BMC Cancer

RESEARCH

Open Access

Preoperative monocyte-to-lymphocyte ratio as a prognosis predictor after curative hepatectomy for intrahepatic cholangiocarcinoma

Bin-Feng Tao[1†], Hai-Qiang Zhu[1†], Lu-Nan Qi[1,2,3], Jian-Hong Zhong[1,2,3], Rong-yun Mai[1,2,3*] and Liang Ma[1,2,3*]

Abstract

Background Several inflammatory indicators have been reported to have predictive value in many types of malignant cancer. This research was aimed to explore the ability of the monocyte-to-lymphocyte ratio (MLR) to predict prognosis in patients with intrahepatic cholangiocarcinoma (ICC) who subjected to curative hepatectomy.

Methods This retrospective analysis included 196 patients with ICC who underwent curative hepatectomy between May 2018 and April 2023. The predictive abilities of the preoperative MLR in assessing overall survival (OS) and disease-free survival (DFS) in those patients were compared with other inflammation-based scores, including monocyte-to-white ratio, neutrophil-to-lymphocyte ratio, neutrophil-to-white ratio, platelet-to-lymphocyte ratio, platelet-to-white ratio, and systemic immune-inflammation index, as well as tumor markers, like carcinoembryonic antigen (CEA) and carbohydrate antigen 19−9 (CA19-9).

Results The area under the time-dependent receiver operating characteristic curve indicated that the preoperative MLR had higher predictive efficiency in contrast with other inflammation-based scores and tumor markers in assessing OS and DFS. Stratifying patients according to the optimal cut-off value for the preoperative MLR, the data showed that both OS and DFS in the high MLR group were significantly worse than those in the low MLR group ($p < 0.05$ for all). Univariable and multivariable Cox analyses revealed that the preoperative MLR was an independent risk factor for OS and DFS in patients with ICC. In addition to predicting OS in patients with high CEA levels and predicting DFS in patients with high CA19-9 levels, patients with different CEA and CA19-9 levels were divided into completely different OS and DFS subgroups based on the risk stratification of the preoperative MLR.

Conclusions Our results demonstrated that the preoperative MLR was a good prognosis indicator to predict DFS and OS following curative hepatectomy in patients with ICC.

†Bin-Feng Tao and Hai-Qiang Zhu contributed equally to this work.

*Correspondence:
Rong-yun Mai
mairongyun@sr.gxmu.edu.cn
Liang Ma
malianggxyd@163.com

Full list of author information is available at the end of the article

Keywords Intrahepatic cholangiocarcinoma, Monocyte-to-lymphocyte ratio, Prognosis, Surgery

Introduction

Intrahepatic cholangiocarcinoma (ICC), is the most common biliary cancer and the second most prevalent primary liver cancer, accounting for up to 20% of all hepatic malignancies [1, 2]. Hepatectomy is considered the curative therapy for patients with ICC. However, the effectiveness of this method is not ideal due to high recurrence rates [1, 3–6]. The tendency of ICC to spread extensively throughout the body results in tumors found in multiple locations, lymph node metastasis, and blood vessel infiltration, ultimately leading to poor long-term survival after curative hepatectomy [1]. Additionally, the initial symptoms of ICC are vague, and most cases cannot undergo curative hepatectomy when symptoms arise, resulting in a pessimistic outcome for these patients [5]. The American Joint Committee on Cancer (AJCC) staging system prescribes the use of imaging, pathology, and immunohistochemistry for diagnosing and predicting ICC. However, further exploration is needed to identify more convenient indicators for prognosis assessment. Therefore, the development of precise predictive models is invaluable in identifying those at high risk of illness and assisting in their care management.

Studies conducted in both laboratory and clinical settings have shown a strong correlation between inflammation and the emergence and growth of tumors [7, 8]. Inflammatory cells release various cytokines that can modify the tumor microenvironment, thereby stimulating tumor cell growth, inhibiting tumor cell death, increasing the likelihood of metastasis, and impacting the disease outcome for the patient [9]. This understanding presents us with a valuable opportunity to predict tumor development, resulting in improved patient care and more effective treatment choices.

Several prognostic markers of inflammation are already widely used and connected to distinct cancer prognosis. For example, elevated levels of monocyte-to-white ratio (MWR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet-to-white ratio (PWR), as well as systemic immune-inflammation index (SII) have been shown to predict poor prognosis in patients with gastric cancer [10], hypopharyngeal cancer [11], breast cancer [12], acute myeloid leukemia [13], and colorectal cancer [14]. High neutrophil-to-white ratio (NWR) has been recognized as an independent risk factor for poor overall survival (OS) in patients with non-small cell lung cancer [15]. Moreover, the preoperative monocyte-to-lymphocyte ratios (MLR) have been studied to predict the recurrence of gastrointestinal stromal tumors [16]. However, no studies have yet investigated whether the preoperative MLR could be used as a prognostic marker in ICC.

We conducted this retrospective project aiming to investigate the prognostic value of the MLR in estimating prognosis in ICC patients who underwent curative hepatectomy. The predictive performance of the MLR was compared with other scores and tumor markers.

Patients and methods

A total of 196 patients with ICC who underwent curative hepatectomy at Guangxi Medical University Cancer Hospital between May 2018 and April 2023 were selected as the study subjects. Patients who had undergone any of the following procedures before curative hepatectomy were excluded from the study: transarterial chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or immunotherapy for ICC. The research was conducted in accordance with the Helsinki Declaration and approved by the Institutional Ethics Committee of Guangxi Medical University Cancer Hospital.

Diagnosis and definitions

The diagnosis of ICC was confirmed through postoperative histological examination. Staging of ICC was performed based on the staging criteria of the AJCC [17]. Clinically significant portal hypertension (CSPH), which had a noticeable impact on the patient, was defined as the presence of an enlarged spleen or varicose veins in the stomach or esophagus accompanied by thrombocytopenia [18]. The removal of more than three hepatic segments was considered a major hepatectomy [19].

Predictive models based on peripheral serum biomarkers

The serum inflammation markers were calculated as follows: MLR = monocyte counts / lymphocyte counts; MWR = monocyte counts / white blood cell counts; NLR = neutrophil counts / lymphocyte counts; NWR = neutrophil counts / white blood cell counts; PLR = platelet counts / lymphocyte counts; PWR = platelet counts / white blood cell counts; SII = platelet counts × neutrophil counts / lymphocyte counts. An assessment was conducted seven days prior to the curative hepatectomy.

Operation and followup

All individuals involved in this study underwent curative hepatectomy, as the pre-surgery imaging indicated that the tumors could be removed without compromising the function of the remaining liver. Previous research has provided detailed information and indications regarding the surgical procedure [20], lymphadenectomy was

performed according to intrahepatic cholangiocarcinoma surgery criteria [21].

After discharge, follow-up evaluations were conducted on patients who had undergone liver resection at 1 month, and subsequently every three months until the end of the study or death. During subsequent follow-ups, various examinations such as tests of liver function, abdominal CT or MRI scans were used to monitor the tumor. If there was suspicion of recurrence, further investigations including hepatic angiography and cholangiography were conducted. Patients with tumor recurrence received treatments such as re-operation, chemotherapy, radiofrequency ablation, or targeted therapy based on their specific situation. The definitions of OS and disease-free survival (DFS) have been described in detail in our previous research [22]. Patient follow-up lasted until death or the cut-off date of April 2023.

Statistical analysis

Continuous factors were showed as median (interquartile range [IQR] 25–75) or mean ± SD and compared using the Mann-Whitney U-test or T-test, while categorical factors were expressed as numbers (%) and compared using the chi-square test or Fisher's exact test.

The predictive ability of prognostic models based on inflammation to estimate OS and DFS was assessed by time-dependent receiver operating characteristic (t-ROC) curves [23]. The X-tile analysis determined the optimal cut-off value for 5-years OS [24]. Kaplan-Meier (KM) method was applied to evaluate OS and DFS, and the log-rank test was used to identify differences between groups. Multivariable Cox analysis was carried out to confirm independent risk indicators for OS and DFS. Factors with a p-value < 0.05 in the univariable analysis were incorporated in the multivariable analysis.

The statistical analysis was performed using X-Tile (v3.6.1), SPSS (v25.0), and RStudio (v1.4.1106) software programs. A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

The detailed data of patient characteristics of 196 cases are presented in Table 1. The average age of the patients was 59 years old, and 73.5% were male. Among the patients, 49.0% were infected with hepatitis B virus, 36.2% were diagnosed with liver cirrhosis, and 5.1% had CSPH. 89.8% showed satisfactory liver reserve function, while only 10.2% were classified as Child-Pugh B. The median values for the prognostic indicators MLR, NLR, NWR, PLR, and SII were 0.27 (IQR 0.20–0.38), 2.31 (IQR 1.57–3.64), 0.61 (IQR 0.53–0.68), 122.22 (IQR 98.55-172.86), and 522.20 (IQR 340.50-887.90), respectively. Regarding the TNM stage, 71.4% were classified as stage 1, followed by 16.8% at stage 2, and 11.7% at stage 3. 83.7% showed low AFP levels (< 200 ng/ml), 82.1% had lower carcinoembryonic antigen (CEA) levels (< 10 ng/ml), and 69.4% had lower carbohydrate antigen 19−9 (CA19-9) levels (< 100 U/ml). A total of 196 hepatectomies were performed, of which 67 were major and 129 were minor.

Differential findings based on prognostic models of inflammation

The t-ROC curves (AUC) were compared and showed that the preoperative MLR had better predictive performance for measuring DFS than other inflammation-related scores, such as MWR, NLR, NWR, PLR, PWR, SII, CEA, and CA19-9. The t-ROC curve of PWR was the lowest, indicating that it was difficult to predict postoperative DFS (Fig. 1A). Similarly, the preoperative MLR demonstrated a higher t-ROC curve than the other models when assessing OS after curative hepatectomy, while PWR still had the lowest curve. These results were consistent across time points (Fig. 1B). The MLR analysis revealed better predictive accuracy than other inflammation-based prognostic systems for OS and DFS, with AUCs of 0.78, 0.74, and 0.73 for 1-, 3-, and 5-years OS, respectively. For DFS, the AUCs were 0.74, 0.77, and 0.76 (Supplementary Table 1).

Cut-off values of prognostic scores

The X-tile program was used to determine the best cut-off values for these scores. As shown in Supplementary Fig. 1, the optimal cut-off values for MLR, MWR, NLR, NWR, PLR, PWR, and SII were 0.44, 0.06, 2.53, 0.68, 225.69, 48.68, and 706.40, respectively. The cases were classified into a low MLR group (≤ 0.44, $n = 161$) and a high MLR group (> 0.44, $n = 35$) based on an MLR value of 0.44.

Correlation between the preoperative MLR and clinicopathological variables

As shown in Table 1, the high MLR group had similar median age as the low MLR group, but showed higher serum levels of white blood cells, neutrophils, monocytes, lower serum albumin, and more severe liver conditions (including a higher incidence of Child–Pugh B grade, cirrhosis, ascites and CSPH). Additionally, the high MLR group showed worse tumor conditions with a larger volume, more microvascular invasion, lymphatic metastasis and satellites, as well as more challenging surgical conditions with increased blood loss and larger liver removal, in contrast with the low MLR group. Furthermore, the high MLR group demonstrated significantly increased levels of NLR, NWR, PLR, and SII ($p < 0.05$ for all).

Table 1 Clinicopathological characteristics of 196 patients with included patients and different MLR risk groups

Variables	Total ($n=196$)	Low MLR ($n=161$)	High MLR ($n=35$)	*P* value
Age(years)	59 (49, 66)	59 (49, 66)	59 (52, 67)	0.594
Sex				0.033
Male	144 (73.5)	113 (70.2)	31 (88.6)	
Female	52 (26.5)	48 (29.8)	4 (11.4)	
Hight (cm)	164.0 (159.0, 168.5)	164.0 (158.0, 168.8)	164.0 (160.0, 168.3)	0.586
Weight (kg)	60.0 (54.0, 70.0)	60.0 (55.0, 69.5)	60.0 (51.5, 73.3)	0.704
Positive HBsAg	96 (49.0)	81 (50.3)	15 (42.9)	0.424
HBV-DNA (IU/mL)				1.000
≥ 2000	27 (13.8)	22 (13.7)	5 (14.3)	
< 2000	169 (86.2)	139 (86.3)	30 (85.7)	
White blood count (10^9/L)	7.3 (5.4, 8.6)	7.0 (5.4, 8.4)	8.4 (6.1, 10.7)	0.030
Neutrophil count (10^9/L)	4.1 (3.1, 5.7)	3.9 (3.0, 5.1)	6.0 (4.0, 7.8)	< 0.001
Lymphocyte count (10^9/L)	1.8 (1.4, 2.3)	1.9 (1.5, 2.4)	1.4 (1.1, 1.8)	< 0.001
Monocyte count (10^9/L)	0.5 (0.4, 0.7)	0.5 (0.4, 0.6)	0.7 (0.6, 0.9)	< 0.001
PLT count (10^9/L)	236.0 (181.0, 291.0)	227.0 (177.0, 290.5)	260.0 (205.5, 325.3)	0.196
TBil (μmol/L)	12.6 (9.2, 16.7)	12.6 (9.2, 16.5)	12.8 (10.3, 19.1)	0.079
PA (mg/L)	193.0 ± 73.0	201.0 ± 70.7	155.4 ± 73.2	< 0.001
Albumin (g/L)	38.4 (34.5, 40.9)	38.5 (34.8, 41.0)	36.6 (33.9, 40.6)	0.171
ALT(U/L)	27.0 (16.0, 42.0)	27.0 (17.0, 41.0)	20.5 (13.8, 47.8)	0.679
AST (U/L)	32.0 (25.0, 46.0)	32.0 (24.0, 46.5)	32.0 (26.5, 46.5)	0.200
GGT (U/L)	68.0 (39.0, 133.0)	60.0 (37.5, 104.5)	107.5 (67.0, 252.8)	0.010
ALP (U/L)	86.0 (71.0, 128.0)	83.0 (71.0, 117.0)	124.0 (70.8, 213.5)	0.054
CR (μmol/L)	65.0 (55.0, 83.0)	73.0 (64.0, 84.0)	74.5 (65.8, 82.3)	0.990
BUN (mmol/L)	4.7 (3.7, 5.4)	4.7 (3.8, 5.5)	4.5 (3.4, 5.3)	0.234
PT (s)	12.0 (11.2, 13.0)	12.0 (11.2, 13.0)	12.4 (11.4, 12.9)	0.199
INR	0.98 (0.93, 1.06)	0.98 (0.93, 1.06)	1.00 (0.91, 1.08)	0.482
Child-Pugh grade				0.761
A	176 (89.8)	145 (90.1)	31 (88.6)	
B	20 (10.2)	16 (9.9)	4 (11.4)	
AFP (ng/mL)				1.000
≥ 200	32 (16.3)	27 (16.8)	5 (14.3)	
< 200	164 (83.7)	134 (83.2)	30 (85.7)	
CEA (ng/mL)				0.010
≥ 10	35 (17.9)	22 (13.7)	13 (37.1)	
< 10	161 (82.1)	139 (86.3)	22 (62.9)	
CA19-9 (U/mL)				0.032
≥ 100	60 (30.6)	44 (27.3)	16 (45.7)	
< 100	136 (69.4)	117 (72.7)	19 (54.3)	
MLR	0.27 (0.20, 0.38)	0.25 (0.19, 0.32)	0.56 (0.49, 0.76)	< 0.001
MWR	0.07 ± 0.02	0.07 ± 0.02	0.09 ± 0.02	
NLR	2.31 (1.57, 3.64)	2.08 (1.47, 2.89)	4.80 (3.29, 5.64)	< 0.001
NWR	0.61 (0.53, 0.68)	0.27 ± 0.09	0.27 ± 0.09	< 0.001
PLR	122.22 (98.55, 172.86)	116.26 (94.21, 158.48)	713.05 (147.50, 241.06)	< 0.001
PWR	33.84 ± 10.45	34.26 ± 10.24	31.82 ± 11.35	0.198
SII	522.2 (340.5, 887.9)	463.40 (306.3, 766.4)	1145.41 (784.1, 1822.6)	< 0.001
CSPH	10 (5.1)	7 (4.3)	3 (8.6)	0.388
Ascites	15 (7.7)	11 (6.8)	4 (11.4)	0.354
Cirrhosis	71 (36.2)	51 (31.7)	20 (57.1)	0.004
Tumor size				0.002
> 5 cm	124 (63.3)	94 (58.4)	30 (85.7)	
≤ 5 cm	72 (36.7)	67 (41.6)	5 (14.3)	
Tumor number				0.656
Multiple	33 (16.8)	28 (17.4)	5 (14.3)	

Table 1 (continued)

Variables	Total ($n=196$)	Low MLR ($n=161$)	High MLR ($n=35$)	*P* value
Single	163 (83.2)	133 (82.6)	30 (85.7)	
Macrovascular invasion	22 (11.2)	18 (11.2)	4 (11.4)	1.000
Lymphatic metastasis	23 (11.7)	18 (11.2)	5 (14.3)	0.605
TNM stage				0.818
Stage I	140 (71.4)	115 (71.4)	25 (71.4)	
Stage II	33 (16.8)	28 (17.4)	5 (14.3)	
Stage III	23 (11.7)	18 (11.2)	5 (14.3)	
Operation time (min)	220 (180, 280)	220 (180, 285)	233 (194, 265)	0.475
Blood loss (mL)				0.096
≥ 400	66 (33.7)	50 (31.1)	16 (45.7)	
< 400	130 (66.3)	111 (68.9)	19 (54.3)	
Blood transfusion	28 (14.3)	23 (14.3)	5 (14.3)	1.000
Extent of resection				0.048
Major-hepatectomy	67 (34.2)	50 (31.1)	17 (48.6)	
Minor-hepatectomy	129 (65.8)	111 (68.9)	18 (51.4)	
Resection margin				0.059
> 1 cm	66 (33.7)	59 (36.6)	7 (20.0)	
≤ 1 cm	130 (66.3)	102 (63.4)	28 (80.0)	
Satellite	26 (13.3)	17 (10.6)	9 (25.7)	0.017
Necrosis	146 (74.5)	118 (73.3)	28 (80.0)	0.409
Microvascular invasion	57 (29.1)	47 (29.2)	10 (28.6)	0.942
Tumor capsule				0.829
Complete	128 (65.3)	106 (65.8)	22 (62.9)	
Incomplete	25 (12.8)	21 (13.0)	4 (11.4)	
None	43 (21.9)	34 (21.1)	9 (25.7)	

Abbreviation MLR, monocyte-to-lymphocyte ratio; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PLT, platelet; TBil, total bilirubin; PA, prealbumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase; CR, creatinine; BUN, blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19−9; MWR, monocyte-to-white ratio; NLR, neutrophil-to-lymphocyte ratio; NWR, neutrophil-to-white ratio; PLR, platelet-to-lymphocyte ratio; PWR, platelet-to-white ratio; SII, systemic immune-inflammation index; CSPH, clinically significant portal hypertension

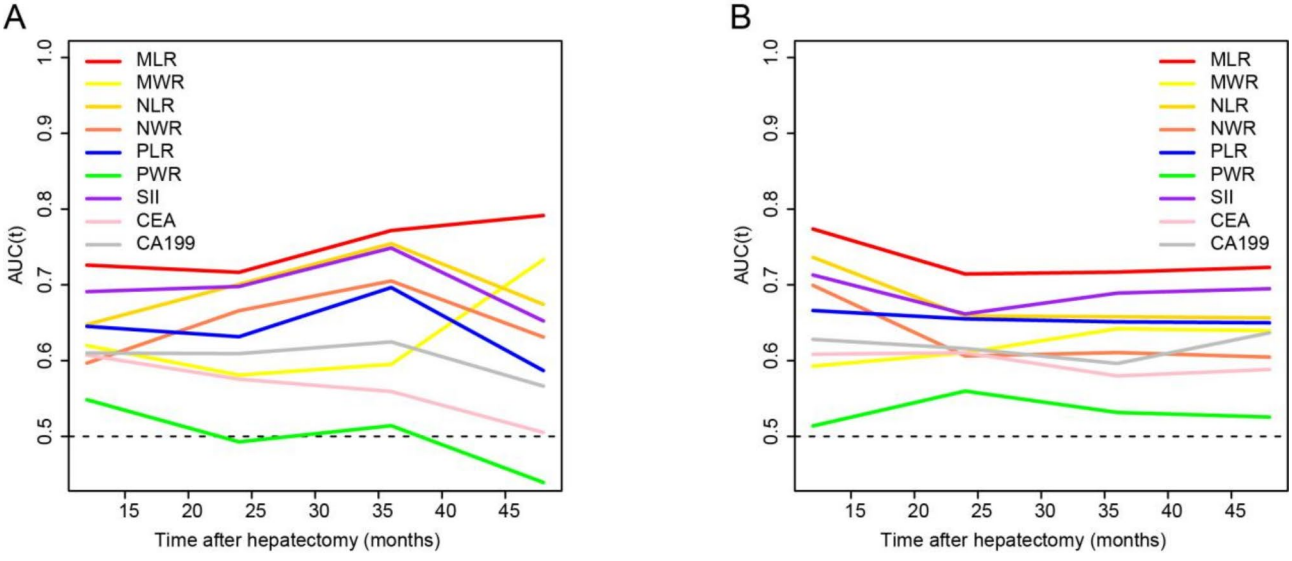

Fig. 1 Time-dependent receiver operating characteristic curve analysis to compare the efficacy of MLR, MWR, NLR, NWR, PLR, PWR, SII, CEA, and CA19-9 in predicting (**a**) DFS and (**b**) OS

Correlation of the MLR with DFS and OS

During the follow-up period, the 1-, 3-, and 5-years DFS rates in the high MLR group were worse in contrast with those in the low MLR group, with survival rates of 11.10%, 2.78%, and 0.00%, respectively ($p<0.05$ for all; Fig. 2A and supplementary Table 2). Furthermore, the 1-, 3-, and 5-years OS rates in the high MLR group were significantly lower than those in the low MLR group with statistical significance, with rates of 36.97%, 9.51%, and 9.51%, respectively, in contrast to 76.50%, 54.47%, and 49.91% ($p<0.05$ for all; Fig. 2B and Supplementary Table 2).

Independent predictors of OS

Univariable Cox analyses revealed that OS was significantly associated with MLR, NLR, NWR, PLR, PWR, and SII, as well as prealbumin (PA), aspartate aminotransferase (AST), alkaline phosphatase (ALP), CEA, CA19-9, tumor size, multiple tumor number, macrovascular invasion (MVI), lymphatic metastasis, TNM stage, blood loss, major curative hepatectomy, satellite, and tumor capsule ($p<0.05$ for all; Table 2). The multivariable Cox analysis demonstrated that the preoperative MLR (HR 2.242, 95% CI 1.291–3.893; $p=0.004$) independently predicted OS, along with other factors such as PA, CEA, lymphatic metastasis, TNM stage, and satellite ($p<0.05$ for all; Table 2).

Independent predictors of DFS

The univariable Cox analysis revealed that prognostic models associated with inflammation (MLR, NLR, NWR, PLR, PWR and SII) had a statistically significant correlation with DFS, as well as PA, AST, gamma-glutamyltransferase, ALP, CEA, CA19-9, tumor size, multiple tumor number, MVI, lymphatic metastasis, TNM stage, blood loss, major curative hepatectomy, and satellite ($p<0.05$ for all, Table 3). The multivariable Cox analysis further revealed that the preoperative MLR independently predicted DFS (HR 2.608, 95% CI 1.379–4.932; $p=0.003$), while other indicators included CEA, NLR, PWR, and multiple tumor number ($p<0.05$ for all, Table 3).

Subgroup analysis

To further assess the clinical practicability and effectiveness of the preoperative MLR, stratified analyses were carried out based on the different statuses of tumor markers. The data indicated that patients in the lower CEA group (<10 ng/mL) and lower CA19-9 group (<100 U/mL) could be divided into two subgroups with substantial differences in both DFS and OS, depending on their preoperative MLR values ($p<0.001$ for both Figs. 3A-B and 4A-B). In contrast, for patients in the higher CEA group (≥10 ng/mL) and higher CA19-9 group (≥100 U/mL), there was a remarkable difference in the preoperative MLR when predicting DFS in the high CEA group ($p<0.05$, Fig. 3C), but no difference was observed when assessing OS ($p=0.190$, Fig. 3D). Furthermore, although no statistical significance was found for DFS in relation to the preoperative MLR in the high CA19-9 ($p=0.130$, Fig. 4C), there was a significant difference in the preoperative MLR when predicting OS in this group ($p<0.001$, Fig. 4D).

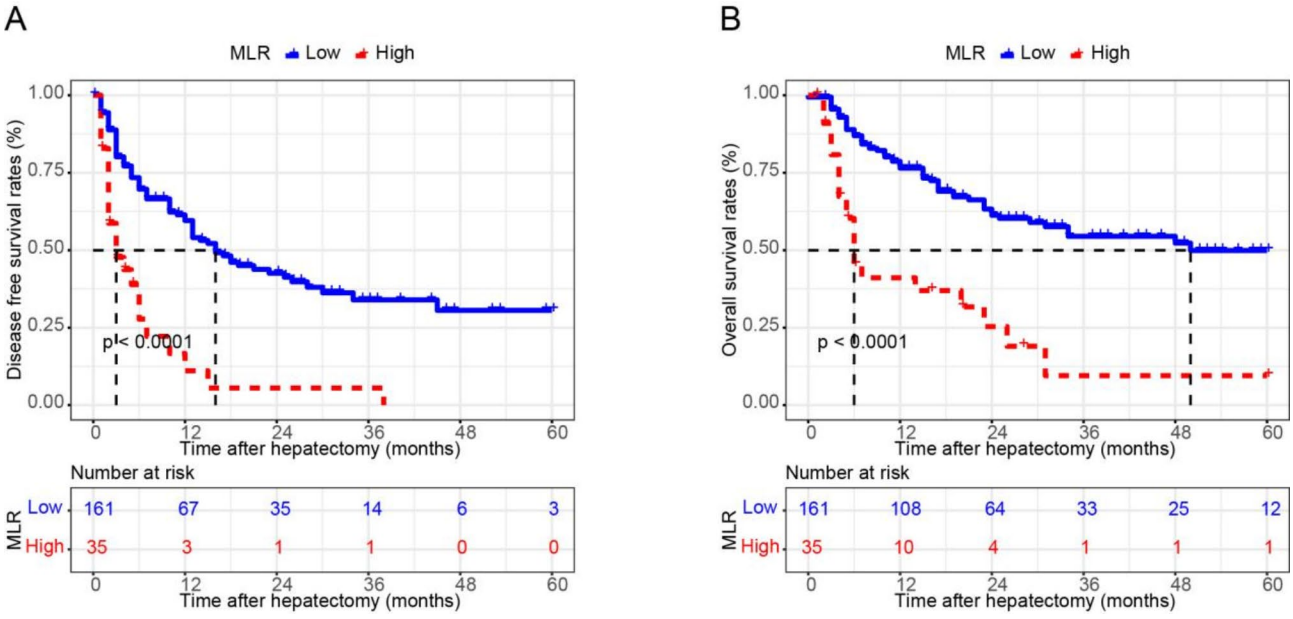

Fig. 2 Kaplan-Meier curves illustrating **(a)** DFS (p < 0.001) and **(b)** OS (p < 0.001) based on the high and low MLR groups in the entire cohort

Table 2 Univariable and multivariable analyses to identify independent prognostic indicators of overall survival in patients with included patients

Variables	Overall survival			
	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.021 (0.999, 1.044)	0.067		
Male sex	0.778 (0.488, 1.242)	0.293		
Positive HBsAg	0.722 (0.466, 1.117)	0.722		
HBV-DNA ≥ 2000 IU/mL	1.350 (0.780, 2.336)	1.350		
PA (mg/L)	0.993 (0.989, 0.996)	< 0.001	0.995 (0.992, 0.999)	0.010
ALT (U/L)	1.002 (1.000, 1.005)	0.105		
AST(U/L)	1.005 (1.000, 1.009)	0.039	1.003 (0.998, 1.009)	0.256
GGT (U/L)	1.001 (1.000, 1.002)	0.112		
ALP (U/L)	1.003 (1.000, 1.005)	0.018	0.998 (0.995, 1.002)	0.340
CR (μmol/L)	0.990 (0.975, 1.004)	0.155		
BUN (mmol/L)	1.010 (0.980, 1.042)	0.511		
AFP ≥ 200 ng/mL	1.196 (0.671, 2.130)	0.544		
CEA ≥ 10 ng/mL	2.671 (1.586, 4.496)	< 0.001	2.088 (1.210, 3.601)	0.008
CA19-9 ≥ 100 U/mL	1.971 (1.264, 3.073)	0.003	0.966 (0.515, 1.811)	0.913
Child-Pugh grade	1.409 (0.704, 2.818)	0.333		
MLR	3.404 (2.071, 5.594)	< 0.001	2.242 (1.291, 3.893)	0.004
MWR	1.335 (0.790, 2.254)	0.280		
NLR	3.085 (1.972, 4.826)	< 0.001	1.937 (0.917, 4.093)	0.083
NWR	2.843 (1.807, 4.471)	< 0.001	0.992 (0.484, 2.037)	0.983
PLR	3.155 (1.754, 5.677)	< 0.001	1.362 (0.528, 3.514)	0.523
PWR	1.900 (1.067, 3.382)	0.029	1.666 (0.915, 3.036)	0.095
SII	3.046 (1.963, 4.726)	< 0.001	0.911 (0.391, 2.122)	0.829
CSPH	0.210 (0.029, 1.508)	0.121		
Ascites	1.356 (0.653, 2.816)	0.414		
Cirrhosis	0.820 (0.502, 1.338)	0.426		
Tumor size > 5 cm	2.418 (1.447, 4.040)	0.001	1.106 (0.596, 2.051)	0.750
Multiple tumor number	2.305 (1.409, 3.772)	0.001	1.064 (0.425, 2.662)	0.894
Macrovascular invasion	2.118 (1.237, 3.625)	0.006	0.709 (0.291, 1.728)	0.450
Lymphatic metastasis	2.379 (1.330, 4.256)	0.003	2.234 (1.144, 4.363)	0.019
TNM stage				
Stage I	Ref		Ref	
Stage II	2.412 (1.455, 3.998)	0.001	2.397 (1.413, 4.069)	0.001
Stage III	2.988 (1.629, 5.481)	< 0.001	2.234 (1.144, 4.363)	0.019
Operation time (min)	1.001 (0.999, 1.003)	0.354		
Blood loss ≥ 400mL	1.951 (1.262, 3.016)	0.003		
Blood transfusion	0.893 (0.483, 1.652)	0.893		
Major-hepatectomy	1.993 (1.290, 3.079)	0.002		
Resection margin > 1 cm	0.695 (0.429, 1.125)	0.139		
Satellite	3.315 (1.924, 5.712)	< 0.001	1.836 (1.004, 3.356)	0.048
Necrosis	1.092 (0.675, 1.766)	0.719		
Microvascular invasion	1.392 (0.880, 2.201)	0.157		
Tumor capsule				
Complete	Ref		Ref	
Incomplete	2.924 (1.126, 7.598)	0.028	2.355 (0.842, 6.588)	0.103
None	2.787 (1.335, 5.818)	0.006	2.047 (0.932, 4.497)	0.074

Abbreviation HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PA, prealbumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase; CR, creatinine; BUN, blood urea nitrogen; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19 – 9; MLR, monocyte-to-lymphocyte ratio; MWR, monocyte-to-white ratio; NLR, neutrophil-to-lymphocyte ratio; NWR, neutrophil-to-white ratio; PLR, platelet-to-lymphocyte ratio; PWR, platelet-to-white ratio; SII, systemic immune-inflammation index; CSPH, clinically significant portal hypertension

Table 3 Univariable and multivariable analyses to identify independent prognostic indicators of disease-free survival in included patients

Variables	Disease-free survival			
	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.014 (0.994, 1.034)	0.165		
Male sex	0.947 (0.613, 1.463)	0.807		
Positive HBsAg	0.679 (0.460, 1.003)	0.052		
HBV-DNA ≥ 2000 IU/mL	0.872 (0.485, 1.569)	0.649		
PA (mg/L)	0.996 (0.993, 1.000)	0.024	0.999 (0.995, 1.003)	0.610
ALT (U/L)	1.002 (1.000, 1.004)	0.069		
AST(U/L)	1.004 (1.000, 1.008)	0.032	1.000 (0.994, 1.005)	0.883
GGT (U/L)	1.002 (1.001, 1.003)	< 0.001	1.002 (0.999, 1.005)	0.280
ALP (U/L)	1.005 (1.003, 1.007)	< 0.001	0.998 (0.993, 1.003)	0.525
CR (μmol/L)	0.996 (0.987, 1.005)	0.386		
BUN (mmol/L)	1.007 (0.978, 1.037)	1.007		
AFP ≥ 200 ng/mL	1.116 (0.670, 1.859)	0.672		
CEA ≥ 10 ng/mL	2.366 (1.466, 3.819)	< 0.001	2.639 (1.327, 5.249)	0.006
CA19-9 ≥ 100 U/mL	1.737 (1.148, 2.628)	0.009	0.753 (0.414, 1.370)	0.353
Child-Pugh grade	1.224 (0.626, 2.471)	0.533		
MLR	3.334 (2.084, 5.334)	< 0.001	2.608 (1.379, 4.932)	0.003
MWR	1.357 (0.833, 2.212)	0.221		
NLR	3.190 (2.119, 4.802)	< 0.001	3.394 (1.683, 6.845)	0.001
NWR	2.232 (1.467, 3.398)	< 0.001	0.643 (0.329, 1.259)	0.198
PLR	3.011 (1.772, 5.115)	< 0.001	1.197 (0.501, 2.858)	0.686
PWR	2.352 (1.373, 4.030)	0.002	3.121 (1.480, 6.579)	0.003
SII	2.506 (1.694, 3.706)	< 0.001	0.711 (0.334, 1.514)	0.376
CSPH	1.011 (0.411, 2.485)	0.981		
Ascites	1.321 (0.612, 2.850)	0.479		
Cirrhosis	1.055 (0.703, 1.584)	0.796		
Tumor size > 5 cm	1.934 (1.270, 2.945)	0.002	1.077 (0.624, 1.858)	0.685
Multiple tumor number	2.115 (1.359, 3.293)	0.001	2.125 (1.334, 3.385)	0.002
Macrovascular invasion	2.281 (1.361, 3.824)	0.002	1.147 (0.483, 2.727)	0.755
Lymphatic metastasis	2.520 (1.480, 4.289)	0.001	1.482 (0.543, 4.052)	0.442
TNM stage				
Stage I	Ref		Ref	
Stage II	2.195 (1.380, 3.492)	0.001	1.026 (0.391, 2.694)	0.958
Stage III	3.046 (1.755, 5.287)	< 0.001	1.482 (0.543, 4.052)	0.442
Operation time(min)	1.002 (0.99, 1.004)	0.162		
Blood loss ≥ 400mL	1.825 (1.231, 2.705)	0.003	1.115 (0.661, 1.881)	0.683
Blood transfusion	0.912 (0.498, 1.671)	0.766		
Major-hepatectomy	1.510 (1.016, 2.244)	0.041	0.880 (0.533, 1.454)	0.618
Resection margin > 1 cm	0.793 (0.525, 1.196)	0.268		
Satellite	2.718 (1.588, 4.653)	< 0.001	1.504 (0.815, 2.777)	0.192
Necrosis	1.317 (0.840, 2.066)	0.231		
Microvascular invasion	1.429 (0.936, 2.181)	0.098		
Tumor capsule				
Complete	Ref			
Incomplete	1.609 (0.811, 3.192)	0.243		
None	1.347 (0.817, 2.223)	0.243		

Abbreviation HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PA, prealbumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase; CR, creatinine; BUN, blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; MLR, monocyte-to-lymphocyte ratio; MWR, monocyte-to-white ratio; NLR, neutrophil-to-lymphocyte ratio; NWR, neutrophil-to-white ratio; PLR, platelet-to-lymphocyte ratio; PWR, platelet-to-white ratio; SII, systemic immune–inflammation index; CSPH, clinically significant portal hypertension

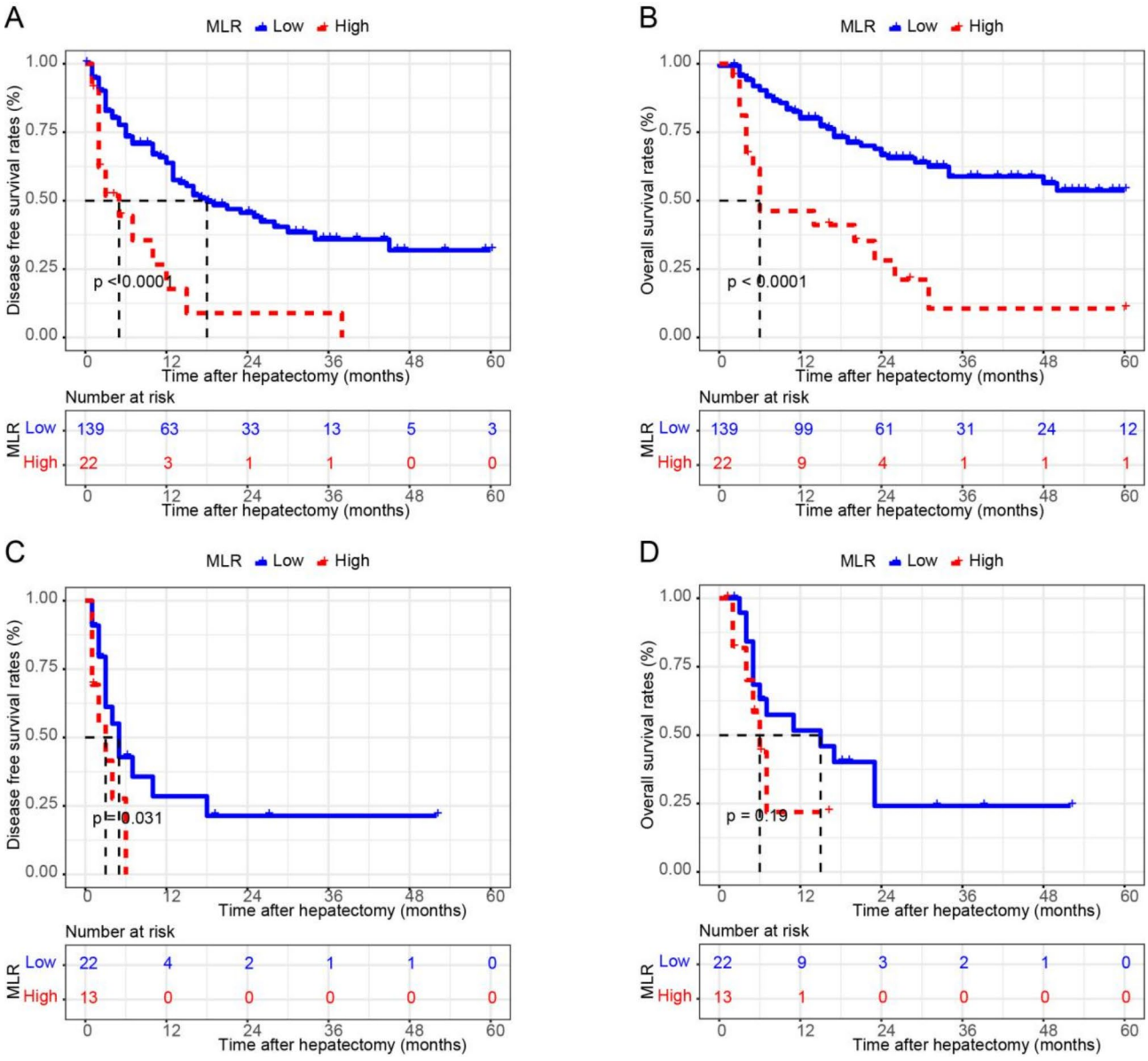

Fig. 3 The DFS and OS of patients with high and low MLR were subgroup analyzed according to CEA level. **(a)** DFS in patients with low CEA ($p < 0.001$); **(b)** OS in patients with low CEA ($p < 0.001$); **(c)** DFS in patients with high CEA ($p = 0.031$); and **(d)** OS in patients with high CEA ($p = 0.190$)

Discussion

In this study, we compared the effectiveness of the preoperative MLR, MWR, NLR, NWR, PLR, PWR, SII, CEA, and CA19-9 in predicting prognosis for ICC patients who underwent curative hepatectomy. The findings revealed that the preoperative MLR demonstrated a higher predictive value in comparison to other prognostic models and tumor markers when predicting DFS and OS. The preoperative MLR showed superior predictive capabilities and a more reliable prognostic outcome for patients with diverse clinical and pathological characteristics. Additionally, the preoperative MLR was identified as an independent risk factor for predicting both DFS and OS. Therefore, the preoperative MLR served as a significant inflammation-related indicator for ICC patients who subjected to hepatectomy.

The specific mechanisms linking a high preoperative MLR to poor outcomes in ICC remain unclear. Recent studies have suggested a strong link of inflammation to tumorigenesis, as well as tumor progression [7, 8]. Peripheral blood contains monocytes and lymphocytes, both of which are associated with inflammation. Preoperative analysis of peripheral blood is a cost-effective and standard procedure. A higher preoperative MLR indicates an increase in monocyte numbers or a decrease in lymphocyte numbers. Monocytes present in the

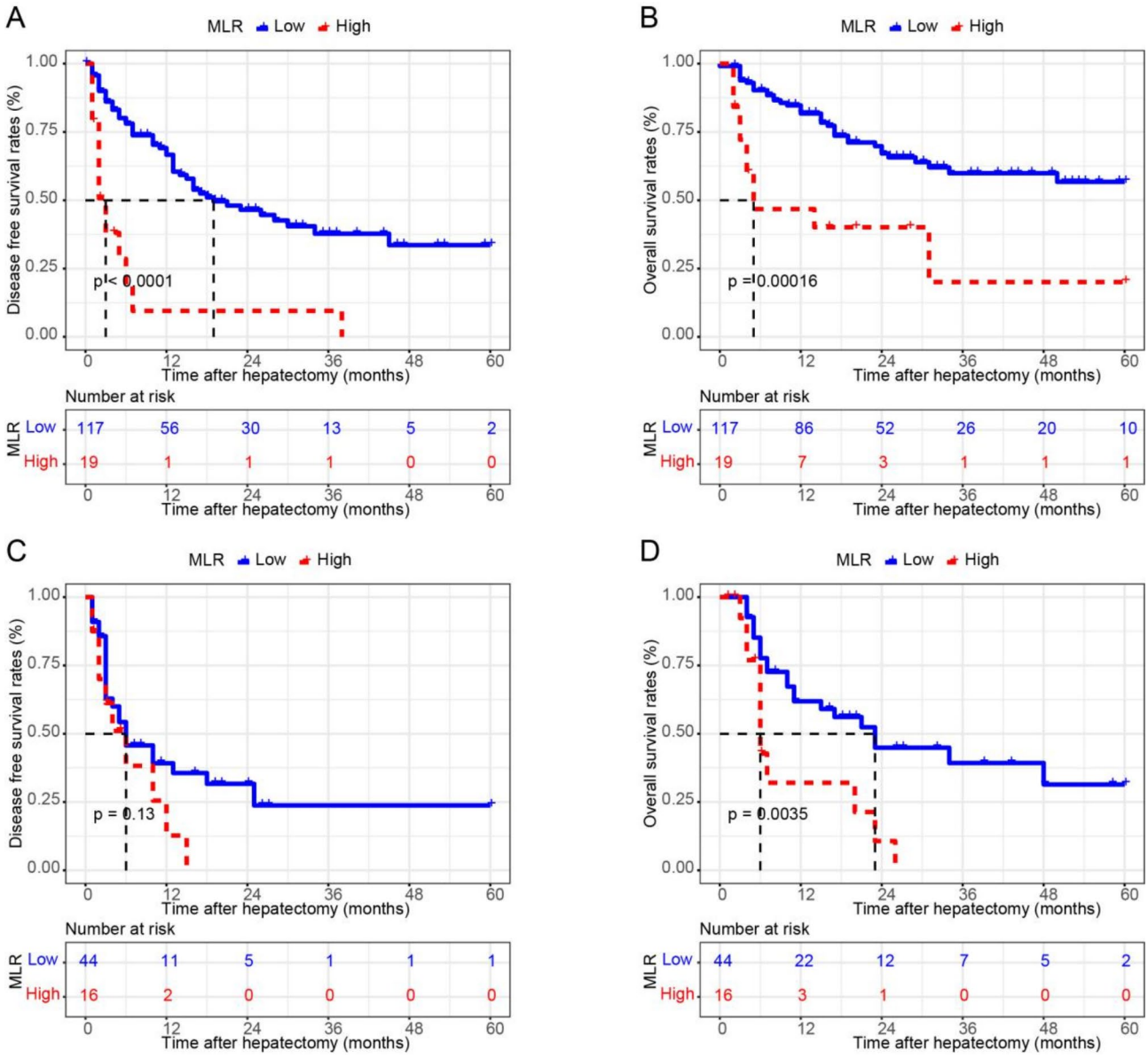

Fig. 4 The DFS and OS of patients with high and low MLR were subgroup analyzed according to CA19-9 level. **(a)** DFS in patients with low CA19-9 ($p<0.001$); **(b)** OS in patients with low CA19-9 ($p<0.001$); **(c)** DFS in patients with high CA19-9 ($p=0.130$); and **(d)** OS in patients with high CA19-9 ($p=0.0035$)

bloodstream are recruited to the tumor microenvironment, thereby contributing to tumor growth [25]. Furthermore, monocytes within the tumor transform into macrophages, which can impede the immune system, promote metastasis, and facilitate the development of new blood vessels [26]. Conversely, a decrease in lymphocyte numbers is often linked to a weakened ability of T lymphocytes to combat tumors [27]. The compromised immune system, resulting from low levels of lymphocytes, may hinder the body's ability to fight against tumor growth and metastasis [28]. In sum, a higher preoperative MLR indicates two sides of cancer progression: the escalation of tumors and the weakening of the immune system, which are likely the primary reasons and processes behind it.

Our research revealed that the preoperative MLR provided more accurate postoperative prognosis predictions for ICC patients compared to NLR, NWR, PLR, PWR, SII, CEA, and CA19-9. X-tile analysis indicated that the most appropriate cut-off value for the preoperative MLR was 0.44. Patients with more advanced cancer forms, such as large tumors, multiple tumors, MVI, or TNM stages, were more likely to have a high MLR (>0.44), suggesting that a high MLR may reflect the progression as well as the metastasis of ICC. Our survival analysis demonstrated that individuals with a high MLR had greatly

lower OS and DFS compared to those with a low MLR. The study findings highlighted that the preoperative MLR might be a valuable tool for predicting outcomes for ICC patients after curative hepatectomy. The performance of other prognostic models based on inflammation was evaluated alongside the preoperative MLR, but they were found to lack independent predictive capability.

Several studies have demonstrated that preoperative CEA and CA19-9 serve as prognostic markers for ICC patients undergoing hepatectomy [29, 30]. Notably, t-ROC analyses revealed that the preoperative MLR had greater accuracy than CEA and CA19-9 in assessing both OS and DFS. Subgroup analyses further indicated that the preoperative MLR was an effective marker for predicting OS as well as DFS in ICC patients, regardless of CEA and CA19-9 levels, except for predicting OS among patients with high CEA and predicting DFS in those with high CA19-9. This indicated that the combination of the preoperative MLR with CEA and CA19-9 could accurately identify patients with exceptionally poor DFS and OS. It may be necessary to evaluate this combination with other indicators when predicting OS in the high CEA subgroup and predicting DFS in the high CA19-9 subgroup. Therefore, perioperative adjuvant therapies may be beneficial for patients with a high MLR by potentially reducing the risk of recurrence, extending survival, and improving quality of life. Furthermore, more frequent monitoring should be implemented to detect relapses earlier in these individuals, enabling timely administration of treatment.

This research also had some limitations. Firstly, this was a single-center retrospective study, leading to inevitable selection bias, and impossible to validate this research with the available data, so further prospective researches are needed to validate these findings. Secondly, this study did not consider inflammatory markers associated with C-reactive protein (CRP) since our center did not routinely measure CRP in preoperative blood tests. Additionally, our research included a small sample size, more studies with large sample sizes are needed to verify our findings. Moreover, the use of medication and postoperative complications may not have been adequately taken into account, potentially impacting both monocyte and lymphocyte counts. Finally, it is possible that other medical centers may have different criteria for assessing operability and resectability, which might be inconsistent with our standards.

Conclusion

The preoperative MLR could be a reliable prognostic indicator for post-curative hepatectomy in ICC patients. It showed higher accuracy in predicting OS and DFS compared to previous inflammation-based prognostic scores and tumor markers, which can guide clinical decision making.

Abbreviations

ICC	Intrahepatic cholangiocarcinoma
SIR	Systemic inflammation response
OS	Overall survival
DFS	Disease-free survival
NLR	Neutrophil-lymphocyte ratio
MLR	Monocyte-lymphocyte ratio
PLR	Platelet-lymphocyte ratio
SII	Systemic immune-inflammation index
MWR	Monocyte-white ratio
NWR	Neutrophil-white ratio
PWR	Platelet-white ratio
AFP	α-Fetoprotein
AUC	Area under the receiver operating characteristic curve
CI	Confidence interval
CEA	Carcinoembryonic antigen
CA19-9	Carbohydrate antigen19-9
MVI	Macrovascular invasion
CSPH	Clinically signifcant portal hypertension
t-ROC	Time-dependent receiver operating characteristic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12929-9.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

None.

Author contributions

R.-Y.M and L.M conceived the study; all authors participated in the acquisition of the data; B.-F.T and H.-Q.Z performed follow-up the data; R.-Y.M analyzed data; B.-F.T and R.-Y.M drafted and revised the manuscript; all authors read and approved the final version of the manuscript.

Funding

This work was supported by Project for Enhancing Young and Middle-aged Teacher's Research Basis Ability in Colleges of Guangxi (NO. 2024KY0133), Youth Program of Scientific Research Foundation of Guangxi Medical University Cancer Hospital (NO.2023-7), Specific Research Project of Guangxi for Research Bases and Talents (GuiKe AD22035057), Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor (Guangxi Medical University), Ministry of Education (GKE-ZZ202217), and Guangxi TCM appropriate technology development and promotion project (GZSY23-66).

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was supervised by the ethics committee of Guangxi Medical University Cancer Hospital, and written informed consent was not needed since this was a retrospective study by decision of the ethics committee of Guangxi Medical University Cancer Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details
[1]Hepatobiliary & Pancreatic Surgery, Guangxi Medical University Cancer Hospital, He Di Rd. #71, Nanning 530021, China
[2]Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor, Guangxi Medical University, Ministry of Education, Nanning, China
[3]Guangxi Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor, Nanning, China

Received: 29 October 2023 / Accepted: 10 September 2024
Published online: 27 September 2024

References

1. Moris D, Palta M, Kim C, et al. Advances in the treatment of intrahepatic cholangiocarcinoma: an overview of the current and future therapeutic landscape for clinicians. CA Cancer J Clin. 2023;73(2):198–222.
2. Saha SK, Zhu AX, Fuchs CS, et al. Forty-year trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the rise. Oncologist. 2016;21(5):594–9.
3. Ye L, Schneider JS, Ben Khaled N, et al. Combined Hepatocellular-Cholangiocarcinoma: Biology, diagnosis, and management. Liver Cancer. 2024;13(1):6–28.
4. Hewitt DB, Brown ZJ, Pawlik TM. Surgical management of intrahepatic cholangiocarcinoma. Expert Rev Anticancer Ther. 2022;22(1):27–38.
5. Nguyen M, Toan NL, Bozko M, et al. Cholangiocarcinoma therapeutics: an update. Curr Cancer Drug Targets. 2021;21(6):457–75.
6. Banales JM, Marin J, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020;17(9):557–88.
7. Venakteshaiah SU, Kumar KH. Inflammation and Cancer. Endocr Metab Immune Disord Drug Targets. 2021;21(2):193–4.
8. Denk D, Greten FR. Inflammation: the incubator of the tumor microenvironment. Trends Cancer. 2022;8(11):901–14.
9. Lv Q, Xia Q, Li A, et al. The potential role of IL1RAP on Tumor Microenvironment-related inflammatory factors in stomach adenocarcinoma. Technol Cancer Res Treat. 2021;20:1533033821995282.
10. Feng F, Sun L, Zheng G, et al. Low lymphocyte-to-white blood cell ratio and high monocyte-to-white blood cell ratio predict poor prognosis in gastric cancer. Oncotarget. 2017;8(3):5281–91.
11. Hu X, Tian T, Zhang X, et al. Neutrophil-to-lymphocyte and hypopharyngeal cancer prognosis: System review and meta-analysis. Head Neck. 2023;45(2):492–502.
12. Gong Z, Xin R, Li L, et al. Platelet-to-lymphocyte ratio associated with the clinicopathological features and prognostic value of breast cancer: a meta-analysis. Int J Biol Markers. 2022;37(4):339–48.
13. Zhao S, Pan H, Guo Q, et al. Platelet to white blood cell ratio was an independent prognostic predictor in acute myeloid leukemia. Hematology. 2022;27(1):426–30.
14. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol. 2017;23(34):6261–72.
15. Wang L, Si H, Wang J, et al. Blood cell parameters as prognostic predictors of disease development for patients with advanced non-small cell lung cancer. Oncol Lett. 2020;20(2):1101–10.
16. Cananzi F, Minerva EM, Samà L, et al. Preoperative monocyte-to-lymphocyte ratio predicts recurrence in gastrointestinal stromal tumors. J Surg Oncol. 2019;119(1):12–20.
17. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21(5):671–84.
18. Vogel A, Meyer T, Sapisochin G, et al. Hepatocellular carcinoma. Lancet. 2022;400(10360):1345–62.
19. DelPiccolo N, Onkendi E, Nguyen J, et al. Outcomes of minimally invasive Versus Open Major hepatic resection. J Laparoendosc Adv Surg Tech A. 2020;30(7):790–6.
20. Mai RY, Ye JZ, Long ZR, et al. Preoperative aspartate aminotransferase-to-platelet-ratio index as a predictor of posthepatectomy liver failure for resectable hepatocellular carcinoma. Cancer Manag Res. 2019;11:1401–14.
21. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary cancers, Version 2.2021, NCCN Clinical Practice guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(5):541–65.
22. Mai RY, Lu TL, Lu RJ, et al. C-Reactive protein-albumin ratio (CAR): a more promising inflammation-based prognostic marker for patients undergoing curative hepatectomy for Hepatocellular Carcinoma. J Inflamm Res. 2024;17:919–31.
23. Dey R, Hanley JA, Saha-Chaudhuri P. Inference for covariate-adjusted time-dependent prognostic accuracy measures. Stat Med. 2023;42(23):4082–110.
24. Zhuang W, Chen J, Li Y, et al. Valuation of lymph node dissection in localized high-risk renal cell cancer using X-tile software. Int Urol Nephrol. 2020;52(2):253–62.
25. Johnstone MS, McSorley ST, McMillan DC, et al. The relationship between systemic inflammatory response, screen detection and outcome in colorectal cancer. Colorectal Dis. 2024;26(1):81–94.
26. Mantovani A, Allavena P, Marchesi F, et al. Macrophages as tools and targets in cancer therapy. Nat Rev Drug Discov. 2022;21(11):799–820.
27. Peng D, Lu J, Hu H, et al. Lymphocyte to monocyte ratio predicts resectability and early recurrence of Bismuth-Corlette type IV Hilar Cholangiocarcinoma. J Gastrointest Surg. 2020;24(2):330–40.
28. Cupp MA, Cariolou M, Tzoulaki I, et al. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med. 2020;18(1):360.
29. Moro A, Mehta R, Sahara K, et al. The impact of preoperative CA19-9 and CEA on outcomes of patients with Intrahepatic Cholangiocarcinoma. Ann Surg Oncol. 2020;27(8):2888–901.
30. Zheng BH, Yang LX, Sun QM, et al. A New Preoperative Prognostic System combining CRP and CA19-9 for patients with Intrahepatic Cholangiocarcinoma. Clin Transl Gastroenterol. 2017;8(10):e118.

Publisher's note