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Research article

The conditional recurrence-free survival after R0 hepatectomy for locally advanced intrahepatic cholangiocarcinoma: A competing risk analysis based on inflammation-nutritional status

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ABSTRACT

Background: Conditional survival analysis can serve as a dynamic prognostic metric, which helps to estimate the real-time survival probability over time. The present study conducted a conditional recurrence-free survival (CRFS) analysis for locally advanced intrahepatic cholangiocarcinoma (ICC) after R0 hepatectomy from an inflammatory-nutritional perspective using the competing risk method.

Methods: We extracted the medical data of 164 locally advanced ICC patients after R0 resection from Sun Yat-sen University Cancer Center. The calculation formula of the CRFS rate is CRFS(y/x) = RFS(y + x)/RFS(x). Univariable and multivariable COX regression analysis and competing risk analysis were conducted to identify RFS indicators.

Results: Considering death before recurrence as a competing risk factor, the conditional RFS rates every 6 months gradually increased over time. The 24-month RFS rate increased from 29.2 % to 49.9 %, 68.5 %, and 85.1 % given 6, 12, and 18-month already recurrence-free survival, respectively. Both in multivariate COX regression analysis and competing risk analysis, tumor diameter and number, lymph node metastasis, aggregate systemic inflammation index score (AISI), and albumin-bilirubin score (ALBI) all remained significant. For both AISI and ALBI variables, the CRFS rates in the low-value set were higher than those of the high-value set.

Conclusions: Conditional RFS rates of locally advanced ICC after R0 hepatectomy dynamically increased over time, which contributed to reducing survivors' psychological distress and facilitating personalized follow-up schedules. In addition, a person's inflammatory and nutritional status significantly impact the recurrence risk. Oncologists should consider the role of inflammation-nutritional status when making decisions for patients with locally advanced ICC.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC), is one of the most common hepatic tumors, accounting for about 20%–30 % of all liver

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malignancies [1,2]. It is featured by pathological biliary tract differentiation, possibly originating from the intrahepatic biliary tracts [3]. Curative surgery is considered the optimal way to treat ICC, regrettably, the majority of patients are not eligible candidates to accept liver resection due to the advanced stages [4,5]. Notably, there is lacking a standardized definition for locally advanced ICC. Some researchers have proposed that locally late-stage ICC involved a singular tumor or multiple lesions > 2 cm without invasion of major vessels or lymph nodes [6]. Moustafa et al. defined stages III and IVa of the AJCC-7th TNM version (stage III of the AJCC-8th TNM) as locally advanced ICC, which aligned with Yi et al. [7,8]. Locally advanced ICC often necessitates technically surgical intricacies such as extensive liver resection and complex biliary tract reconstruction [3]. Therefore, developing effective medical strategies for this subset of late-stage ICC remains challenging. In comparison to palliative chemotherapy, hepatectomy has shown the potential to improve outcomes for patients with ICC [7]. However, limited studies have investigated the risk of recurrence after R0 resection in cases of locally advanced ICC. Furthermore, current research predominantly relies on traditional survival analyses like the 5-year recurrence-free rate (RFS) to assess long-term prognosis from a static perspective [9]. For patients with longer survival times, this static assessment may not enhance follow-up compliance due to inaccurate prognostic information [10]. Thus it would be reasonable to adopt real-time evaluation methods to assess oncological outcomes following surgery in cases of locally advanced ICC.

Conditional survival (CS) analysis can serve as a dynamic prognostic metric, helping to estimate the survival probability that a patient could survive for more y months after having survived for x months [11,12]. It has been employed in various digestive tract tumors such as pancreatic, gastric, esophageal, and colorectal cancer, with significant improvement in long-term prognosis over time [13–16]. This favorable prognostic evaluation alleviates psychological distress among survivors and facilitates personalized follow-up schedules and adjuvant treatment strategies.

Emerging evidence supports the association between inflammation in the body and tissue micro-environment with the occurrence and progression of malignancies [17]. Recently, it has been proved that systemic and local inflammation response could predict short- and long-term outcomes as well as guide personalized medical strategies. In line with this view, several papers have proposed hematological predictors to evaluate tumor prognosis [18,19]. Additionally, an individual's nutritional level is partially correlated to anti-tumor immune function. Malnutrition suppresses anti-tumor immune surveillance and response, thereby accelerating tumor initiation and progression [20]. Several nutritional predictors have been developed to assess cancer prognosis such as Controlling Nutritional Status score (CONUT), Geriatric Nutritional Risk Index (GNRI), and Albumin-Bilirubin score (ALBI) [21–23]. However, the clinical associations between inflammation-nutritional indicators and the prognosis of locally advanced ICC after R0 resection remain unclear.

To the best of our knowledge, there is currently no existing literature on conditional recurrence-free survival (CRFS) for locally advanced ICC after R0 resection based on inflammation-nutritional status. Thus, we conducted this study to assess the recurrence-related indicators and provide clincians and ICC patients with dynamic information regarding recurrence risk. Additionally, considering that competing risk events can potentially compromise the accuracy of statistical inference, we employed a combination of COX regression analysis and competing risk methodology to mitigate potential biases.

2. Methods and Materials

2.1. Patient selection and medical variables

We extracted the medical data of 291 ICC patients accepting R0 surgical resection at our center between January 2000 and January 2018. The main inclusion criteria were as follows: a) age $\geq$18 years; b) exact pathological evidence; c) R0 hepatectomy; d) no post-operative death within 60 days of hospitalization and no recurrence within 30 days after surgery. R0 hepatectomy was defined as complete resection with negative margins. The definition of locally advanced ICC was similar to Yi et al. and Moustafa et al. [7,8]. Concretely, we took stages III and IVa of the AJCC-7th TNM version (stage III of the AJCC-8th TNM) as locally advanced ICC. Major hepatectomy was defined as the resection of more than three Couinaud segments. To evaluate the predictive value of various combined inflammation scores on the recurrence risk of locally advanced ICC following surgery, we selected several commonly used inflammation-nutritional indicators in this study [aggregate systemic inflammation index (AISI), systemic inflammation response index (SIRI), Monocyte to lymphocyte ratio (MLR), Platelet to lymphocyte ratio (PLR), Neutrophil to lymphocyte ratio (NLR), gamma-glutamyl- transpeptidase to platelet ratio (GPR), ALBI, Fibrosis-4 index (FIB-4), Naples prognostic score (NPS), CONUT, and GNRI]. The definitions of these indexes were summarized in Supplementary Table 1. All enrolled patients were followed up regularly after discharge, with the final follow-up day being October 18th, 2020. RFS refers to the period between the date of surgery and the date of imaging or pathological diagnosis of recurrence during follow-up. Overall survival (OS) after recurrence was limited to the interval between the recurrence date and the time of death. This study was approved by the Ethics Committee of Sun Yat-Sen University Cancer Center (ID: B2022- 492–01). The need for informed consent was waived due to the nature of the retrospective study, and we conducted a necessarily anonymized process for all included patient data.

2.2. Statistical analysis

All analytical procedures were conducted by IBM SPSS Statistics 25.0, R 4.1.3, and Medcalc 19.0.4. A two-tailed p-value less than 0.05 was considered statistically significant. Continuous variables were summarized as 'mean $\pm$ SD' or 'median (QL, QU)', and categorical variables were expressed as frequency and percentage. We conducted Pearson's Chi-Square test or Fisher's Exact test to assess the statistical difference between groups. We employed the median value as the optimal cutoff to separate continuous factors into low- and high-value sets. The median value of CEA, CA19-9, AISI, SIRI, MLR, PLR, NLR, GPR, ALBI, FIB-4, and GNRI were 3.1, 38.88,

219.65, 9.5, 0.27, 123.43, 2.47, 0.32, −3, 1.3, and 108.77, respectively. COX regression analysis and competing risk analysis were taken to evaluate significant variables of RFS after R0 resection. Specifically, significant variables ($P < 0.05$) in the univariable analysis were retained for further multivariate Cox regression evaluation by the method 'Forward: LR'. For competing risk analysis, we took the Fine and Gray model to evaluate the competing risk events. We took variables with a p-value less than 0.05 in univariate analysis based on the R 'cmprsk' package to perform multivariate competing risk evaluation. To assess the impact of collinearity, we calculated the variance inflation factor (VIF) value of each significant variable based on the results of multivariate analysis. In this study, we regarded death without relapse as a competing risk event. The Kaplan-Meier curve method was taken by the log-rank test to evaluate the survival and recurrent difference in recurrence between groups.

In conducting CRFS analysis, we adhered to the prescribed formula to calculate the value: $CRFS(y/x) = RFS(y + x)/RFS(x)$. CRFS (y/x) denotes the likelihood that a locally advanced ICC patient, having survived x months without disease progression, would then go on to recurrence-freely survive for additional y months. The RFS(y + x) and RFS(x) represent the RFS rates at y + x and x months after liver resection. For instance, the CRFS(18/12) signifies the CRFS rate for patients who have recurrence-freely survived twelve months and then remained for another six months.

3. Results

3.1. General characteristics

We reviewed the medical data of 291 patients with pathological diagnoses of ICC. Of these, 164 cases met the inclusion criteria and remained for further analysis. The baseline data are summarized in Supplementary Table 2. Among the cohort, 99 cases (60.4 %) were male, with a mean age of 55.4 years. The average tumor size was 6.6 ± 2.8 cm, with 68.3 % of tumors being solitary. Furthermore, 69.5 % of the lesions were poorly differentiated to undifferentiated. The majority of the patients (51.8 %) received major hepatectomy and 60.4 % got a surgical margin greater than 1 cm. Adjuvant postoperative therapy was administered to 37.8 % of the patients. The median CA19-9 value was 38.88 U/mL, and that for CEA was 3.09 U/mL. Additionally, the median values for AISI, SIRI, and ALBI were 219.65, 9.5, and −3, respectively. Notably, 8 patients died without recurrence, which was regarded as a competing risk event.

3.2. Actual and conditional recurrence-free survival rate evaluation

During the follow-up period, 121 cases (73.7 %) experienced postoperative recurrence, resulting in a median RFS of 8.85 months. When considering competing risk events, the actual RFS rates at 6, 12, 18, 24, and 30 month after R0 hepatectomy were 58.5 %, 42.6 %, 34.3 %, 29.2 %, and 27.7 %, respectively (Table 1). Fig. 1A and B depict the actual and conditional RFS rate curves, respectively. The conditional RFS rate for each successive 6-months interval diplayed a gradual increase over time. Specifically, the 24-month RFS rate climbed up from 29.2 % to 49.9 %, 68.5 %, and 85.1 % given 6-, 12-, and 18-month already recurrence-free survival, respectively. They can be mathematical as CRFS (24/0), CRFS (18/6), CRFS (12/12), and CRFS (6/18). For patients who survived without a recurrence for 6, 12, 18, and 24 months after surgery, the probabilities of achieving an additional 6 recurrence-free survival months were 72.8 %, 80.5 %, 85.1 %, and 94.9 %, respectively (Table 1 and Fig. 1B). They can be calculated by the formula as CRFS (6/6), CRFS (6/12), CRFS (6/18), and CRFS (6/24), respectively.

3.3. Recurrence-free survival analysis

The results of the univariable COX regression and competing risk analyses are exhibited in Table 2. Multivariate COX regression analysis showed that tumor diameter (HR:1.872, 95%CI:1.256–2.792, P = 0.002), tumor number (HR:1.776, 95%CI:1.197–2.635, P = 0.004), lymph node metastasis (HR:1.65, 95%CI:1.052–2.588, P = 0.029), AISI (HR:1.594, 95%CI:1.081–2.348, P = 0.019), and ALBI (HR:1.754, 95%CI:1.184–2.598, P = 0.005) were significantly associated with poorer RFS among patients with locally advanced ICC (Table 3). After considering competing risk events, these factors remained statistically significant with the hazard ratio adjustment. In addition, multi-variable competing risk analysis figured out that preoperative CA19-9 levels significantly associated with recurrence-free survival (HR:1.505, 95%CI:1.03–2.2, P = 0.035, Table 3). The VIF value of each factor was below 5, indicating no severe collinearity issues. Besides, all significant variables satisfied the proportional hazards assumption.

Moreover, the conditional RFS rates of each 6 months increased over time for all prognostic factors after eliminating competing risk

Table 1
Conditional RFS rates for locally advanced ICC after R0 resection after removing competing risk events.

Already survival months	Total months of RFS after R0 resection				
	6 months	12 months	18 months	24 months	30 months
0 month	58.5 %	42.6 %	34.3 %	29.2 %	27.7 %
6 months		72.8 %	58.6 %	49.9 %	47.4 %
12 months			80.5 %	68.5 %	65 %
18 months				85.1 %	80.8 %
24 months					94.9 %

RFS, recurrence-free survival; ICC, intrahepatic cholangiocarcinoma.

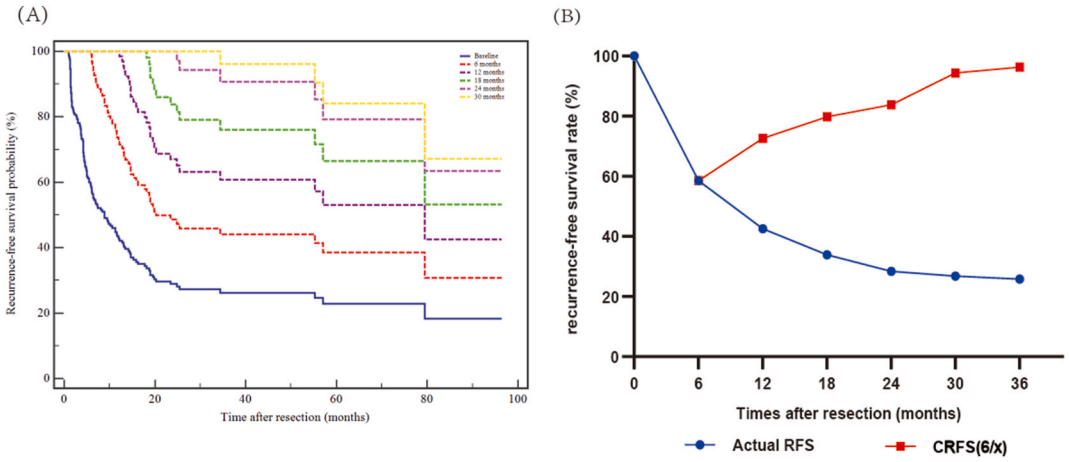

Fig. 1. Conditional recurrence-free survival analysis of locally advanced intrahepatic cholangiocarcinoma after R0 hepatectomy. A) Kaplan-Meier curves estimating real-time recurrence-free survival after recurrence-freely surviving for 0–30 months; B) CRFS(6/x) curve showing the probability of recurrence-free survival another 6 months after recurrence-freely surviving for x months after primary treatment.

events (Fig. 2A–F). For the inflammation variable, both the actual and conditional RFS rates were higher in the low AISI group compared to the high AISI group. For instance, the actual 24-month RFS rates for the low-AISI and high-AISI groups were 43.3 % and 14.9 %, respectively. Patients in the low-AISI group who had already survived without a recurrence for 6, 12, 18, and 24 months after initial treatment had probabilities of an additional 6 months of recurrence-free survival of 79.7 %, 90.5 %, 89.5 %, and 93.3 %, respectively, which were superior to those in the high-AISI group (63.4 %, 64 %, 73.4 %, and 73.4 %). A similar finding was observed in the low-ALBI and high-ALBI sets (Fig. 2F).

3.4. Survival analysis after recurrence of different recurrent patterns

During the follow-up period, a total of 121 cases recurred after R0 liver resection. Of these, 53 cases (43.8 %) had intrahepatic recurrence (IR), 38 (31.4 %) cases had extra-hepatic recurrence (ER), and 30 cases (24.8 %) presented with both intrahepatic and extra-hepatic recurrence (IR + ER). Kaplan-Meier curves showed that the IR + ER group has the poorest survival after recurrence (The median OS after recurrence: ER + IR group VS. ER groups VS. IR group: 4.37 months VS. 12.93months VS. 16.63 months, $P < 0.001$, Fig. 3A). Conditional OS rates after relapse (COSr) improved gradually over time (Fig. 3B–D). Specifically, the COSr (6/18) of the ER + IR group, ER group, and IR group were 74.6 %, 84.8 %, and 82.7 %, respectively.

Compared with the non-recurrence cohort, the recurrence cohort displayed a higher proportion of larger tumors, multiple lesions, lymph node metastasis, narrow surgical margin, and an elevated inflammatory status ($P < 0.05$, Table 4). Notably, 56.2 % and 57 % of the recurrence group had higher ALBI and MLR values, respectively, exceeding those of the non-recurrence group (27.9 % and 25.6 %). Although the recurrence set had a higher proportion of high AISI values, this difference did not reach statistical significance (54.5 % vs. 37.2 %, $P = 0.075$). Preoperative CA19-9 and NPS levels were elevated in patients with recurrence. However, in a subgroup analysis stratified by different recurrence patterns, only lymph node metastasis exhibited a statistically significant difference. ($P = 0.048$, Table 4).

4. Discussion

In this study, we conducted a dynamic evaluation of the recurrence risk for locally advanced ICC following R0 resection. After accounting for the confounding effect of death preceding recurrence, we observed a significant improvement in the 24-month RFS rate, rising from an initial 29.2 % to a remarkable 85.1 % when patients recurrence-freely survived for 18 months. The curves depicting the cumulative recurrence-free survival (CRFS) rates, specifically CRFS(6/x), exhibited a striking upward trajectory over time following surgery. Multi-variable COX regression analysis and competing risk analysis revealed that tumor size and number, lymph node metastasis, as well as preoperative AISI and ALBI levels, were significantly associated with RFS among locally late-stage ICC patients.

Nowadays, the most optimal treatment for ICC is surgical resection. Due to the poor prognoses of patients who are unsuitable for surgical treatment, some researchers and guidelines have attempted to expand the indications for surgery in locally advanced ICC [17, 24,25]. In comparison to palliative chemotherapy, hepatectomy was correlated to a more favorable long-term outcome for locally advanced ICC (3-year OS rate: 40.8 % VS. 5.5 %, $P = 0.007$) [7]. Unfortunately, even among those who can accept R0 resection, they cannot escape from the recurrence threat. It makes sense that adequate evaluation of prognostic factors may help reduce the disease's recurrence. Traditional prognostic analysis often ignores the impact of competing risk events and does not convey real-time survival information, especially for patients who have survived many years. Contrarily, CS analysis provides clinicians with a dynamic survival evaluation way that reflects real-time probabilities that change over time, while the competing risk analysis contributes to better

Table 2
The results of univariate analysis for RFS in locally advanced ICC after R0 resection.

Variables	Cox regression analysis		Competing risk analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age (years)				
≤ 65	Ref.	–	Ref.	–
>65	1.291 (0.824–2.022)	0.264	1.28 (0.842–1.94)	0.25
Gender				
Male	Ref.	–	Ref.	–
Female	0.729 (0.501–1.061)	0.098	0.74 (0.505–1.08)	0.12
Smoking				
No	Ref.	–	Ref.	–
Yes	1.154 (0.777–1.712)	0.478	1.19 (0.818–1.73)	0.36
Drinking				
No	Ref.	–	Ref.	–
Yes	1.502 (0.843–2.675)	0.168	1.42 (0.768–2.61)	0.27
Liver Cirrhosis				
No	Ref.	–	Ref.	–
Yes	1.22 (0.708–2.101)	0.474	1.24 (0.71–2.17)	0.45
Unknown	1.316 (0.756–2.289)	0.331	1.31 (0.735–2.34)	0.36
Tumor Diameter				
≤ 5 cm	Ref.	–	Ref.	–
>5 cm	2.292 (1.563–3.36)	**< 0.001**	2.27 (1.55–3.33)	**< 0.001**
Tumor number				
Single	Ref.	–	Ref.	–
Multiple	2.045 (1.409–2.969)	**< 0.001**	2.04 (1.4–2.96)	**< 0.001**
Grade				
Well/Moderately differentiated	Ref.	–	Ref.	–
Poorly differentiated/undifferentiated	1.322 (0.888–1.967)	0.169	1.32 (0.905–1.94)	0.15
MVI				
Absence	Ref.	–	Ref.	–
Presence	1.334 (0.899–1.979)	0.152	1.33 (0.884–1.99)	0.17
LNM				
Negative	Ref.	–	Ref.	–
Positive	2.856 (1.898–4.298)	**< 0.001**	2.78 (1.9–4.05)	**< 0.001**
liver capsule invasion				
No	Ref.	–	Ref.	–
Yes	0.655 (0.319–1.344)	0.248	0.665 (0.314–1.41)	0.29
Adjacent organ invasion				
No	Ref.	–	Ref.	–
Yes	1.659 (1.065–2.585)	**0.025**	1.56 (0.974–2.5)	0.064
Resection Scope				
Minor	Ref.	–	Ref.	–
Major	1.534 (1.067–2.204)	**0.021**	1.49 (1.04–2.14)	**0.029**
Surgical Margin (cm)				
≥ 1	Ref.	–	Ref.	–
0 - 1	1.453 (1.014–2.083)	**0.042**	1.46 (1.03–2.07)	**0.034**
AOT				
No	Ref.	–	Ref.	–
Yes	0.896 (0.619–1.298)	0.563	0.89 (0.622–1.27)	0.52
CEA				
Low	Ref.	–	Ref.	–
High	1.529 (1.068–2.191)	**0.021**	1.46 (1.02–2.08)	**0.038**
CA19-9				
Low	Ref.	–	Ref.	–
High	1.916 (1.332–2.757)	**< 0.001**	1.89 (1.32–2.7)	**< 0.001**
pCEA				
Low	Ref.	–	Ref.	–
High	1.497 (0.97–2.312)	0.069	1.5 (0.963–2.34)	0.073
Unknown	1.436 (0.894–2.305)	0.135	1.33 (0.806–2.18)	0.27
pCA19-9				
Low	Ref.	–	Ref.	–
High	2.354 (1.54–3.599)	**< 0.001**	2.35 (1.507–3.68)	**< 0.001**
Unknown	1.378 (0.843–2.252)	0.2	1.27 (0.754–2.15)	0.37
AISI				
Low	Ref.	–	Ref.	–
High	2.113 (1.463–3.051)	**< 0.001**	2.03 (1.42–2.91)	**< 0.001**
SIRI				
Low	Ref.	–	Ref.	–
High	0.848 (0.593–1.213)	0.367	0.85 (0.596–1.21)	0.37
MLR				

(*continued on next page*)

Table 2 (*continued*)

Variables	Cox regression analysis		Competing risk analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Low	Ref.	–	Ref.	–
High	1.794 (1.247–2.58)	**0.002**	1.78 (1.24–2.56)	**0.002**
PLR				
Low	Ref.	–	Ref.	–
High	1.332 (0.931–1.905)	0.117	1.32 (0.922–1.88)	0.13
NLR				
Low	Ref.	–	Ref.	–
High	1.333 (0.928–1.914)	0.12	1.31 (0.915–1.88)	0.14
GPR				
Low	Ref.	–	Ref.	–
High	1.505 (1.048–2.162)	**0.027**	1.42 (0.993–2.03)	0.055
ALBI				
Low	Ref.	–	Ref.	–
High	2.031 (1.411–2.923)	**< 0.001**	1.95 (1.37–2.79)	**< 0.001**
FIB-4				
Low	Ref.	–	Ref.	–
High	1.057 (0.739–1.511)	0.762	1.06 (0.743–1.51)	0.74
NPS				
≤ 1	Ref.	–	Ref.	–
>1	2.02 (1.396–2.924)	**< 0.001**	1.99 (1.37–2.88)	**< 0.001**
GNRI				
Low	Ref.	–	Ref.	–
High	0.868 (0.607–1.24)	0.435	0.889 (0.623–1.27)	0.51
CONUT				
≤ 1	Ref.	–	Ref.	–
>1	1.387 (0.933–2.062)	0.105	1.36 (0.911–2.03)	0.13

RFS, recurrence-free survival; ICC, intrahepatic cholangiocarcinoma; MVI, microvascular invasion; LNM, lymph node metastasis; AOT, Adjuvant postoperative therapy; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; pCEA, postoperative CEA; pCA19-9, postoperative CA19-9; AISI, aggregate systemic inflammation index; SIRI, systemic inflammation response index; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; GPR, gamma-glutamyl-transpeptidase to platelet ratio; ALBI, albumin- bilirubin score; FIB-4, four-factor-based fibrosis index; NPS, Naples prognostic score; GNRI, Geriatric nutritional risk index; CONUT, controlling nutritional status score

Table 3
The results of multivariate analysis of RFS for locally advanced ICC after R0 resection.

Variables	Cox regression analysis		Competing risk analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Tumor Diameter				
≤ 5 cm	Ref.	–	Ref.	–
>5 cm	1.872 (1.256–2.792)	**0.002**	1.98 (1.229–3.19)	**0.005**
Tumor number				
Single	Ref.	–	Ref.	–
Multiple	1.776 (1.197–2.635)	**0.004**	1.906 (1.291–2.81)	**0.001**
LNM				
Negative	Ref.	–	Ref.	–
Positive	1.65 (1.052–2.588)	**0.029**	1.749 (1.12–2.73)	**0.014**
CA19-9				
Low	–	–	Ref.	–
High	–	–	1.505 (1.03–2.2)	**0.035**
AISI				
Low	Ref.	–	Ref.	–
High	1.594 (1.081–2.348)	**0.019**	1.677 (1.083–2.6)	**0.021**
ALBI				
Low	Ref.	–	Ref.	–
High	1.754 (1.184–2.598)	**0.005**	1.643 (1.108–2.44)	**0.013**

RFS, recurrence-free survival; ICC, intrahepatic cholangiocarcinoma; CI, confidence interval; LNM, lymph node metastasis; CI, confidence interval; AISI, aggregate systemic inflammation index; ALBI, albumin-bilirubin score.

validating the accuracy of the conclusions from COX regression analysis [26,27]. Thus, by combining CS analysis with competing risk method, we could more precisely predict the recurrence risk for locally advanced ICC. In the present study, conditional RFS rates after initial treatment for locally advanced ICC significantly increased with time. For example, the actual RFS rate of 36 months was 25.8 % after considering competing risk events, however, the real-time rate of recurrence-freely surviving to 36 months was increased to 60.1 % after 12 months of relapse-free survival. CRFS appears to provide inspiring prognostic information and may help reduce the

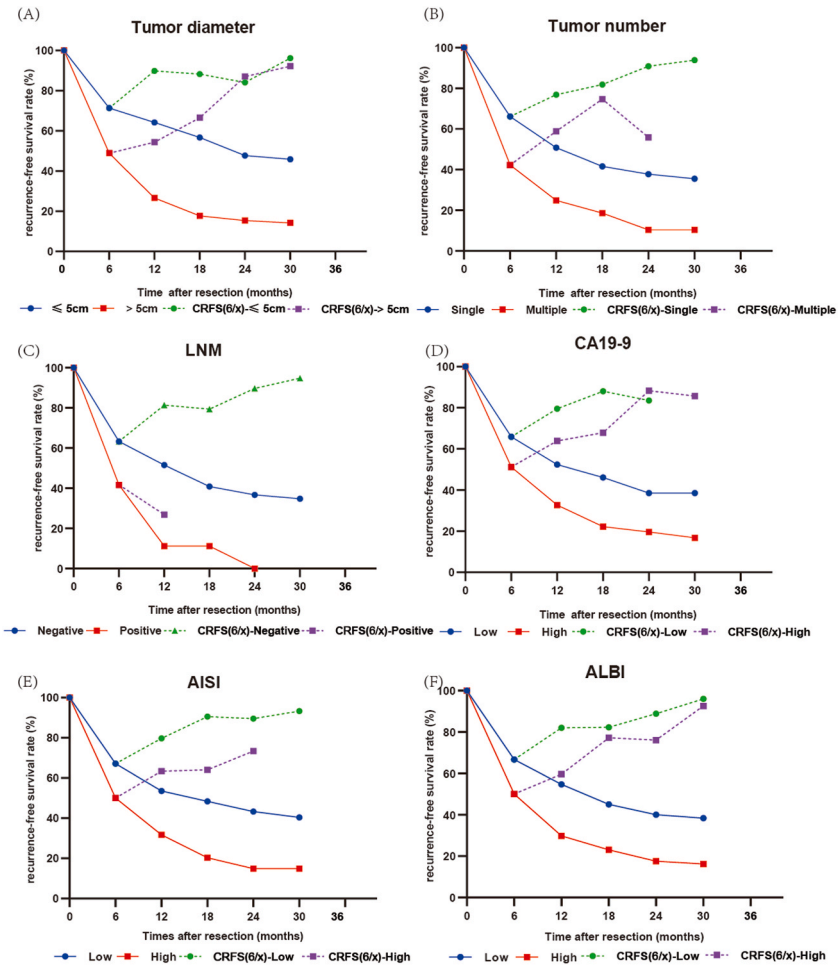

Fig. 2. Kaplan-Meier curves to evaluate the recurrence-free survival of locally advanced intrahepatic cholangiocarcinoma after R0 resection stratified by variables from multivariate analysis. Plots of Kaplan–Meier survival curves for tumor diameter (A), tumor number (B), lymph node metastasis (C), CA19-9 (D), AISI (E), and ALBI (F).

psychological stress in ICC patients and enhance their compliance with medical follow-up.

According to the results of multi-factor analyses, large tumor (>5 cm), multiple lesions, and lymph node metastasis were hazardous factors for ICC recurrence. After reducing the bias caused by competing risk events, the above tumor-related variables were closely related to postoperative RFS rate, along with increased HR values. All the above variables have been reported to be detrimental to RFS in patients with ICC [28–30]. However, surgery-related variables including resection scope and surgical margin width did not increase significantly recurrence risk after multivariate analysis. Whether surgical margin width has prognostic ability remains controversial. A retrospective study reported no significant influence of surgical margin width on recurrence risk for ICC [31]. Jiang et al. performed a meta-analysis to explore the clinical value of surgical margin width on prognosis of ICC after resection [32]. Although their conclusions supported the notion that narrow surgical margins were detrimental to RFS, their study noted heterogeneity between groups, and they did not assess bias caused by other variables such as tumor diameter, number, and stage in subgroup analysis. The question about the association between surgical margin width and recurrence risk requires further discussion.

In recent years, the topic of the role of chronic inflammation in carcinogenesis and malignant progression has aroused great interest among scientific researchers. Both systemic and local inflammation can remodel the composition of the tumor microenvironment to favor a more tumor-permissive condition [33]. Regrettably, the regulatory mechanisms are intricate and remain unclear. However, the question of how to evaluate the inflammation status in a cost-effective, convenient, and accessible deserves attention. To date, several serum-based inflammatory markers have been developed for preoperatively and postoperatively assessing the prognosis of malignancies [34–37]. The AISI index, also known as the pan-immune- inflammation value, is calculated based on counts of four types of peripheral blood cells: neutrophil, monocyte, platelet, and lymphocyte. All participating immune cells can secrete a series of pro-inflammatory compounds such as chemokines, cytokines, metabolites, etc., which exert huge impacts on the host's immune defense and safeguard the host against benign and malignant diseases[33,38–40]. For instance, platelets can release adenine nucleotides to activate P2YE receptors to strengthen the migration and extravasation capabilities of tumor cells, which would promote tumor

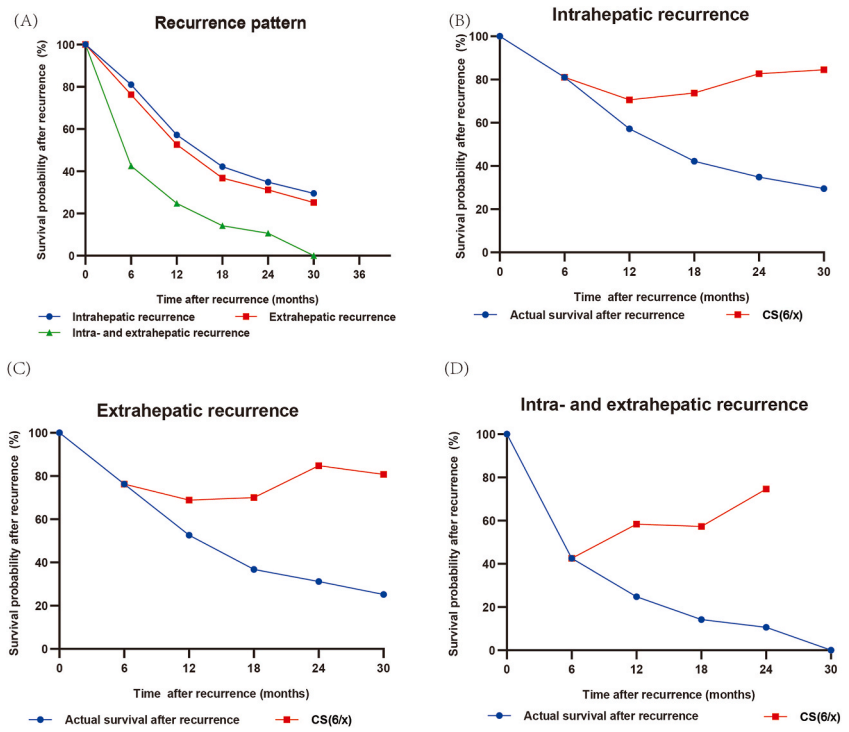

Fig. 3. Conditional survival analysis after recurrence of locally advanced intrahepatic cholangiocarcinoma after R0 hepatectomy. A) Kaplan-Meier curves estimating survival after recurrence stratified by different recurrent patterns. CRFS(6/x) curve of intrahepatic recurrence (B), extrahepatic recurrence (C), and intra- and extrahepatic recurrence (D) showing the probability of survival another 6 months after survival for x months after recurrence.

progression and metastasis [40]. In addition, lymphocytes and neutrophils can interact with T cells or other immune cells in the TME to reshape anti-tumor immune surveillance. ALBI, first proposed by Jonhson et al. is a nutritional index combining albumin and bilirubin to evaluate liver function [41]. Low ALBI level indicates better nutritional status and is significantly associated with improved prognosis in multiple cancers [42–44]. A person's nutritional status has been shown to be partially related to immune function [45]. Malnutrition suppresses anti-tumor immune surveillance and response, thereby accelerating tumor initiation and progression. To the best of our knowledge, there is no literature reporting the associations between AISI and ALBI, and RFS and CRFS in locally advanced ICC. In multivariate COX regression and competing risk analyses, higher AISI or ALBI values were associated with higher HR values than the reference values. The actual RFS rates of the high-value group were worse in both the AISI group and the ALBI group. For the AISI variable, the CRFS curve of an additional 6 months in the low-value group gradually climbed over time and was higher than that of in high-value group throughout. But for the ALBI factor, even though the CRFS curves rose with time between groups, the CRFS rates of a more 6-month RFS after already recurrence-freely surviving 24 months [CRFS(6/24)] were similar (96 % VS. 92.6 %). The main reason for this phenomenon was the specific statistical algorithms of conditional analysis [$CRFS(y/x) = RFS(y + x)/RFS(x)$]. Additionally, we hypothesized that the administration of postoperative adjuvant therapy, the pathological characteristics of primary tumor lesions, alterations in inflammation and nutritional levels during recovery following initial treatment, as well as patients' spiritual confidence collectively contributed to an incremental conditional recurrence-free probability over time for individuals who had endured a prolonged period without recurrence.

The investigation of systemic inflammation-nutritional indicators as therapeutic predictors for cancer patients has been fostered by the opinion that tumor acceleration could be caused by inflammatory immune cells and malnutrition conditions. A recently published meta-analysis revealed that regorafenib treatment was more suitable for cancer patients with low ALBI grades. After receiving regorafenib treatment, patients with low ALBI scores exhibited an approximately three times higher disease control rate compared to those with high ALBI scores [46]. Similarly, Liu et al. found that ALBI could predict tumor response in HCC patients undergoing transarterial chemoembolization [47]. Although there have been few studies on the correlation between AISI and therapeutic effect, several circulating blood biomarkers, including low neutrophil count, low monocyte count, and high lymphocyte count have been identified as predictors of immune checkpoint inhibitor response in various malignancies [48]. However, it remains unclear whether circulating blood biomarkers can contribute to evaluating the therapeutic effect of anti-cancer treatments. Therefore, a large-scale prospective study should be conducted to assess the practical application value of inflammation-nutritional indices in predicting tumor response. These findings would aid in making individualized medical choices and improving long-term outcomes for ICC patients. Given the potential predictive value of ALBI and AISI, we strongly recommend strict follow-up strategies for locally advanced ICC patients after R0 resection if they exhibit high ALBI and AISI values before treatment.

Table 4
Basic clinicopathological characteristics in different recurrence patterns.

Variables (%)	NR (n = 43)	R (n = 121)	*P*-value	R (n = 121)			
				IR (n = 53)	ER (n = 38)	IR + ER (n = 30)	*P*-value
Age (years)			0.255				0.549
≤ 65	38 (88.4)	97 (80.2)		44 (83)	31 (81.6)	22 (73.3)	
> 65	5 (11.6)	24 (19.8)		9 (17)	7 (18.4)	8 (26.7)	
Gender			**0.045**				0.817
Male	20 (46.5)	79 (65.3)		36 (67.9)	23 (60.5)	20 (66.7)	
Female	23 (53.5)	42 (34.7)		17 (32.1)	15 (39.5)	10 (33.3)	
Smoking			0.228				0.133
No	35 (81.4)	86 (71.1)		40 (75.5)	29 (76.3)	17 (56.7)	
Yes	8 (18.6)	35 (28.9)		13 (24.5)	9 (23.7)	13 (43.3)	
Drinking			0.565				0.324
No	40 (93)	108 (89.3)		45 (84.9)	36 (94.7)	27 (90)	
Yes	3 (7)	13 (10.7)		8 (15.1)	2 (5.3)	3 (10)	
Liver Cirrhosis			0.352				0.992
No	10 (23.3)	17 (14)		7 (13.2)	6 (15.8)	4 (13.3)	
Yes	19 (44.2)	56 (46.3)		24 (45.3)	18 (47.4)	14 (46.7)	
Unknown	14 (32.5)	48 (39.7)		22 (41.5)	14 (36.8)	12 (40)	
Tumor Diameter			**< 0.001**				0.383
≤ 5 cm	29 (67.4)	41 (33.9)		17 (32.1)	16 (42.1)	8 (26.7)	
> 5 cm	14 (32.6)	80 (66.1)		36 (67.9)	22 (57.9)	22 (73.3)	
Tumor number			**0.004**				0.363
Single	37 (86)	75 (62)		30 (56.6)	27 (71.1)	18 (60)	
Multiple	6 (14)	46 (38)		23 (43.4)	11 (28.9)	12 (40)	
Grade			0.335				0.057
Well/Moderately differentiated	16 (37.2)	34 (28.1)		20 (37.7)	10 (26.3)	4 (13.3)	
Poorly differentiated/undifferentiated	27 (62.8)	87 (71.9)		33 (62.3)	28 (73.7)	26 (86.7)	
MVI			0.554				0.364
Absence	33 (76.7)	86 (71.1)		41 (77.4)	26 (68.4)	19 (63.3)	
Presence	10 (23.3)	35 (28.9)		12 (22.6)	12 (31.6)	11 (36.7)	
LNM			**0.001**				**0.048**
Negative	41 (95.3)	87 (71.9)		44 (83)	23 (60.5)	20 (66.7)	
Positive	2 (4.7)	34 (28.1)		9 (17)	15 (39.5)	10 (33.3)	
liver capsule invasion			1				0.223
No	2 (4.7)	8 (6.6)		2 (3.8)	2 (5.3)	4 (13.3)	
Yes	41 (95.3)	113 (93.4)		51 (96.2)	36 (94.7)	26 (86.7)	
Adjacent organ invasion			0.252				0.079
No	38 (88.4)	96 (79.3)		47 (88.7)	27 (71.1)	22 (73.3)	
Yes	5 (11.6)	25 (20.7)		6 (11.3)	11 (28.9)	8 (26.7)	
Resection Scope			0.076				0.395
Minor	26 (60.5)	53 (43.8)		23 (43.4)	14 (36.8)	16 (53.3)	
Major	17 (39.5)	68 (56.2)		30 (56.6)	24 (63.2)	14 (46.7)	
Surgical Margin (cm)			**0.031**				0.506
≥ 1	32 (74.4)	67 (55.4)		30 (56.6)	23 (60.5)	14 (46.7)	
0 - 1	11 (25.6)	54 (44.6)		23 (43.4)	15 (39.5)	16 (53.3)	
AOT			0.855				0.075
No	26 (60.5)	76 (62.8)		34 (64.2)	19 (50)	23 (76.7)	
Yes	17 (39.5)	45 (37.2)		19 (35.8)	19 (50)	7 (23.3)	
CEA			0.157				0.096
Low	26 (60.5)	57 (47.1)		28 (52.8)	20 (52.6)	9 (30)	
High	17 (39.5)	64 (52.9)		25 (47.2)	18 (47.4)	21 (70)	
CA19-9			**0.001**				0.058
Low	31 (72.1)	51 (42.1)		19 (35.8)	22 (57.9)	10 (33.3)	
High	12 (27.9)	70 (57.9)		34 (64.2)	16 (42.1)	20 (66.7)	
pCEA			0.459				0.827
Low	29 (67.4)	69 (57)		33 (62.3)	20 (52.6)	16 (53.3)	
High	7 (16.3)	29 (24)		11 (20.8)	11 (28.9)	7 (23.3)	
Unknown	7 (16.3)	23 (19)		9 (17)	7 (18.4)	7 (23.3)	
pCA19-9			0.061				0.722
Low	31 (72.1)	68 (56.2)		30 (56.6)	24 (63.2)	14 (46.7)	
High	4 (9.3)	32 (26.4)		14 (26.4)	9 (23.7)	9 (30)	
Unknown	8 (18.6)	21 (17.4)		9 (17)	5 (13.1)	7 (23.3)	
AISI			0.075				0.946
Low	27 (62.8)	55 (45.5)		24 (45.3)	18 (47.4)	13 (43.3)	
High	16 (37.2)	66 (54.5)		29 (54.7)	20 (52.6)	17 (56.7)	
SIRI			0.376				0.881
Low	19 (44.2)	64 (52.9)		27 (50.9)	20 (52.6)	17 (56.7)	
High	24 (55.8)	57 (47.1)		26 (49.1)	18 (47.4)	13 (43.3)	
MLR			**0.001**				0.795

(*continued on next page*)

Table 4 (*continued*)

Variables (%)	NR (n = 43)	R (n = 121)	*P*-value	R (n = 121)			
				IR (n = 53)	ER (n = 38)	IR + ER (n = 30)	*P*-value
Low	32 (74.4)	52 (43)		21 (39.6)	17 (44.7)	14 (46.7)	
High	11 (25.6)	69 (57)		32 (60.4)	21 (55.3)	16 (53.3)	
PLR			0.478				0.89
Low	24 (55.8)	58 (47.9)		26 (49.1)	17 (44.7)	15 (50)	
High	19 (44.2)	63 (52.1)		27 (50.9)	21 (55.3)	15 (50)	
NLR			0.111				0.53
Low	26 (60.5)	55 (45.5)		26 (49.1)	18 (47.4)	11 (36.7)	
High	17 (39.5)	66 (54.5)		27 (50.9)	20 (52.6)	19 (63.3)	
GPR			0.076				0.389
Low	27 (62.8)	56 (46.3)		23 (43.4)	21 (55.3)	12 (40)	
High	16 (37.2)	65 (53.7)		30 (56.6)	17 (44.7)	18 (60)	
ALBI			**0.002**				0.013
Low	31 (72.1)	53 (43.8)		30 (56.6)	16 (42.1)	7 (23.3)	
High	12 (27.9)	68 (56.2)		23 (43.4)	22 (57.9)	23 (76.7)	
FIB-4			0.478				0.358
Low	24 (55.8)	58 (47.9)		27 (50.9)	20 (52.6)	11 (36.7)	
High	19 (44.2)	63 (52.1)		26 (49.1)	18 (47.4)	19 (63.3)	
NPS			**< 0.001**				0.639
≤ 1	31 (72.1)	49 (40.5)		24 (45.3)	14 (36.8)	11 (36.7)	
> 1	12 (27.9)	72 (59.5)		29 (54.7)	24 (63.2)	19 (63.3)	
GNRI			1				0.153
Low	21 (48.8)	60 (49.6)		21 (39.6)	22 (57.9)	17 (56.7)	
High	22 (51.2)	61 (50.4)		32 (60.4)	16 (42.1)	13 (43.3)	
CONUT			0.554				0.098
≤ 1	33 (76.7)	86 (71.1)		43 (81.1)	24 (63.2)	19 (63.3)	
> 1	10 (23.3)	35 (28.9)		10 (18.9)	14 (36.8)	11 (36.7)	

NR, no recurrence; R, recurrence; IR, intrahepatic recurrence; ER, extrahepatic recurrence; MVI, microvascular invasion; LNM, lymph node metastasis; AOT, Adjuvant postoperative therapy; CEA, carcino-embryonic antigen; CA19-9, carbohydrate antigen 19–9; pCEA, postoperative CEA; pCA19-9, postoperative CA19-9; AISI, aggregate systemici nflammation index; SIRI, systemic inflammation response index; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; GPR, gamma-glutamyl-transpeptidase to platelet ratio; ALBI, albumin-bilirubin score; FIB-4, four-factor-based fibrosis index; NPS, Naples prognostic score; GNRI, Geriatric nutritional risk index; CONUT, controlling nutritional status score.

Importantly, even after curative surgery, recurrence rates in patients with ICC remain high, with a 3-year RFS rate below 30 %. In our study, the 30-month RFS rate of locally advanced ICC after R0 resection was 27.7 %. To improve the poor prognosis, an increasing number of studies have been employed to evaluate the clinical value of AOT [49–51]. Adjuvant therapy has been evaluated for many years due to the high recurrence rates of ICC. Regrettably, the prognostic benefit of AOT for ICC after resection remains controversial, and a standard chemotherapy regimen is lacking [52]. Recently, Edeline and his colleagues conducted a multicenter, randomized phase III trial to evaluate the prognostic benefit of postoperative gemcitabine and oxaliplatin chemotherapy in resected biliary tract cancer [42]. They did not observe any survival and recurrence differences between the two groups. Similarly, in a retrospective study from Japan, no significant difference was observed in RFS among ICC patients who underwent AOT and those who did not [53]. In our study, multivariate analysis results showed no difference in RFS between AOT patients and non-AOT patients, regardless of whether the impact of competing risk events was taken into account. In contrast, results obtained from 412 ICC cases who accepted curative surgery at 12 medical centers revealed that postoperative chemotherapy was related to better disease-free survival [54]. Given this discrepancy, more randomized trials should be performed to provide high-quality evidence to help evaluate the true prognostic benefit derived from AOT.

Different recurrence patterns have distinct prognostic differences. In comparison to mono-intrahepatic or mono-extrahepatic recurrence, patients with intrahepatic and extra-hepatic recurrence have the worst post-recurrence survival (median OS:4.37 months, $P < 0.001$). The most common sites of extrahepatic recurrence included lung, bone, peritoneum, and lymph nodes in this study. After being diagnosed with recurrence, most patients received palliative chemotherapy. Alternative strategies included S-1, ablation, targeted therapy, and interventional treatment. Unfortunately, due to the limited number of cases, we did not compare the difference in survival after disease progression between different treatment regimens.

There are several limitations existing in this study. Firstly, this was a retrospective study conducted at a single medical institution. Further multi-center and prospective studies to re-assess the accuracy of our conclusions are requisite. Secondly, we excluded locally advanced ICC patients with R1 resection. In future studies, the prognostic impact of positive margins on locally advanced ICC should be comprehensively evaluated. Thirdly, we did not discuss the influence of neoadjuvant treatment on RFS. Whether neoadjuvant therapy is beneficial for locally advanced ICC patients requires further studies. Limited by the number of included cases, we did not further discuss the impact of covariate interactions on the recurrence of locally advanced ICC. Further large-scale multi-center studies should be done to evaluate interaction in the future.

5. Conclusions

In summary, CRFS analysis provided a significantly different perspective for real-time prognostic evaluation of locally advanced ICC patients undergoing R0 hepatectomy when compared with conventional survival estimations. Specifically, the CRFS rate gradually climbed up with the prolongation of postoperative recurrence-free survival time, which contributed to tailoring follow-up strategies to reduce the psychological burden of survivors. In addition, we figured out that a higher inflammatory condition or a malnutritional status disfavorably affected RFS.

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Ethical approval statement

This retrospective study was approved by the local Ethics Committee (ID:B2022-492-01). The need for informed consent was waived due to the nature of the retrospective study, and we conducted a necessarily anonymized process for all included patient data.

Data availability statement

Data are requestable from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Guizhong Huang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Pu Xi:** Writing – review & editing, Writing – original draft, Validation, Project administration, Investigation, Formal analysis, Conceptualization. **Zehui Yao:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Conceptualization. **Chongyu Zhao:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Xiaohui Li:** Writing – review & editing, Writing – original draft. **Xiaojun Lin:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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