepatobiliary Surgery Hospital (No. EHBHKY2016-01-018). Because of the retrospective nature of the study, the requirement for informed consent was waived.

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