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Original Article

Preoperative neutrophil-to-lymphocyte ratio is prognostic for early recurrence after curative intrahepatic cholangiocarcinoma resection

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Backgrounds/Aims: Within two years of surgery, 70% of resected intrahepatic cholangiocarcinoma (iCCA) recur. Better biomarkers are needed to identify those at risk of "early recurrence" (ER). In this study, we defined ER and investigated whether preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic-inflammatory index were prognostic of both overall relapse and ER after curative hepatectomy for iCCA.

Methods: A retrospective cohort of patients who underwent curative-intent hepatectomy for iCCA between 2005 and 2017 were created. The cut-off timepoint for the ER of iCCA was estimated using a piecewise linear regression model. Univariable analyses of recurrence were conducted for the overall, early, and late recurrence periods. For the early and late recurrence periods, multivariable Cox regression with time-varying regression coefficient analysis was used.

Results: A total of 113 patients were included in this study. ER was defined as recurrence within 12 months of a curative resection. Among the included patients, 38.1% experienced ER. In the univariable model, a higher preoperative NLR (> 4.3) was significantly associated with an increased risk of recurrence overall and in the first 12 months after curative surgery. In the multivariable model, a higher NLR was associated with a higher recurrence rate overall and in the ER period (≤ 12 months), but not in the late recurrence period.

Conclusions: Preoperative NLR was prognostic of both overall recurrence and ER after curative iCCA resection. NLR is easily obtained before and after surgery and should be integrated into ER prediction tools to guide preoperative treatments and intensify postoperative follow-up.

Key Words: Cholangiocarcinoma; Hepatectomy; Recurrence; Liver

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INTRODUCTION

The incidence of intrahepatic cholangiocarcinoma (iCCA) appears to be increasing worldwide [1-6]. However, the 5-year overall survival rate is as low as 10%, and this dismal survival rate is partly explained by the 70% recurrence rate of iCCA after curative-intent surgery [7-10]. In fact, most recurrences occur relatively early, with 25% occurring within six months and approximately 50% within two years after surgery [11].

The present research addresses the fact that early recurrence (ER) can happen anywhere from 12 to 24 months after curative-intent surgery for iCCA [12-14]. There is a need to better identify patients at high risk for ER who might benefit from additional treatment strategies such as neoadjuvant chemotherapy or intensified postoperative follow-up [11,15]. Several observational studies have identified risk factors for ER after iCCA resection, such as older age, race, cirrhosis, larger tumor size on imaging, high CA19-9, hepatitis B, a high number of tumor lesions, and suspicious lymph nodes [11-14]. Preoperative neutrophil-to-lymphocyte ratio (NLR) is associated with ER in hepatocellular carcinoma (HCC) and hilar cholangiocarcinoma, but this has not been studied in the context of iCCA ER [16,17]. Systemic inflammatory biomarkers such as NLR, platelet-to-lymphocyte ratio (PLR), and the systemic-inflammatory index (SII) are theorized to enhance the tumor growth environment, lymph node metastasis, and subsequently, disease recurrence [18]. In support of this theory, NLR and SII have been shown to be associated with worse recurrence-free survival (RFS) after iCCA resection, with the endpoint being death or recurrence [19-26]. However, whether these systemic inflammatory biomarkers are prognostic of recurrence in the ER period is unknown. Detection of systemic inflammatory biomarkers has several advantages, as it is inexpensive, non-invasive, and readily available before surgery to be incorporated into iCCA recurrence risk stratification tools [27-33].

Therefore, we aimed to identify patients with high iCCA ER risk by considering systemic inflammatory biomarkers before surgery, as this may determine the need for additional treatments such as neoadjuvant chemotherapy, which is the subject of great debate [8]. The objectives of this study were to (1) Define the optimal cut-off timepoint for early vs. late recurrence after curative iCCA resection; (2) Determine if preoperative NLR, PLR, and/or SII are associated with ER after curative iCCA resection.

MATERIALS AND METHODS

Study design and population

A retrospective, observational cohort study was conducted in a large tertiary academic hospital, University Health Network (UHN), Toronto, Ontario, Canada. All patients aged 18 years and older who underwent elective surgery with a histological diagnosis of iCCA between October 2005 and October 2017 were identified. The electronic patient record system of UHN was used to collect all data. The last date of follow-up was in March 2019, allowing up to 1.5 years of follow-up from the latest surgery date. Patients histologically diagnosed with hilar cholangiocarcinoma, distal cholangiocarcinoma, or HCC were excluded. Patients who received neoadjuvant chemotherapy, had an R1 positive margin status at final pathology, were infected, had ongoing steroid use, or had chronic hematological disease were excluded from the study. Patients with stage R1 were excluded because this study aimed to study recurrence in patients who underwent curative resection. Postoperatively, the clinic follow-up was scheduled with computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis, every 3 months for the first two years, followed by every 6 months for an additional 2 years and annual clinic visits thereafter. The UHN Research Ethics Board approved the study protocol (approval no. 18-5233).

Outcome

The primary outcome was ER of the iCCA. Both loco-regional and distant recurrence of iCCA were coded as recurrence. The date of recurrence was quantified in the following order of priority: (1) date of biopsy confirming recurrence (2) date of radiologic imaging (ultrasound, CT, MRI) when a recurring lesion was found (3) the date of clinical notes reporting recurrence. The time-to-recurrence was calculated by the number of days between the date of surgery and the date of recurrence. The ER time point was derived from this cohort.

Independent factors

The association between preoperative NLR, PLR, and SII with iCCA recurrence was examined in both continuous and categorical classifications. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. SII was calculated by multiplying the absolute neutrophil count by the platelet count and dividing by the absolute lymphocyte count. Absolute neutrophil, platelet, and lymphocyte counts were collected from a complete blood count (CBC). If multiple CBC levels were measured, the preoperative CBC measured closest to the time of surgery was used. Subjects without a CBC measurement within six months of surgery were excluded.

Covariates

Based on clinical significance and the literature review, the following covariates were chosen: age (continuous), sex (binary), carbohydrate antigen 19-9 (CA19-9, continuous) at diagnosis, major (3 or more segments) vs. minor hepatectomy, number of tumors based on preoperative imaging, largest tumor diameter based on preoperative imaging (continuous), and receipt of adjuvant systemic chemotherapy (binary). The following covariates were measured from the final surgical pathology report: cirrhosis (binary), largest tumor diameter in centimeters (continuous), number of tumors (continuous), microvascular invasion (binary), macrovascular invasion (binary), tumor differentiation (well, moderate, poor differentiation), tumor growth pattern (intraductal, periductal-infiltrating, mass-forming, and mixed types) and N stage (N0, N1, Nx).

Statistical analysis

To estimate the cut-off time point for separating early and

late recurrence of iCCA, we constructed a piecewise linear regression model from the overall time-to-recurrence plot using the R 'segmented' package version 1.3-4. The intersection of these two fitted linear regression lines was used as an estimate for ER. A landmark analysis was performed at this chosen 12-month time interval, dividing the univariable analysis to estimate early and late recurrence risks. For the first landmark period (≤ 12 months) or ER analysis, time zero was set as the date of surgery, and patients were censored at the date of death, when they were lost to follow-up, or at 12 months if the patient was alive with no recurrence. For the second landmark period (> 12 months) or late recurrence analysis, time zero was set at 12 months, and the remainder of patients were censored on the date of death and lost to follow-up. A univariable Cox regression model was used and reported as hazard ratios (HRs) with 95% confidence intervals (CIs). To create the multivariable model, covariates with p values of less than 0.20 were kept until there were no more degrees of freedom. Multivariable Cox regression analysis was conducted for all-time recurrence. NLR was defined using two time-varying regression coefficients or regression parameters to estimate the effect of NLR before and after 12 months (landmark time) for violating the proportional hazards assumption. NLR, PLR, and SII were also classified as binary variables (high vs. low) based on the cut-off selected using maximally selected rank statistics by the 'maxstat' R package [34,35]. Statistical significance was thus defined as a probability of 0.05 α, and two-sided tests were conducted throughout. Only one variable, CA19-9, had a value greater than 20% (61.1% were missing due to chart review restrictions). CA19-9 was excluded from the primary analysis due to a large amount of missing data. Sensitivity analyses were performed, including patients with CA19-9 values, and incorporating NLR as a continuous variable. All analyses were performed using the IBM SPSS Statistics software v27 and R version 4.0.5 [36].

Table 1. Patient characteristics

Variable	All patients (n = 113)
Age (yr)	63.2 (55.1–72.7)
Sex	
Male	66 (58.4)
Female	47 (41.6)
Cirrhosis	15 (13.3)
NLR	2.6 (1.9–3.8)
PLR	136.0 (101.5–167.5)
SII	586.0 (380.7–810.0)
CA19-9 at diagnosis (U/mL)	27.0 (13.0–54.0)
Operation type	
Major Hepatectomy	97 (85.8)
Minor Hepatectomy	16 (14.2)
Tumor size on imaging (cm)	5.0 (3.7–7.0)
Tumor size on pathology (cm)	5.6 (4.0–7.3)
Number of tumors on imaging	1.3 ± 0.8
Number of tumors on pathology	1.3 ± 0.8
Tumor differentiation	
Well	24 (21.2)
Moderate	55 (48.7)
Poor	31 (27.4)
Tumor growth pattern	
Intraductal	6 (5.3)
Periductal infiltrating	9 (8.0)
Mass forming	96 (85.0)
Mixed type	2 (1.8)
Microvascular invasion	54 (47.8)
Macrovascular invasion	44 (38.9)
N stage on pathology	
N0	37 (32.7)
N1	13 (11.5)
Nx	63 (55.8)
Adjuvant systemic therapy	26 (23.0)

Values are presented as median (interquartile range), number (%), or mean ± standard deviation.
CA19-9, carbohydrate antigen 19-9; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic inflammatory index.

RESULTS

Study population

A total of 129 charts were reviewed. Patients with neoadjuvant chemotherapy (n = 7), R1 margin status (n = 7) and hematological disease (n = 2) were excluded. After exclusions, 113 patients were included in the final cohort, and the patient characteristics are presented in Table 1. The median age was 63.2 years (IQR 55.1–72.7 years). Sixty-six (58.4%) patients were male, and 15 (13.3%) patients had cirrhosis. The median tumor size on the most recent preoperative imaging was 5.0 cm (IQR

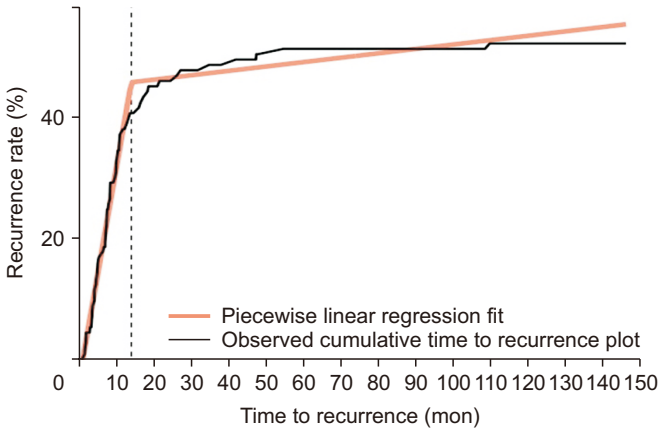

Fig. 1. Piecewise linear regression model to estimate the cut-off time point for differentiating early versus late recurrence of iCCA. Each line's function was y = 3.52x – 3.45 and y = 0.073x + 44.8, with an intersect at x = 14 months. This cut-off was rounded to 12 months to match those published in the literature.

3.7–7.0 cm). Twenty-six (23.0%) subjects received adjuvant systemic chemotherapy. Sixty-one percent of CA19-9 values were missing due to chart review restrictions of any measures outside our institution. The median follow-up after surgery was 2.03 years (IQR 0.95–4.91 years).

Recurrence outcome

The overall recurrence rate was 52.2% (59 patients), and the median time-to-recurrence was 18.6 months. The optimal cut-off time point for differentiating early and late recurrence after resection was estimated to be 12 months (y = 3.52x – 3.45 and y = 0.073x + 44.8, x = 14 months, rounded to 12 months cut-off to match the published literature, Fig. 1). Forty-three (38.1%) patients experienced ER, and 16 (14.2%) patients experienced late (> 12 months) recurrence. The absolute recurrence rate measured five years after surgery was 51.3%. Among those who relapsed during ER, liver-only relapse occurred in 13 patients (30.2%).

Early vs. late recurrence analysis

The results of the univariable analyses are summarized in Table 2. The high vs. low NLR, PLR, and SII cut-off values were estimated as 4.3, 80.0, 795.0, respectively. High preoperative NLR (> 4.3) was significantly associated with an increased risk of recurrence in both the overall and first 12 months after curative surgery (HR 3.04 [95% CI 1.46–6.34]; p = 0.003) and (HR 3.42 [95% CI 1.61–7.23]; p = 0.001), respectively. High preoperative PLR (> 80) was only associated with an increased risk of recurrence overall but not in the early or late recurrence period. High preoperative SII was not associated with the increased risk of recurrence in any time periods. Sex, underlying cirrhosis, tumor size on imaging, microvascular invasion, poor tumor differentiation on pathology, and pathological N1 stage were significantly associated with ER. The number of tumors on pathology (HR 2.35 [95% CI 1.35–4.09]; p = 0.002) and microvascular invasion (HR 6.94 [95% CI 2.23–21.63]; p = 0.001] were significantly associated with late recurrence. The tumor size on pathology and the number of tumors on imaging were removed (HRs closer to 1) due to collinearity with the tumor size on imaging and the number of tumors on pathology, respectively.

Multivariable Cox regression was conducted on all time-recurrence outcomes (Table 3). Effect estimates of preoperative NLR during the ER and late recurrence periods were adjusted

Table 2. Univariable Cox regression with the overall and landmark method analysis of factors associated with early (≤ 12 month) vs. late (> 12 month) iCCA recurrence

Variable	Overall recurrence period		Early recurrence period		Late recurrence period	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (per unit increase) (yr)	1.01 (0.97–1.01)	0.44	1.00 (0.97–1.02)	0.87	0.97 (0.93–1.02)	0.20
Sex (ref.: male)	1.69 (0.98–2.90)	0.06	2.08 (1.07–4.07)	0.03	1.03 (0.39–2.76)	0.95
Cirrhosis (ref.: no)	2.53 (1.29–4.97)	0.01	2.65 (1.30–5.44)	0.01	1.75 (0.23–13.97)	0.58
Major hepatectomy (ref.: no)	2.47 (0.98–6.2)	0.06	2.10 (0.75–5.87)	0.16	3.98 (0.52–30.3)	0.18
NLR > 4.3 (ref.: ≤ 4.3)	3.04 (1.46–6.34)	0.003	3.42 (1.61–7.23)	0.001	1.31e-08 (0–inf)	0.99
PLR > 80 (ref.: ≤ 80)	0.44 (0.23–0.86)	0.02	0.57 (0.26–1.24)	0.16	0.14 (0.04–0.53)	0.003
SII > 795 (ref.: ≤ 795)	1.46 (0.83–2.54)	0.19	1.61 (0.85–3.05)	0.14	1.08 (0.35–3.38)	0.89
Tumor size (imaging; per unit increase)	1.21 (1.10–1.35)	< 0.001	1.25 (1.11–1.40)	< 0.001	1.08 (0.85–1.38)	0.54
Number of tumors (pathology; per unit increase)	1.38 (1.09–1.75)	0.01	1.28 (0.96–1.69)	0.09	2.35 (1.35–4.09)	0.002
Microvascular invasion (ref.: no)	2.85 (1.66–4.88)	< 0.001	2.07 (1.12–3.82)	0.02	6.94 (2.23–21.63)	0.001
Macrovascular invasion (ref.: no)	0.91 (0.53–1.56)	0.72	1.05 (0.56–1.94)	0.89	0.58 (0.19–1.83)	0.36
Tumor differentiation (ref.: well)						
Moderate	1.71 (0.83–3.51)	0.14	2.61 (1.0–6.81)	0.05	0.68 (0.19–2.38)	0.55
Poor	2.60 (1.20–5.61)	0.02	3.00 (1.07–8.43)	0.04	2.52 (0.76–8.36)	0.13
Tumor growth pattern (ref.: Intraductal)						
Periductal infiltrating	0.83 (0.14–4.99)	0.84	0.31 (0.03–3.42)	0.34	1.00 (0.22–4.5)	0.99
Mass forming	1.73 (0.42–7.14)	0.45	1.31 (0.32–5.42)	0.71	4.72e07 (0–inf)	0.99
Mixed type	3.46 (0.48–24.7)	0.22	1.53 (0.14–16.9)	0.73	6.68 (0.81–54.8)	0.08
N stage (ref.: N0)						
N1	3.65 (1.67–7.92)	0.001	4.86 (1.97–12.03)	0.001	1.99 (0.24–16.2)	0.52
Nx	1.10 (0.61–1.99)	0.76	1.60 (0.74–3.45)	0.23	0.52 (0.19–1.45)	0.21
Adjuvant systemic therapy (ref.: no)	1.44 (0.83–2.51)	0.20	1.24 (0.63–2.41)	0.53	3.98 (0.52–30.3)	0.18

iCCA, intrahepatic cholangiocarcinoma; HR, hazard ratio; CI, confidence interval; ref., reference; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic inflammatory index; inf, infinity.

Table 3. Multivariable Cox regression analysis for all-time iCCA recurrence

Variable	HR (95% CI)	*p*
Cirrhosis (ref.: no)	3.42 (1.45–8.09)	0.005
NLR > 4.3 (ref.: ≤ 4.3)	2.85 (1.21–6.71)	0.02
Tumor size (imaging, per unit increase)	1.21 (1.07–1.37)	0.003
Number of tumors (pathology, per unit)	0.93 (0.70–1.23)	0.60
Microvascular invasion (ref.: no)	2.72 (1.50–4.94)	0.001
N stage (ref.: N0)		
N1	3.73 (1.64–8.50)	0.002
Nx	1.37 (0.74–2.52)	0.30

iCCA, intrahepatic cholangiocarcinoma; CI, confidence interval; HR, hazard ratio; ref., reference; NLR, neutrophil-to-lymphocyte ratio.

for underlying cirrhosis, tumor size on imaging, microvascular invasion, and pathologic N stage. High preoperative NLR was significantly associated with a higher overall recurrence rate (HR 2.85 [95% CI 1.21–6.71]; $p = 0.02$). High preoperative NLR was associated with higher recurrence rate in the first 12 months after curative surgery (HR 5.16 [95% CI 1.59–16.8]; $p = 0.006$), but not after 12 months (HR 2.00 [95% CI 0.69–5.84]; $p = 0.20$). Underlying cirrhosis, tumor size on imaging, microvascular invasion, and pathologic N1 stage were associated with higher all-time iCCA recurrence (Table 4).

Sensitivity analysis

The analysis was repeated, keeping the CA19-9 variable with 61.1% missing values and the conclusion of the results did not change. The analysis was also repeated using a continuous NLR variable. The continuous NLR was associated with an increased risk of recurrence in the first 12 months after curative surgery (HR 1.39 [95% CI 1.12–1.71]; $p = 0.002$) but not in the overall period (HR 1.21 [95% CI 0.9–1.54]; $p = 0.10$).

DISCUSSION

In this study, ER was defined as recurrence occurring within 12 months after curative hepatectomy for iCCA. Forty-three (38.1%) patients experienced ER. A high preoperative NLR was significantly associated with a higher risk of ER, while high PLR and SII were not. In the adjusted analysis, high preoperative NLR was significantly associated with a higher recurrence rate in the first 12 months after curative surgery. This study is the first to examine the prognostic performance of systemic inflammatory biomarkers for pure recurrence events during the early iCCA recurrence period.

Based on current evidence, the ER of iCCA is defined as recurrence within 12 to 24 months after curative-intent surgery [12,14,37]. One study defined "very early recurrence" as recurrence within 6 months after curative-intent iCCA resection [11]. Although our 38% ER rate is lower than their 50% ER rate, our results corroborate the 12-month ER definition reported

Table 4. Multivariable Cox regression analysis for all-time iCCA recurrence with the NLR effect in early (≤ 12 month) vs. late recurrence (> 12 month) periods

Variable	HR (95% CI)	*p*
Cirrhosis (ref.: no)	3.58 (1.51–8.52)	0.004
NLR > 4.3 (ref.: ≤ 4.3)[a]		
Effect estimate for early recurrence period	5.16 (1.59–16.8)	0.006
Effect estimate for late recurrence period	2.00 (0.69–5.84)	0.20
Tumor size (imaging, per unit increase)	1.22 (1.08–1.37)	0.001
Number of tumors (pathology, per unit)	0.92 (0.70–1.23)	0.58
Microvascular invasion (ref.: no)	2.46 (1.34–4.52)	0.004
N stage (ref.: N0)		
N1	4.22 (1.80–9.89)	< 0.001
Nx	1.41 (0.76–2.59)	0.27

iCCA, intrahepatic cholangiocarcinoma; HR, hazard ratio; CI, confidence interval; ref., reference; NLR, neutrophil-to-lymphocyte ratio.
[a]NLR was defined using two time-varying regression coefficients or regression parameters to estimate the effect of NLR before and after the landmark time of 12 months for violating the proportional hazard assumption.

by Wang et al. [14]. Our results are further supported by some authors who advocate a 12-month ER definition in the field of HCC compared to the traditional 24 months ER definition [38,39]. External validation of this 12-month ER definition will be needed to correctly select patients who might be harboring aggressive type of iCCA that leads to ER and worse survival [40]. Our study specifically analyzed patients who achieved R0 or negative margin resections, and 70.0% of ER occurred in extrahepatic locations, suggesting that microscopic systemic disease might have been present around the time of surgery and thereafter [41]. The association between high preoperative NLR and higher recurrence rate in the first 12 months suggests that high preoperative NLR status may reflect a higher tumor burden with an increased risk of harboring microscopic systemic disease. These highlight the need for new treatment and surveillance strategies for patients at risk of ER and suggest that we consider providing neoadjuvant or adjuvant systemic treatments [41].

Systemic inflammatory biomarkers such as NLR have been used to augment risk stratification tools for iCCA survival. However, to our knowledge, there are no studies examining NLR in the context of 12-month ER after iCCA resection [27,30]. Instead, many studies have selected RFS as the primary endpoint, which is a composite outcome of both recurrence and death [19-26]. For example, worse RFS was reported in patients with a NLR greater than 2.49 after iCCA resection [20,21]. In contrast, two studies reported that preoperative NLR was not associated with worse RFS after iCCA resections [13,26]. To keep the statistical analysis reflective of our objectives, our study used only recurrence as the primary endpoint and censored death. Furthermore, to demonstrate that the proportion-

al hazards assumptions of NLR were not met after adjusting for other covariates, we kept the early and late effects of NLR in one combined model.

Whether or not systemic inflammatory biomarkers should be analyzed as continuous variables is debatable, as some evidence suggests that these marker levels may be patient-specific rather than a universal fixed value to categorize as high or low [42]. Nevertheless, we decided to categorize it based on a cut-off value for easier interpretation by clinicians. In our sensitivity analysis using a continuous NLR value, the significance of NLR was retained in the ER period, but not in the overall period. This implies that the preoperative inflammatory effects of NLR have a stronger association with recurrence in the first 12 months after surgery. One possible explanation for our findings is that neutrophilia is a sign of inflammation caused by cancer, while lymphocytopenia is a sign of decline in a patient-specific adaptive immune response [42]. Only one other group studied NLR in the pure context of ER and showed that NLR was not associated with ER. However, their definition of ER was set at 24-months, and the analysis of NLR was not adjusted for potential confounders [12]. Our findings demonstrate that preoperative NLR can provide prognostic information for patients undergoing iCCA surgery.

Currently published iCCA ER risk factors are either post-operative factors reported with tumor pathology (pathologic tumor stage, grade, multifocality, lymph node metastasis), or preoperative factors that are difficult to measure accurately (i.e., cirrhosis, CA19-9) [9,43-46]. NLR is easily obtained by non-invasive blood tests, is inexpensive, and is routinely collected before surgery [32]. This makes NLR an attractive biomarker to be implemented in recurrence risk stratification tools designed to guide preoperative treatment decisions and intensify post-operative follow-up [11].

Several strengths and limitations of this study should be noted. In terms of strengths, our study adds a new prognostic factor to the literature in the context of ER. Rather than using the combined effect of both recurrence and death to measure RFS, a Cox regression with a time-varying regression coefficient model was used to focus only on the recurrence effect. However, this study is limited by its single-center and retrospective nature and may be subject to confounding bias from unmeasured confounders. The small sample size may have attenuated the association between NLR level and ER observed in this study. Many CA19-9 tumor markers were measured outside our institution and external chart reviews were restricted by our Research Ethics Board. However, a sensitivity analysis conducted, including 38.9% of CA19-9 values, showed no difference in the conclusion of our results. Routine lymphadenectomy for iCCA resections was recently implemented at our institution following the introduction of the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines in 2017 [47].

In conclusion, we identified that ER can be defined within 12-months after hepatectomy for iCCA. High preoperative NLR was associated with a higher recurrence rate in the first 12 months after curative surgery, but not after 12 months. Because preoperative NLR is easily obtainable by non-invasive tests, this information can be incorporated into existing ER risk prediction tools to help guide preoperative therapies and to intensify postoperative follow-up.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceptualization: All authors. Data curation: WJC, AG, LA, PA. Methodology: WJC, FMP, TI, MPAWC, BEH, GS. Visualization: WJC. Writing - original draft: WJC. Writing - review & editing: All authors.

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