Diagn Interv Radiol 2024; DOI: 10.4274/dir.2024.242929

INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Evaluating the prognostic impact of inflammatory markers on treatment outcomes in patients with intrahepatic cholangiocarcinoma undergoing radioembolization

Sinan Sözütok
Ferhat Can Pişkin
Hüseyin Tuğsan Ballı
Berkay Dik

Çukurova University Faculty of Medicine, Balcalı Hospital, Department of Radiology, Adana, Türkiye

PURPOSE

Intrahepatic cholangiocarcinoma (iCCA) is a rare and aggressive malignancy with limited treatment options, often diagnosed at advanced stages. Radioembolization has emerged as a promising therapy, but its efficacy varies among patients, necessitating reliable biomarkers to predict treatment response. This study evaluates the prognostic impact of systemic inflammatory response markers on treatment outcomes in patients with iCCA undergoing radioembolization.

METHODS

This retrospective study included 70 patients with iCCA treated with radioembolization between January 2016 and December 2023. Inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), were measured from peripheral blood samples. Treatment response was assessed using the modified RECIST criteria, and survival analyses were performed using the Kaplan–Meier method and Cox proportional hazards regression.

RESULTS

Patients with lower NLR, PLR, and SII values exhibited significantly higher objective response rates ($P = 0.032$, $P = 0.016$, and $P = 0.001$, respectively). High levels of NLR, PLR, and SII were associated with shorter overall survival (12 vs. 16 months, $P = 0.007$; 12 vs. 16 months, $P = 0.004$; and 10 vs. 22 months, $P < 0.001$, respectively) and progression-free survival (3 vs. 7 months, $P = 0.046$ for SII). Multivariate analysis identified high SII ($P = 0.040$), lymph node metastasis ($P = 0.042$), and high serum total bilirubin ($P = 0.013$) as significant independent prognostic factors.

CONCLUSION

Systemic inflammatory markers such as NLR, PLR, and SII are valuable prognostic indicators for patients with iCCA undergoing radioembolization. These markers can aid in identifying patients likely to benefit from personalized treatment strategies, potentially improving clinical outcomes.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its demonstration that systemic inflammatory markers (NLR, PLR, and SII) serve as valuable prognostic indicators for predicting treatment outcomes in patients with iCCA undergoing radioembolization, thus aiding in the identification of patients who may benefit from personalized treatment strategies and potentially improving clinical outcomes.

KEYWORDS

Intrahepatic cholangiocarcinoma, radioembolization, systemic inflammatory markers, treatment response, outcomes

Corresponding author: Ferhat Can Pişkin

E-mail: ferhatcpiskin@gmail.com

Received 14 July 2024; revision requested 02 September 2024; accepted 17 October 2024.

Epub: 25.11.2024

Publication date: xx.xx.2024

DOI: 10.4274/dir.2024.242929

You may cite this article as: Sözütok S, Pişkin FC, Ballı HT, Dik B. Evaluating the prognostic impact of inflammatory markers on treatment outcomes in patients with intrahepatic cholangiocarcinoma undergoing radioembolization. *Diagn Interv Radiol.* 25 November 2024 DOI: 10.4274/dir.2024.242929 [Epub Ahead of Print].

Intrahepatic cholangiocarcinoma (iCCA) is a rare and highly aggressive malignancy originating from the intrahepatic bile ducts. The global incidence of iCCA is projected to increase tenfold over the next 20–30 years.[1] This rise is attributed to various risk factors, including chronic liver diseases such as hepatitis B and C, cirrhosis, and lifestyle factors such as alcohol consumption and obesity.[2,3] Despite advancements in medical science, treatment options for iCCA remain limited, and most patients are diagnosed at advanced stages, minimizing the benefits of available systemic therapies.[4] Consequently, there is a pressing need to explore novel and more effective therapeutic strategies for iCCA.

Radioembolization has emerged as a promising treatment option for patients with iCCA. It is a form of locoregional therapy that involves the injection of radioactive microspheres directly into the tumor's blood supply, effectively delivering high doses of radiation while sparing surrounding healthy tissues.[5] Clinical studies have demonstrated that radioembolization, either as a monotherapy or in combination with chemotherapy, can significantly improve overall survival (OS) and progression-free survival (PFS) in patients with iCCA.[6] However, the therapeutic efficacy of radioembolization varies considerably among patients, underscoring the necessity for reliable biomarkers to predict treatment response and optimize patient selection.

Main points

- Systemic inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), serve as significant prognostic indicators for patients with intrahepatic cholangiocarcinoma (iCCA) undergoing radioembolization.
- Lower levels of NLR, PLR, and SII are significantly associated with an improved treatment response, as well as enhanced overall survival and progression-free survival.
- Elevated SII, the presence of lymph node metastasis, and increased serum total bilirubin levels are identified as independent prognostic factors correlating with reduced survival in patients with iCCA.
- The integration of inflammatory markers into clinical decision-making processes has the potential to guide personalized treatment strategies, thereby optimizing outcomes for patients receiving radioembolization.

In recent years, the systemic inflammatory response (SIR) has garnered significant attention for its role in influencing cancer treatment outcomes. Biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been identified as indicators reflecting the impact of the SIR on the tumor microenvironment. Elevated SIR levels are known to substantially affect tumor growth, invasion, and metastasis, thereby influencing treatment outcomes.[7] Emerging evidence suggests that the relationship between inflammation and cancer progression involves complex signaling pathways, including cytokine release, immune cell recruitment, and changes in the extracellular matrix, which collectively create a tumor-promoting microenvironment.[8]

The SIR has been demonstrated to significantly impact treatment response in liver tumors. Notably, in patients with hepatocellular carcinoma (HCC), elevated SIR levels are associated with poorer outcomes following radioembolization therapy.[9,10] However, the literature on the effects of the SIR in patients with iCCA undergoing radioembolization remains limited.[11] By evaluating multiple inflammatory markers, this study aims to fill this gap by providing crucial insights into how these markers impact treatment outcomes in patients with iCCA. Our findings highlight the potential of implementing personalized therapies for this malignancy, which has a generally poor prognosis. To our knowledge, this is one of the first studies to comprehensively evaluate the impact of these markers in iCCA, and it includes the largest patient cohort studied to date. These contributions are critical for optimizing treatment strategies and facilitating more personalized approaches for patients with iCCA.

Therefore, this study aims to evaluate the prognostic impact of inflammatory responses on treatment outcomes in patients with iCCA undergoing radioembolization.

Methods

Study population

The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki, and signed informed consent forms were obtained from all patients. The Institutional Clinical Research Ethical Committee (Çukurova University Faculty of Medicine Research Ethics Committee, meeting dated: 14.06.2024, decision number: 62/145) approved this single-center observational study.

This retrospective study reviewed the clinical records of patients diagnosed with iCCA who underwent radioembolization therapy at the radiology department between January 2016 and December 2023. The inclusion criteria were as follows: patients aged ≥18 years, with histopathologically confirmed iCCA, suitable for radioembolization therapy, and with complete clinical and imaging data. Patients with a minimum follow-up period of 3 months were included in the study. The exclusion criteria were as follows: patients who had previously undergone other local treatments such as transarterial chemoembolization or thermal ablation, those who did not achieve a response to treatment, those with incomplete medical records, and those who underwent surgery after radioembolization (Figure 1).

Pre-treatment clinical and imaging assessment

All patients underwent clinical, laboratory, and radiological evaluation before treatment. The Eastern Cooperative Oncology Group (ECOG) performance scores of the patients were assessed. Patients with ECOG performance scores between 0 and 2 were planned for treatment. Laboratory tests were conducted for the complete blood count, biochemistry, and hormone marker values of the patients before treatment. Dynamic contrast-enhanced magnetic resonance imaging (MRI) was performed, and the obtained images were evaluated by two abdominal radiologists with over 5 years' experience. The evaluation included an assessment of tumor size, number, location, presence of macrovascular invasion, and lymph node involvement.

Inflammatory markers measurement

Peripheral blood samples were collected from all patients within 1 week before radioembolization therapy. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. The aspartate aminotransferase (AST) to lymphocyte ratio (ALRI) was calculated by dividing the AST value by the lymphocyte count. The SII was calculated as platelet count × neutrophil count/lymphocyte count.

Radioembolization procedure

All patients underwent a detailed pretreatment evaluation, including contrast-enhanced MRI to assess the extent of the disease, along with liver function tests. The radioembolization procedure was performed using resin- or

glass-based yttrium-90 (90Y)–loaded microspheres in accordance with the Cardiovascular and Interventional Radiological Society of Europe Standards of Practice in Transarterial Radioembolization.[12] The choice of glass or resin microspheres was based on supply or logistical factors, regardless of tumor characteristics. Post-procedural imaging with 90Y positron emission tomography/computed tomography was performed to confirm the distribution of the microspheres within the liver and to detect any extrahepatic shunting.

Follow-up and assessment

Patients were followed up at regular intervals of 1, 3, and 6 months post-treatment and every 3 months thereafter, with clinical examination, laboratory tests, and imaging studies. OS and PFS were the primary endpoints. Treatment response was evaluated using the modified Response Evaluation Criteria in Solid Tumors 1.1 criteria based on imaging studies.[13] Patients who demonstrated a complete response, partial response, or stable response to treatment were classified as having an objective response, whereas those with tumor progression were defined as having no objective response.

Statistical analysis

Data were analyzed using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequencies and percentages. The laboratory values of the patients did not show a homogeneous distribution; therefore, the median value was used to divide the patients into groups. The groups were formed as "below median" and "above median." The chi-square test was employed to compare categorical variables between two groups. The Mann–Whitney U test was used to compare parametric data that did not show a homogeneous distribution. Survival curves for OS and PFS were plotted using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression analysis was employed to identify independent prognostic factors for survival. A *P* value of less than 0.05 was considered statistically significant.

Results

In this study, a total of 70 patients were included, 34 (48.57%) of whom were men. The age range was 34–89 years, with a mean age of 59.29 ± 11.89 years. The demographic and clinicopathological characteristics of the patients are presented in Table 1.

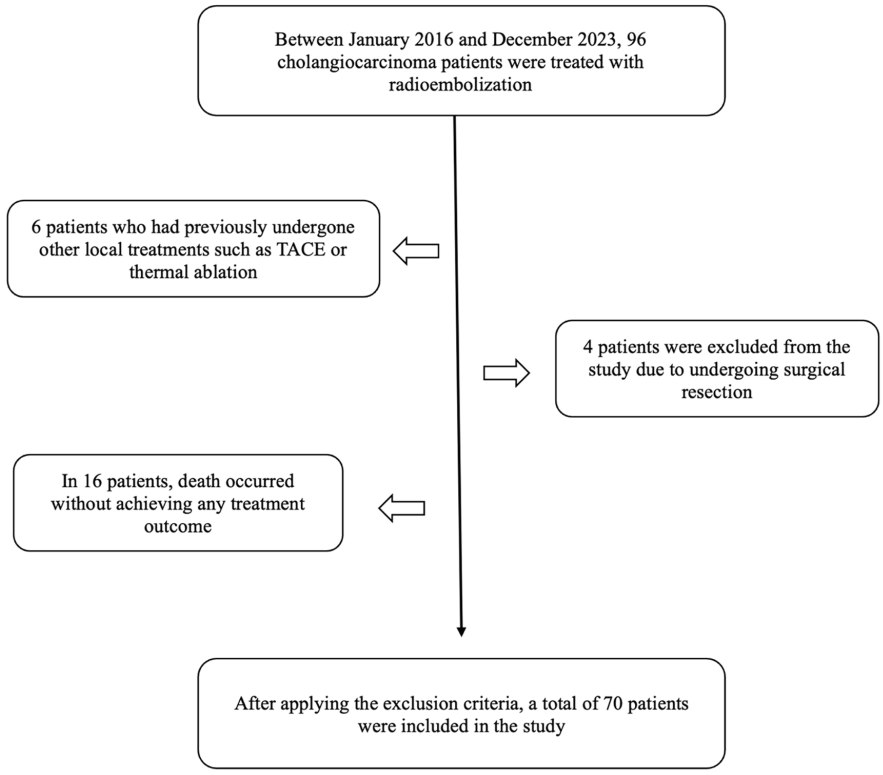

Figure 1. Study flowchart. TACE, transarterial embolization.

Table 1. Baseline demographic and clinical characteristics of the patients (n = 70)

Variables	n (%)
Age, years	59.2 ± 11.8
Gender	
Men	34 (48.5%)
Women	36 (51.4%)
ALT, U/L	22.5 (27.2–38.3)*
AST, U/L	30 (33.3–46.5)*
Albumin, g/L	3.9 (3.5–3.8)*
TBIL, mg/dL	0.6 (0.5–1.1)*
CA19-9, U/mL	95 (770–3516)*
Largest tumor size	
≤6 cm	48 (68.5%)
>6 cm	22 (31.4%)
Lymph node metastasis	
Yes	41 (58.5%)
No	29 (41.4%)
Tumor number	
1	27 (27 (38.5%)
>1	43 (61.4%)
Macrovascular invasion	
Yes	31 (55.7%)
No	39 (55.7%)
NLR	3.3 (3.6–5.7)*
PLR	143 (158–237)*
SII	771 (901–1398)*
ALRI	22.3 (24.6–41.7)*

*Values in parentheses represent median (lower limit–upper limit). ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; ALRI, aspartate aminotransferase-to-lymphocyte ratio index.

Response to treatment

In the follow-up evaluation at 3 months to assess response to treatment, 6 (8.5%) patients achieved a complete response, 31 (44.2%) patients had a partial response, 1 (1.4%) patient had a stable response, and 38 (54.2%) patients exhibited progressive disease. An objective response was observed in 32 (45.7%) patients. Patients with low NLR, PLR, and SII values had a significantly higher objective response rate ($P = 0.032$, $P = 0.016$, and $P = 0.001$, respectively). No significant difference was found between the groups for ALRI ($P > 0.05$) (Table 2). The median NLR, PLR, and SII values of patients who obtained an objective response were significantly lower than those of the other group ($P = 0.037$, $P = 0.002$, and $P = 0.002$, respectively) (Table 3).

Overall survival analysis

In this study, 65 (92.8%) patients died. The median survival time was 14 months [95% confidence interval (CI): 10–16]. The mean survival time for the surviving patients was 28.4 months (95% CI: 11.1–45.6). Kaplan–Meier analysis revealed that patients with high NLR, PLR, and SII values had significantly shorter OS times than other patients (12 vs. 16 months, $P = 0.007$, 12 vs. 16 months, $P = 0.004$, and 10 vs. 22 months, $P < 0.001$, respectively). No significant difference was found between the groups for ALRI (11 vs. 16, $P = 0.071$) (Figure2 a-d). In the univariate analysis, the demographic information of the patients, tumor burden, liver function tests, tumor hormone markers, and inflammatory scores were evaluated. Tumor burden, liver function tests, and inflammatory scores were identified as prognostic factors. In the multivariate analysis, high SII values ($P = 0.040$), the presence of lymph node metastasis ($P = 0.042$), and high serum total bilirubin (TBIL) values ($P = 0.013$) were identified as significant independent prognostic factors (Table 4).

Progression/recurrence analysis

In this study, 44 (62.8%) patients experienced progression/recurrence. The median PFS was 7 months (95% CI: 6–9). Kaplan–Meier analysis showed that patients with high SII values had significantly shorter PFS than other patients (3 months, 95% CI: 3–6 vs. 7 months, 95% CI: 7–22, $P = 0.046$). No significant difference was found between the groups for NLR, PLR, and ALRI ($P > 0.05$) (Figure 3). In the univariate analysis for PFS, the demographic information of the patients, tumor burden, liver function tests, tumor hormone markers, and inflammatory scores were evaluated. However, no prognostic factors were identified ($P > 0.05$).

Table 2. Comparison of treatment response among patients grouped by inflammatory markers

	Objective response n (%)	Non-objective response n (%)	*P*
NLR			
Below median	24 (34.3%)	12 (17.1%)	0.032
Above median	14 (20.0%)	20 (28.6%)	
PLR			
Below median	24 (%34.3)	11 (15.7%)	0.016
Above median	14 (%20.0)	21 (30,0%)	
SII			
Below median	19 (27.1%)	16 (22.9%)	0.001
Above median	19 (27.1%)	16 (22.9%)	
ALRI			
Below median	21 (30.0%)	14 (20.0%)	0.472
Above median	17 (24.3%)	18 (25.7%)	

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; ALRI, aspartate aminotransferase-to-lymphocyte ratio.

Table 3. Comparison of inflammatory markers of values among patients grouped by treatment response

	Objective response	Non-objective response	*P*
NLR	2.7 (1.36–28)	3.9 (1.3–16.2)	0.037
PLR	125 (27.2–1180)	215 (32.5–665)	0.002
SII	605 (119–5503)	1166 (331–4322)	0.002
ALRI	17.9 (6.1–230)	23.9 (6.1–135)	0.120

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; ALRI, aspartate aminotransferase-to-lymphocyte ratio.

Discussion

This study assessed the prognostic impact of inflammatory markers on treatment outcomes in patients with iCCA undergoing radioembolization. Our findings indicate that patients with higher NLR, PLR, and SII values had lower treatment response rates, shorter OS times, and higher progression/recurrence rates. These results align with the existing literature, underscoring the critical role of the SIR in predicting treatment outcomes.

Neutrophils suppress anti-tumor immunity through immunosuppressive cytokines, fostering a pro-tumorigenic environment, whereas platelets promote tumor progression by protecting circulating tumor cells from immune surveillance and facilitating their adhesion to the endothelium, thereby promoting metastasis. Conversely, lymphocytes support anti-tumor immunity by targeting and destroying cancer cells; hence, elevated NLR, PLR, and SII levels indicate a shift toward a pro-tumorigenic state, reflecting tumor biology and significantly affecting treatment outcomes.[1,4] Recent studies have examined the impact of the inflammatory response on treatment outcomes in patients with CCA, emphasizing the prognostic value of these markers in this specific cancer type.[11,14,15]

Yu et al.[15] demonstrated that lower SII values in patients with liver cancer undergoing interventional therapy were associated with improved treatment outcomes, including higher response rates and reduced rates of recurrence and metastasis. Similarly, studies on patients with HCC undergoing radioembolization have shown that lower NLR and PLR values correlate with better treatment responses and OS.[16] In our study, we found that patients with low NLR, PLR, and SII values had significantly higher objective response rates ($P = 0.032$, $P = 0.016$, and $P = 0.001$, respectively). These findings align with the existing literature, suggesting that lower systemic inflammation is also associated with better treatment outcomes in patients with CCA.

Filippi et al.[11] reported that elevated NLR levels were significantly associated with shorter OS times in patients with iCCA treated with 90Y-radioembolization, with a median OS of 7.5 months for patients with high NLR compared with 17.5 months for those with low NLR. In this study, Kaplan–Meier analysis showed that patients with higher SII

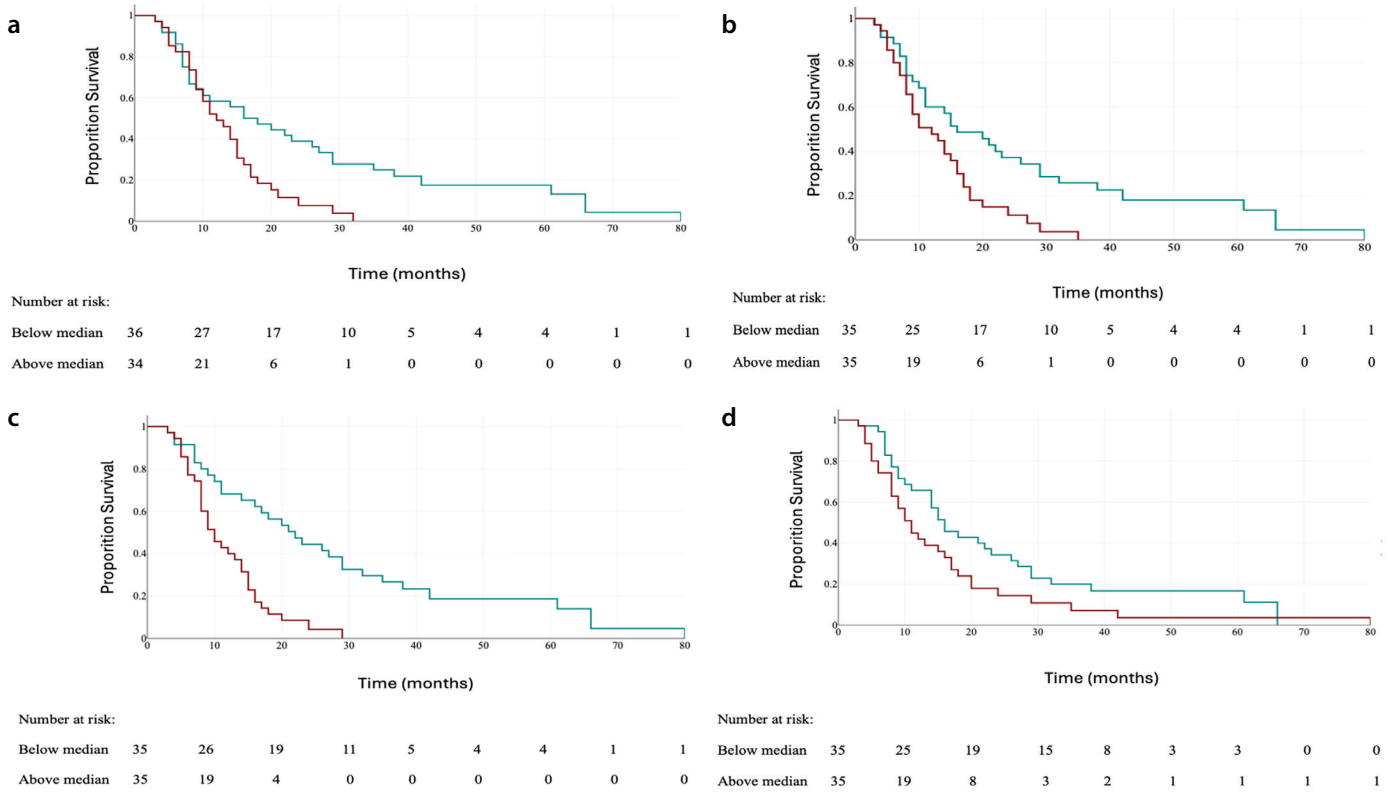

Figure 2. (a-d) Kaplan–Meier curves comparing overall survival for those with an above or below median neutrophil-to-lymphocyte ratio (NLR) **(a)**, platelet-to-lymphocyte ratio (PLR) **(b)**, systemic immune-inflammation index (SII) **(c)**, and aspartate aminotransferase-to-lymphocyte ratio (ALRI) **(d)**. High NLR, PLR, and SII were associated with significantly shorter survival times, whereas no significant difference was observed for ALRI.

Table 4. Univariate and multivariate Cox regression models examining risk factors for overall survival

Variables	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, years	0.87	0.53–1.42	0.572			
Gender, men	1	0.97–1.02	0.754			
ALT, U/L	1.01	1.01–1.02	0.057			
AST, U/L	1.01	0.92–1.02	0.070			
Albumin, g/L	0.08	0.6–1.26	0.447			
TBIL, mg/dL	1.35	1.11–1.66	0.004	1.3	1.06–1.59	0.013
CA19-9, U/mL	1.49	0.81–2.71	0.197			
Largest tumor size, cm (6>/≤6)	2.17	1.19–3.94	0.011	1.49	0.74–3	0.260
Lymph node metastasis (yes/no)	2.36	1.37–4.07	0.002	1.85	1.02–3.34	0.042
Tumor number (>1/1)	1.45	0.87–2.41	0.156			
Macrovascular invasion (yes/no)	1.46	0.89–2.4	0.132			
NLR	2.04	1.19–3.51	0.010	1.21	0.61–2.43	0.584
PLR	2.11	1.24–3.61	0.006	0.99	0.48–2.02	0.975
SII	3.17	1.79–5.51	<0.001	2.36	1.04–5.34	0.04
ALRI	1.55	0.94–2.55	0.082			

HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; ALRI, aspartate aminotransferase-to-lymphocyte ratio.

values had significantly shorter OS times ($P < 0.001$). Specifically, patients with high SII had a median OS of 10 months compared with 22 months for those with low SII. Cox regression analysis in our study identified several independent prognostic factors for OS in patients with iCCA undergoing radioembolization. Specifically, high SII values [hazard ratio (HR): 2.36, 95% CI: 1.04–5.34, $P = 0.04$], the presence of lymph node metastasis (HR: 1.85, 95% CI: 1.02–3.34, $P = 0.042$), and elevated serum TBIL levels (HR: 1.3, 95% CI: 1.06–1.59, $P = 0.013$) were significant independent predictors of poor survival. These findings are consistent with previous studies, such as the work by Li et al.[17], which demonstrate that elevated SII levels are associated with poorer survival outcomes in patients with perihilar

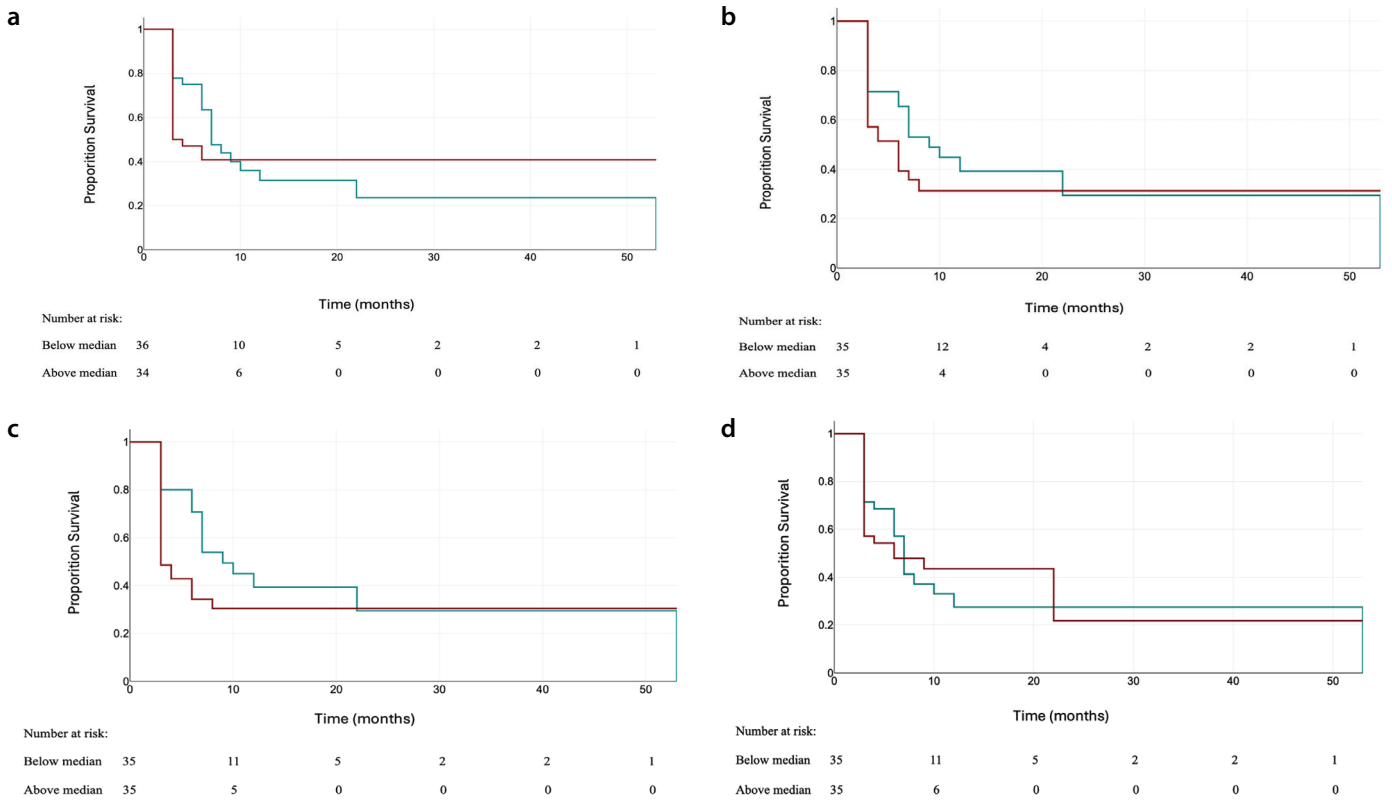

Figure 3. Kaplan–Meier curves comparing progression-free survival for those with an above or below median neutrophil-to-lymphocyte ratio (NLR) **(a)**, platelet-to-lymphocyte ratio (PLR) **(b)**, systemic immune-inflammation index (SII) **(c)**, and aspartate aminotransferase-to-lymphocyte ratio (ALRI) **(d)**. High SII were associated with significantly shorter progression-free survival times, whereas no significant difference was observed for NLR, PLR, and ALRI.

CCA (HR: 1.57, 95% CI: 1.17–2.10, $P = 0.003$). Furthermore, the presence of lymph node metastasis has been widely recognized as a significant prognostic factor in iCCA, as highlighted by Li et al.[18], who reported similar associations with OS (HR: 1.88, 95% CI: 1.32–2.68, $P < 0.001$). Elevated serum TBIL, indicative of impaired liver function, also aligns with findings from multiple studies that underscore its role in predicting survival outcomes in hepatobiliary malignancies.[15]

Several studies have shown that the SIR significantly impacts tumor progression and recurrence. For example, Yu et al.[15] demonstrated that patients with liver cancer and elevated SII levels had a shorter PFS (HR: 1.152, 95% CI: 1.878–5.329, $P < 0.001$). Similarly, Li et al.[18] found that patients with high preoperative SII levels and NLR were significantly correlated with a shorter PFS (HR: 1.385, 95% CI: 1.005–1.909, $P = 0.046$). In our study, patients with iCCA and higher SII values had significantly shorter PFS, with a median PFS of 3 months compared with 7 months for those with lower SII values, indicating a higher risk of tumor progression and recurrence.

This study has several strengths. It includes a comprehensive retrospective analysis of a large patient cohort and a detailed evaluation of inflammatory markers, providing robust data on the prognostic significance of these markers in patients with iCCA undergoing radioembolization. The findings from our study contribute to the growing body of literature by suggesting that systemic inflammatory markers, such as SII, NLR, and PLR, could serve as valuable prognostic indicators in this patient population. These markers may help identify patients who are more likely to benefit from the addition of radioembolization to their treatment regimen, potentially guiding more personalized and effective therapeutic strategies.

This study has several limitations. Its retrospective nature may introduce selection bias and limit the ability to establish causal relationships. The sample size, although sufficient for initial findings, is relatively small and may not fully represent the broader population of patients with iCCA. This study relies on data from a single institution, which may limit the generalizability of the results. Variability in radioembolization techniques and the lack of standardized protocols for measuring inflammatory markers could also influence the outcomes. Future prospective studies with larger, multicentric cohorts and standardized methodologies are necessary to validate these findings and better explain the role of systemic inflammatory markers in predicting treatment outcomes for patients with iCCA.

In conclusion, this study underscores the prognostic significance of systemic inflammatory markers (NLR, PLR, and SII) in patients with iCCA undergoing radioembolization. Elevated levels of these markers correlate with poorer treatment response, shorter OS, and increased progression. Incorporating these biomarkers into clinical practice can aid in patient stratification and personalized treatment planning, potentially improving outcomes. Further prospective studies are needed to validate these findings and enhance the use of inflammatory markers in guiding iCCA treatment.

Footnotes

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Qurashi M, Vithayathil M, Khan SA. Epidemiology of cholangiocarcinoma. *Eur J Surg Oncol*. 2023;9:107064. [CrossRef]

2. Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol*. 2016:13(5):261-280. [CrossRef]
3. Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. *Lancet*. 2021;397(10272):428-444. [CrossRef]
4. Labib PL, Davidson BR, Sharma RA, Pereira SP. Locoregional therapies in cholangiocarcinoma. *Hepat Oncol*. 2017;4(4):99-109. [CrossRef]
5. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: technical and methodologic considerations. *J Vasc Interv Radiol*. 2006;17(8):1251-1278. Erratum in: *J Vasc Interv Radiol*. 2006;17(10):1594. [CrossRef]
6. Elvevi A, Laffusa A, Elisei F, et al. Any role for transarterial radioembolization in unresectable intrahepatic cholangiocarcinoma in the era of advanced systemic therapies? *World J Hepatol*. 2023;15(12):1284-1293. [CrossRef]
7. Dolan RD, Lim J, McSorley ST, Horgan PG, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: systematic review and meta-analysis. *Sci Rep*. 2017;7(1):16717. [CrossRef]
8. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis*. 2009:30(7):1073-1081. [CrossRef]
9. Young S, Rubin N, D'Souza D, et al. Inflammatory scores: correlation with clinical outcomes in hepatocellular carcinoma patients undergoing transarterial radioembolization. *Cardiovasc Intervent Radiol*. 2022;45(4):461-475. [CrossRef]
10. Öcal O, Kupčinskas J, Morkunas E, et al. Prognostic value of baseline interleukin 6 levels in liver decompensation and survival in HCC patients undergoing radioembolization. *EJNMMI Res*. 2021;11(1):51. [CrossRef]
11. Filippi L, Di Costanzo GG, Tortora R, et al. Prognostic value of neutrophil-to-lymphocyte ratio and its correlation with fluorine-18-fluorodeoxyglucose metabolic parameters in intrahepatic cholangiocarcinoma submitted to 90Y-radioembolization. *Nucl Med Commun*. 2020;41(1):78-86. [CrossRef]
12. Mahnken AH, Spreafico C, Maleux G, Helmberger T, Jakobs TF. Standards of practice in transarterial radioembolization. *Cardiovasc Intervent Radiol*. 2013;36(3):613-622. [CrossRef]
13. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30(1):52-60. [CrossRef]
14. Yang Z, Zhang D, Zeng H, et al. Inflammation-based scores predict responses to PD-1 Inhibitor treatment in intrahepatic cholangiocarcinoma. *J Inflamm Res*. 2022;15:5721-5731. [CrossRef]
15. Yu L, Zheng S, Yang J, Fu Z, Zhu X, Su K. Association between the systemic immune inflammation index and recurrence or metastasis after interventional therapy in patients with primary liver cancer- a retrospective cohort study. *J Gastrointest Oncol*. 2023;14(2):780-788. [CrossRef]
16. Ren A, Li Z, Cheng P, Zhang X, Deng R, Ma Y. Systemic immune-inflammation index is a prognostic predictor in patients with intrahepatic cholangiocarcinoma undergoing liver transplantation. *Mediators Inflamm*. 2021;2021:6656996. [CrossRef]
17. Li J, Gao L, Liu T, Feng D. Association of systemic inflammation index with survival in patients with advanced perihilar cholangiocarcinoma treated with interventional therapy. *Front Oncol*. 2022;12:1038759. [CrossRef]
18. Li H, Wang JJ, Zhang M, et al. Prognostic significance of systemic immune-inflammation index in patients with intrahepatic cholangiocarcinoma undergoing hepatic resection. *World J Gastrointest Oncol*. 2020;12(4):467-482. [CrossRef]