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*Original Article*

# Prognostic value of platelet to lymphocyte ratio in patients with intrahepatic cholangiocarcinoma

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**Abstract:** *Aim:* The present study aimed to investigate the prognostic significance of PLR in ICC patients. *Methods:* Data from 90 intrahepatic cholangiocarcinoma patients who underwent surgical resection between 2007 and 2016 were evaluated retrospectively. Preoperative clinicopathological data was collected and analyzed with survival to find any correlation. Overall survival and recurrence free survival were assessed using the Kaplan Meier method. To evaluate the prognostic significance of the PLR, univariate cox regression model was used. *Results:* The 1-, 3-, 5-year overall survival rates of all cases were 81.1%, 43.3% and 20.0% respectively and the 1-, 3-, 5-year recurrence free survival rates were 53.0%, 21.1% and 5.6% respectively. The median survival time was 16.0 months. The PLR cutoff value was calculated to be at 148. For PLR values lower than 148, the overall 1-, 3-, 5-year survival rates were found to be 81.0%, 50.0%, and 26.2% respectively whereas for values higher than 148, the overall 1-, 3-, 5-survival rates were 83.3%, 37.5%, and 14.5% respectively. PLR significantly correlated with an adverse prognosis ($P$=0.018). Multivariate analyses found that the tumor markers CA19-9 and PLR were independently associated with overall survival. *Conclusion:* Our results show that preoperative platelet to lymphocyte ratio represents an independent adverse prognostic factor for individual risk assessment in patients with ICC.

**Keywords:** Platelet-to-lymphocyte ratio, prognostic factors, intrahepatic cholangiocarcinoma (ICC), overall survival (OS), recurrence free survival (RFS)

## Introduction

Cholangiocarcinoma is a type of cancer that originates from the extrahepatic bile duct, hilar bifurcation, and intrahepatic duct. Intrahepatic cholangiocarcinoma is the second most common primary liver tumor after hepatocellular carcinoma. Cholangiocarcinoma represents about 3% of all gastrointestinal malignancies.

Hepatic resection remains the only curative treatment and overall prognosis and survival are poor and only a very small percentage of patients with ICC are resectable at the time of diagnosis. For patients with unresectable disease, palliative radiochemotherapy, ablation, or chemoembolization are the major options [1]. Therefore, it is important to identify factors that would improve survival in these patients. Novel targets for diagnosis and prognostic approaches are urgently needed. Given the rise in incidence of ICC, its poor prognosis and lack of satisfactory treatment choices, it is imperative that further research is done regarding risk factors, outcomes, and prognostic factors.

There are several systemic inflammation-based scores such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet count that have prognostic values in many types of cancer [2, 3]. The link between thrombocytosis, poor prognosis, and shorter survival time has been established in several types of solid tumors including breast, lung, colon, gastric, and ovarian cancer [4]. With the recognition that low lymphocyte counts may also be associated with shorter survival [5], the platelet to lymphocyte ratio (PLR) has been studied as a prognostic biomarker. However, very few studies have reported the prognostic value of such inflammatory markers in ICC patients.

The present aim of the study was to investigate the association between peripheral blood PLR and other factors in intrahepatic cholangiocar-

**Table 1.** Correlation between PLR and clinicopathological indexes (n=90)

| Clinicopathological indexes | | PLR | | *P*-Value |
|---|---|---|---|---|
| | | <148, n=42 | ≥148, n=48 | |
| Age | <50 | 3 | 6 | 0.616 |
| | >50 | 39 | 42 | |
| Gender | Male | 20 | 19 | 0.389 |
| | Female | 22 | 29 | |
| Recurrence | Yes | 32 | 37 | |
| | No | 10 | 11 | |
| Weight | <54 | 19 | 20 | 0.636 |
| | >54 | 23 | 28 | |
| Hepatitis (HBsAg) | Positive | 7 | 10 | 0.609 |
| | Negative | 35 | 38 | |
| CA 19-9 | <37 | 10 | 12 | 0.005 |
| | >37 | 32 | 36 | |
| Cirrhosis | Yes | 4 | 8 | 0.082 |
| | No | 38 | 40 | |
| Intrahepatic duct stone | Yes | 18 | 13 | 0.092 |
| | No | 24 | 35 | |
| Lymph node metastasis | Yes | 18 | 30 | 0.031 |
| | No | 24 | 18 | |

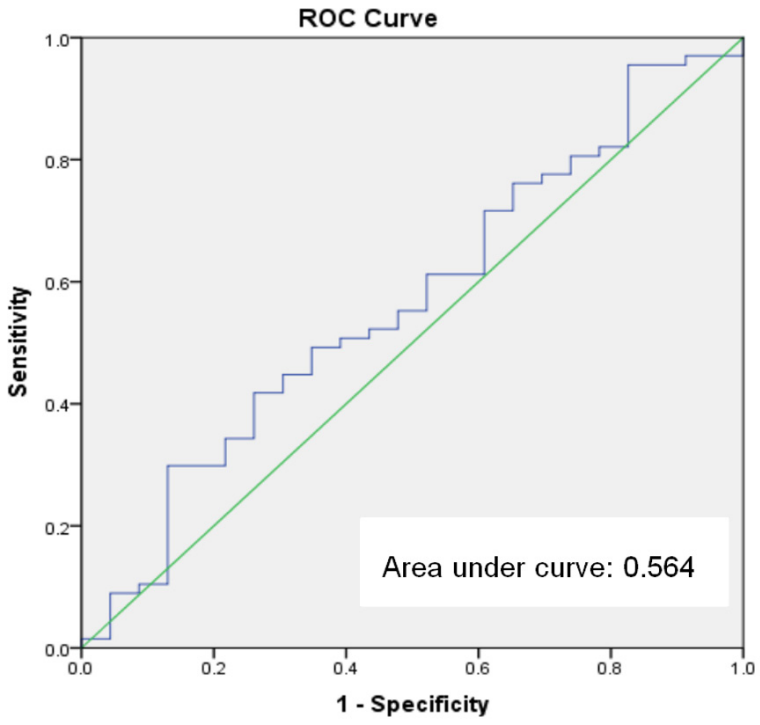


**Figure 1.** Graph of sensitivity against 1-specificity.

cinoma with overall survival. We hypothesized that inflammation is associated with the prognosis of intrahepatic cholangiocarcinoma.

## Materials and methods

Clinical and pathological data were retrospectively collected from 90 patients who underwent radical resection of pathologically confirmed ICC between 2007 and 2016 at the First Affiliated Hospital of Wenzhou Medical University. A total of 90 patients were admitted to our hospital from January 2007 to March 2016. Patients who had received pre-operative chemotherapy or radiofrequency ablation with distant metastasis were excluded from the analysis.

Preoperative blood cell counts including platelet count and lymphocyte count were obtained within 3 days prior to surgery. The following data were collected for all patients: age, gender, race, date of surgery, weight, hepatitis B antigen, CA19-9 level, cirrhosis, platelet, and lymphocyte counts, presence of intrahepatic duct stones, presence of lymph node metastasis, and recurrence. Hepatic resection was the main operation performed as curative treatment.

Overall survival was defined as the time between surgery and death, or the interval between surgery and the last observation of surviving patients. The time for recurrence was defined as the time interval between the date of surgery and the first recurrence. Pathologic examination was carried out on all resected tumors. Computer tomography was performed at postoperative follow-up appointments. Tumor recurrence was indicated by elevated CA19-9 and abnormal findings on the

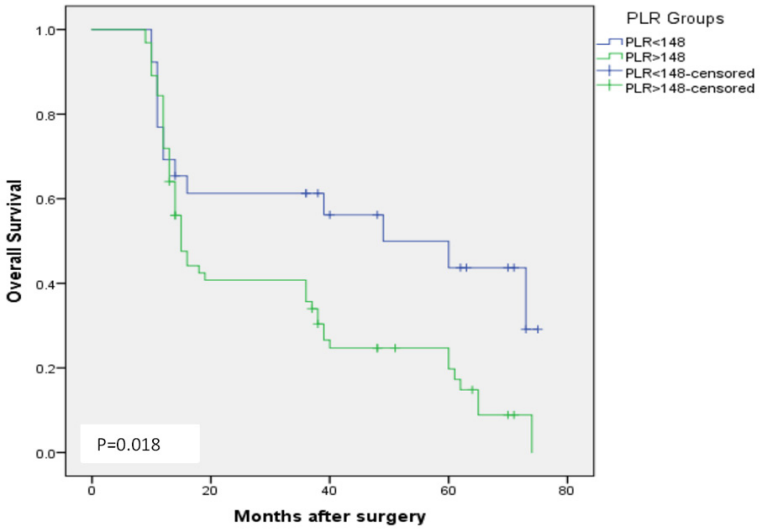


**Figure 2.** Kaplan-Meier survival curves showing the relationship between overall survival (OS) in ICC patients and preoperative PLR.

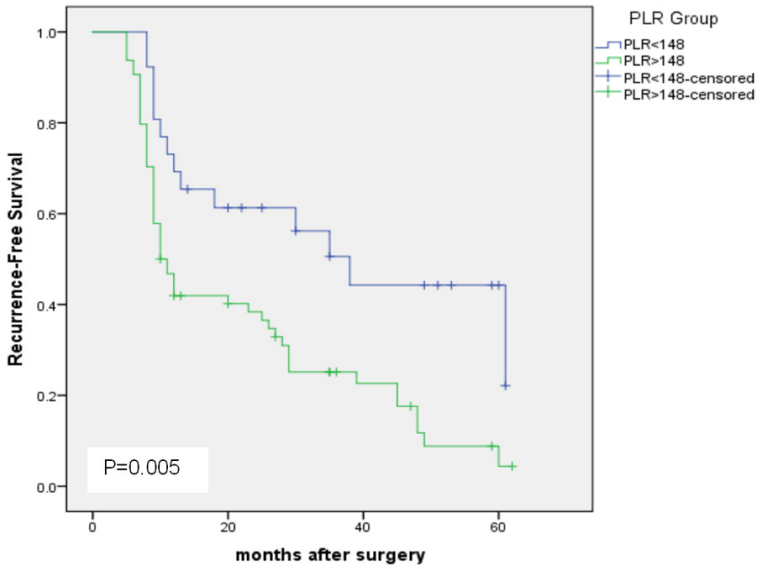


**Figure 3.** Kaplan-Meier survival curves showing the relationship between recurrence-free survival (RFS) in ICC patients and preoperative PLR.

CT scan and radiography imaging of the chest, abdomen, and pelvis.

Patients who were still alive during the course of the follow up were censored at the date last seen alive. Informed consent was obtained from each patient according to Institutional Review Board protocols and ethical approval was obtained by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

All statistical analyses were performed using the SPSS version 19.0 software for Windows. The Platelet to Lymphocyte ratio count was calculated as the absolute platelet count ($\times 10^9$ $L^{-1}$) divided by the absolute lymphocyte count ($\times 10^9$ $L^{-1}$). The postoperative survival rate was performed by the Kaplan-Meier analysis and log rank tests to identify statistical significance between the different groups. Univariate and multivariate analysis of Cox regression proportional hazard model was performed to evaluate the prognostic parameters for survival. *P* values <0.05 were considered statistically significant.

## Results

Ninety patients underwent hepatic resection for suspected intrahepatic cholangiocarcinoma at the First Affiliated Hospital of Wenzhou Medical University between January 2007 and March 2016. There were 39 males (43.3%) and 51 females (56.7%). The mean PLR value was 184.0±10. The clinicopathological features of the patients are detailed in **Table 1**. Median age at the time of diagnosis is 65.0± 10.5. In total, 17 patients (18.9%) were HbsAg+, 68 patients (75.6%) had Ca19-9 level more than 37 U/ml and 12 (13.3%) had liver cirrhosis. Imaging studies and surgical records showed that 31 patients (34.4%) had intrahepatic duct stones and 48 patients (53.3%) had lymph node metastasis.

*Association between PLR and clinicopathological characteristics*

Using time-dependent receiver operating characteristic curve, we determined a cutoff PLR value of 148 as shown in **Figure 1**. Patients were divided into two groups; one with low

**Table 2.** Relationship between clinicopathological parameters and survival rate

| Clinicopathological indexes | N | | Survival rate | | |
|---|---|---|---|---|---|
| | | | 1 year | 3 years | 5 years |
| Age | | | | | |
| | 9 | <50 | 77.8% | 44.4% | 44.4% |
| | 81 | >50 | 82.7% | 43.2% | 17.3% |
| Gender | | | | | |
| | 39 | Male | 82.1% | 43.6% | 20.5% |
| | 51 | Female | 82.4% | 43.1% | 19.6% |
| Recurrence | | | | | |
| | 69 | Yes | 79.7% | 37.7% | 15.9% |
| | 21 | No | 90.5% | 61.9% | 33.3% |
| Weight | | | | | |
| | 39 | <54 | 76.9% | 41.0% | 20.5% |
| | 51 | >54 | 86.3% | 45.1% | 19.6% |
| Hepatitis (HBsAg) | | | | | |
| | 17 | Positive | 88.2% | 47.1% | 23.5% |
| | 73 | Negative | 80.8% | 42.5% | 19.2% |
| CA 19-9 | | | | | |
| | 22 | <37 | 90.9% | 68.2% | 27.3% |
| | 68 | >37 | 79.4% | 35.3% | 17.6% |
| Cirrhosis | | | | | |
| | 12 | Yes | 91.7% | 50% | 25.0% |
| | 78 | No | 80.8% | 42.3% | 19.2% |
| Intrahepatic duct stone | | | | | |
| | 31 | Yes | 71% | 41.9% | 25.8% |
| | 59 | No | 88.1% | 44.1% | 16.9% |
| Lymph node metastasis | | | | | |
| | 48 | Yes | 72.9% | 37.5% | 20.8% |
| | 42 | No | 93.0% | 50.0% | 19.0% |
| Platelet to lymphocyte ratio | | | | | |
| | 42 | <148 | 81.0% | 50.0% | 26.2% |
| | 48 | >148 | 83.3% | 37.5% | 14.5% |

PLR<148 (*n*=42) and high PLR>148 (*n*=48). Comparing the clinical and pathological data between the two groups, we observed that high PLR correlate with Ca19-9 and lymph node metastasis. However, high PLR did not correlate with age, gender, weight, HbsAg, cirrhosis, or intrahepatic duct stone as shown in **Table 1**.

*Survival estimates according to PLR*

In 90 patients who had hepatic resection, it was found that the median survival time was 16.0 months and the median recurrence free survival was 11.5 months. Overall survival for patients in the high PLR group was worse than those in the low PLR group. (11 months *vs*. 49 months) Recurrence free survival for patients with high PLR was also worse than those with low PLR. (10 months *vs*. 38 months).

Out of the 90 patients, 69 (76.7%) patients experienced disease progression, and 67 (74%) patients died. The 1-, 3-, 5-year overall survival rates of the 90 cases were 81.1%, 43.3%, and 20.0% respectively. The 1-, 3-, 5-year recurrence-free survival rates were 54.3%, 10.9%, and 2.2% respectively. As shown by **Figures 2** and **3**, the Kaplan-Meier analysis of OS and RFS demonstrated a progressively lower OS and RFS in elevated PLR groups. Overall survival for patients with high PLR was worse than with those with low PLR: for PLR values lower than 148, the overall 1-, 3-, 5-year survival rates were found to be 81.0%, 50.0%, and 26.2% respectively whereas for values higher than 148; the overall 1-, 3-, 5-survival rates were 83.3%, 37.5%, and 14.5% respectively (**Table 2**). Recurrence free survival for patients with high PLR was also worse than those with low PLR: for PLR values lower than 148; the 1-, 3-, and 5-year survival rates were 59.5%, 26.2%, and 9.5%%, respectively; whereas for PLR values above 148, survival rates were at 48.9%, 16.7%, and 2.1%, respectively.

In addition, elevated PLR values significantly correlated with the cancer recurrence after resection (HR 2.364, 95% CI=1.303-4.288, *P*=0.005). Cox proportional hazard models were used to identify associations between the parameters and OS and RFS in the study population. Univariate analyses showed that high PLR values had a significant influence on intrahepatic cholangiocarcinoma patient survival (Hazard ratio, HR 2.055, 95% CI=1.130-3.373, *P*=0.018). On multivariate analysis, we found that PLR (*P*=0.018) and CA19-9 (*P*=0.002) significantly correlated with prognosis but lymph node metastasis was not significant.

**Table 3.** Univariate analyses for prognostic factors of patients with ICC

| Clinicopathological indexes | | OS | | | RFS | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Age | <50 | 1.475 | 0.630-3.454 | 0.371 | 1.372 | 0.591-3.186 | 0.461 |
| | >50 | | | | | | |
| Gender | Male | 0.957 | 0.587-1.561 | 0.862 | 0.898 | 0.549-1.470 | 0.669 |
| | Female | | | | | | |
| Weight | <54 | 0.991 | 0.611-1.608 | 0.972 | 1.058 | 0.654-1.711 | 0.819 |
| | >54 | | | | | | |
| Hepatitis (HBsAg) | Positive | 0.773 | 0.404-1.481 | 0.438 | 0.847 | 0.443-1.620 | 0.616 |
| | Negative | | | | | | |
| CA 19-9 | <37 | 3.067 | 1.514-6.214 | 0.002 | 2.891 | 1.471-6.039 | 0.002 |
| | >37 | | | | | | |
| Cirrhosis | Yes | 0.683 | 0.310-1.506 | 0.345 | 0.735 | 0.335-1.612 | 0.443 |
| | No | | | | | | |
| Intrahepatic duct stone | Yes | 1.135 | 0.687-1.876 | 0.620 | 1.096 | 0.666-1.803 | 0.718 |
| | No | | | | | | |
| Lymph node metastasis | Yes | 1.818 | 1.106-2.989 | 0.018 | 1.833 | 1.106-3.036 | 0.019 |
| | No | | | | | | |
| PLR | <148 | 2.055 | 1.130-3.737 | 0.018 | 2.364 | 1.303-4.288 | 0.005 |
| | >148 | | | | | | |

**Table 4.** Multivariate analyses of factors for overall survival and recurrence free survival using the Cox proportional hazards model

| Clinicopathological indexes | | OS | | | RFS | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Ca19-9 | <37 | 3.079 | 1.519-6.241 | 0.002 | 3.108 | 1.530-6.314 | 0.002 |
| | >37 | | | | | | |
| PLR | <148 | 2.062 | 1.135-3.747 | 0.018 | 2.480 | 1.357-4.531 | 0.003 |
| | >148 | | | | | | |

## Discussion

ICC usually presents sporadically as a discrete intrahepatic mass in patients over 65 years of age [6]. ICC is classified into 3 types; the mass forming type, located in the peripheral region, is known as cholangiocellular carcinoma, it originates from the hepatic stem cell. Two other types are periductal infiltrating type and intra ductal growth type. Studies show that there is a slight male predominance overall, with a male-to-female ratio for cholangiocarcinoma of 1.2-1.5:1 in patients in their 60s and 70s [7]. Because of the lack of typical symptoms in the early stages of the disease, the majority of ICC patients have unresectable tumors at the time of diagnosis. ICC not only invades the portal region, but also tends to spread by perineural and lymphatic invasion and metastasis to local and distant lymph nodes [8, 9].

The present study was designed to investigate the prognostic role of Platelet to Lymphocyte ratio in cholangiocarcinoma patients who underwent curative surgical resection. The main findings in our study are as follows: We found that high PLR correlated with CA19-9 and lymph node metastasis, but not with age, gender, weight, HbsAg, cirrhosis, and intrahepatic duct stone. The tumor marker ca19-9 and lymph node metastasis were also independent prognostic factors of survival. Univariate analyses (**Table 3**) showed that PLR, lymph node metastasis, and CA19-9 significantly correlated to an adverse prognosis of ICC. Under multivariate analysis as shown in **Table 4**, it was

found that PLR (*P*=0.018) and CA19-9 (*P*= 0.002) significantly correlated with prognosis but lymph node metastasis did not.

As the clinical presentation of ICC is nonspecific, diagnosis cannot be based only on physical examination. Patients in early stages are often asymptomatic and in late stages they may present with weight loss, malaise, painless jaundice, abdominal discomfort, or palpable abdominal mass. Imaging features of ICC from CT scan, MRI and ultrasound imaging may be suggestive of the diagnosis but are not definitive. Histological examination from a biopsy sample is required to distinguish ICC from benign lesions. A study showed an improvement in the trend of prognosis of patients who underwent hepatic resection due to recent advances in imaging technologies, and improved surgical techniques [10].

In recent years, clear evidence showed that inflammation plays pivotal roles in carcinogenesis and tumor metastasis [11, 12]. A systemic inflammatory response is important in carcinogenesis and tumor progression and is associated with short post-operative survival in patients with various types of cancer [13, 14]. There are dynamic interactions between the tumor cells and components of the tumor inflammatory environment which results in tumor progression and metastasis [15].

A study by An Feng Si et al. found that recurrence of ICC after hepatic resection in 10 years incidence was at 80.2% and that most tumor recurrence developed within 5 years after surgery. It also showed that CEA>10 U/mL, Ca19-9>39 U/mL, tumor diameter >5 cm, multiple tumors, vascular tumors, nodal metastasis, and local extrahepatic invasion were associated with recurrence and ICC-related death [16]. In our study, we found that the incidence of recurrence from 2007 to 2016 was at 76.7%. In a recent study, U.F Wellner et al. showed that perineural invasion, lymph node metastasis and positive resection margin status were associated with a shorter survival in distal cholangiocarcinoma [17]. Zhang reported the use of neutrophil to lymphocyte ratio and lymphocyte to monocyte ratio in addition to PLR (*P*=0.048) as prognostic factors in ICC and found that they all correlated adversely with overall survival of the disease. The 1 year survival rate for patients with PLR above the cutoff value of 138 was at 27.7% and for those below the cutoff value, it was at 40.4%. However it should be noted that these patients only received chemotherapy and did not undergo surgery [18].

Immunity control in the body is related to Platelets and lymphocytes. Therefore, PLR, a combined index of platelets and lymphocyte counts, has been investigated as a prognostic factor in various cancers. Recently, a meta-analysis including 12,754 patients demonstrated that high PLR was associated with shorter OS in various solid tumors [19]. It has been shown to be an independent risk factor in other malignant cancers, such as pancreatic ductal adenocarcinoma [20], colon cancer [21] and ovarian cancer [22].

A clear explanation about this mechanism has not been elucidated yet. A high PLR represents both an elevated platelet dependent pro-tumor reaction and a decreased lymphocyte mediated anti-tumor immune response which both contributes to cancer progression and therefore a poor prognosis. A report showed that platelets can secrete VEGF which promote angiogenesis for the tumor and lymphocytes such as $CD3^+$ T cells and $CD8^+$ T cells and NK cells can inhibit tumorigenesis, therefore a decrease in lymphocyte count leads to a diminished anti-tumor activity [23].

In recent studies, PLR has been considered to be an indicator of inflammation and it also correlated with the prognosis of several cancers. A meta-analysis of twenty studies involving more than 12,000 patients found that elevated PLR was associated with poor survival in several malignancies [19]. A study by Liu, Chao et al. found an association between an elevated PLR and OS and RFS in breast cancer [24]. Some previous reports identified Ca19-9 and lymph node metastasis as prognostic factors for ICC, as supported by our study [25]. A study by Xun done on 104 ICC patients reported that the prognosis of ICC was significantly affected by age, gender, AJCC stage, differentiation, Fer, Ca 19-9, CEA levels, lymph node metastasis, and lymph node dissection [26]. In a study by Chen Qing et al., they found that tumor size and number of tumor also influenced prognosis in addition to the factors we found to be significant in our study. Their results are consistent with ours but also need to be independently validated [27].

There are several limitations in our study. The first is the small sample size, which is due to the rarity of the disease under investigation. Biliary tract cancers comprise of less than 3% of all human cancers. Second, the study represents cases seen at a single institution, which may limit its utility in patients with intrahepatic cholangiocarcinoma in general, multicenter studies would consolidate our findings. Third, our study is limited by its retrospective design which results in some patients being lost to follow-up. Finally, we cannot exclude the possibility that nonmalignant factors may have influenced the reported PLR.

In conclusion, this research highlights the potential use of PLR as prognostic factors for overall survival and recurrence free survival in patients with intrahepatic cholangiocarcinoma after surgery. To the best of our knowledge, there is not much significant data regarding the prognostic value of PLR in intrahepatic cholangiocarcinoma patients. The clinical significance of this indicator must be further validated in order to establish it as prognostic factor for ICC. Not only is it cost-effective, but PLR is also readily available from a blood routine test, and therefore it may be very useful in the clinical setting.

## Disclosure of conflict of interest

None.

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