Lymphocyte to Monocyte Ratio Predicts Resectability and Early Recurrence of Bismuth-Corlette Type IV Hilar Cholangiocarcinoma

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Abstract
Background The objective of our research was to investigate the value of the lymphocyte to monocyte ratio (LMR) and its dynamic changes (LMRc) in predicting tumor resectability and early recurrence of radiologically resectable type IV hilar cholangiocarcinoma (HC).
Methods A total of 411 patients with radiologically resectable type IV HC were included. Data on their clinicopathologic characteristics, perioperative features, and survival outcomes were analyzed. Receiver operating characteristic (ROC) analysis was conducted to assess the ability of preoperative LMR (pre-LMR) to predict tumor resectability, and the ability of postoperative LMR (post-LMR) to discriminate between early and late recurrence. Survival curves were calculated using the Kaplan–Meier estimate. Univariate and multivariate logistic regression models were used to identify factors associated with resectability and early recurrence.
Results Of 411 patients with potentially curative type IV HC, 254 underwent curative surgery. The optimal cutoff value of pre-LMR as an indicator of resectability was 3.67, and the optimal cutoff value of post-LMR for detecting early recurrence was 4.10. In the multivariate logistic regression model, CA19-9 > 200 U/mL, pre-LMR ≤ 3.67, and tumor size > 3 cm were found to be independent risk factors for poor resectability. Moreover, multivariate analysis showed that LMRc, resection margin, AJCC N stage, and lymphovascular invasion were independent risk factors associated with early recurrence.
Discussion Pre-LMR is a valuable indicator of resectability and LMRc is a valuable predictor of early recurrence in patients with curative type IV HC.
Keywords Lymphocyte to monocyte ratio · Resectability · Early recurrence · Bismuth-Corlette classification · Hilar cholangiocarcinoma
Recently, an increasing amount of research has been focusing on the effects of systemic inflammatory response (SIR) on oncogenesis, and such research has revealed that there is a significant relationship between SIR and poor tumor-specific survival in numerous cancers.9–11 In particular, the neutrophil to lymphocyte ratio (NLR), which is considered as a biomarker of SIR, has emerged as an independent prognostic factor for biliary tract cancer in operable patients and in advanced disease patients undergoing adjuvant therapy.12, 13 The lymphocyte to monocyte ratio (LMR) is another biomarker of SIR, with a combination of lymphocyte count and monocyte count. The LMR as a prognostic factor for patients with colorectal cancer and hepatocellular carcinoma was recently investigated in a number of studies.14–16 However, the value of LMR in predicting the resectability and early recurrence of type IV HC has never been investigated. Therefore, the current study was conducted to determine whether LMR could be used to predict the resectability and early recurrence rates of radiologically resectable type IV HC.

Materials and Methods

Patient Selection

A total of consecutive 411 patients who underwent surgery for radiologically resectable type IV HC at West China Hospital of Sichuan University between 2001 and 2012 were enrolled in this study. Patients with intrahepatic bile duct carcinoma or gallbladder carcinoma infringing the hilum, or radiologically unresectable malignancy, patients who had undergone preoperative chemotherapy and radiotherapy, and patients who died within 90 days of surgery were excluded. The Ethics Committee of West China Hospital of Sichuan University approved of this retrospective study and waived the need for informed consent.

Preoperative Workup

Data from the patients’ medical history, physical examination, laboratory tests, and radiographic analyses (including contrast-enhanced ultrasound, contrast-enhanced computed tomography, and/or magnetic resonance cholangiography) were obtained. Preoperative biliary drainage was performed in patients with obstructive jaundice (total bilirubin > 85 μmol/L) by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTCD). Portal vein embolism (PVE) was performed 2–3 weeks before surgery for HC patients in whom the future remnant liver volume would be less than 40%.

Treatment

Different surgical strategies were selected based on the preoperative and intraoperative evaluations of the HC patients, the strategies included extrahepatic bile duct resection and caudate lobectomy combined with hemihepatectomy or trisegmentectomy. Patients also underwent routine resection of the regional lymph nodes, including the hilar, pericholedochal, periportal, common hepatic artery, and peripancreatic lymph nodes. Palliative surgery, such as bypass operation and open biopsy, was performed in patients with the following intraoperative discoveries: (1) extensive bile duct infringement that precluded intact tumor resection, (2) invasion of major vascular system such as bilateral portal vein involvement that hampered vascular reconstruction, (3) unilateral hepatic lobe atrophy combined with invasion of the contralateral portal vein or hepatic artery, and (4) evidence of distant metastases.17

Postoperative concurrent chemoradiotherapy or chemotherapy was recommended for patients with advanced TNM stage (III-IV) or microscopic/macroscopic positive resection margin. For 14 consecutive days every 28 days for 2 cycles, patients received a total radiation dose of 40 Gy delivered as a split course of 20 Gy in 10 fractions, followed by 375 mg/m² of 5-FU or 1000 mg/m² gemcitabine as maintenance chemotherapy.

Data Collection

Details of patients’ demographics, clinical examination, laboratory tests, radiological analyses, surgical procedures, and survival outcomes were collected. Blood samples were collected 3 days before surgery for evaluation of preoperative LMR (pre-LMR) or preoperative NLR (pre-NLR), and within 4 months after surgery for postoperative LMR (post-LMR) or postoperative NLR (post-NLR). The largest dimension of tumor demonstrated on preoperative radiological examination was determined as the tumor size. Resected tumor samples were routinely sent to the Department of Pathology, where HC was confirmed by experienced pathologists. Tumor stage was determined using the tumor classification system published in the 8th edition of the American Joint Committee on Cancer (AJCC). Patients with R0 resection (microscopically tumor-free margins) and R1 resection (microscopically positive margins) were classified as resectable, while those with R2 resection (macroscopically positive margins) or palliative surgery were classified as unresectable. Postoperative complications were assessed with the Clavien-Dindo classification (CD).18 Those with more than one postoperative complication were considered to have the highest grade of severity.
Follow-up Protocol

After discharge, all patients were routinely followed up every 3 months in the first year and every 6 months subsequently. Carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), and liver function tests and hepatic ultrasonography were performed for surveillance of recurrence. For those with suspected recurrence after curative resection, additional examinations, such as contrast-enhanced computed tomography and magnetic resonance imaging, were conducted for a definitive diagnosis. Patients with post-LMR lower than or equal to pre-LMR were confined to decreased LMRc group, while those with post-LMR higher than pre-LMR were confined to elevated LMRc group. The definition of Clavien-Dindo grade I complications (CD I) consisted of biliary leak, peritonitis, or intraoperative complications when assessing the recurrence rates and calculating the optimal cutoff point for early recurrence.19, 20 The postoperative complication rate after surgery was 44.8% (n = 184), which included 117 patients with CD II or higher complications. Major complications (CD II-III) consisted of bile leakage (n = 28), peritoneal cavity infection (n = 14), lung infection (n = 18), sepsis (n = 4), hemorrhage (n = 13), hepatic failure (n = 18), renal failure (n = 2), stress ulcer (n = 7), and others (n = 13). In the entire patient group, post-LMR of patients with Clavien-Dindo grade I complications was significantly higher than that of patients with major complications (6.55 ± 5.89 vs 4.68 ± 3.27, p = 0.006), as was in the resectable group (7.35 ± 6.47 vs 4.87 ± 3.54, p = 0.004). However, no significant association was detected between post-LMR and infectious complications neither in the entire patient group (4.59 ± 3.29 vs 4.80 ± 3.28, p = 0.738) nor in the resectable group (4.88 ± 3.62 vs 4.85 ± 3.48, p = 0.963).

Survival

The median follow-up time for the entire patient group was 15 months (range, 4–115 months). In the resectable group, the median overall survival time was 24.6 months, and the 1-, 3-, and 5-year overall survival rates were 75.2, 34.2, and 16.5%, respectively. In patients with unresectable tumors, the median overall survival time was 8.3 months, and the 1-, 3-, and 5-year overall survival rates were 20.4, 0, and 0%, respectively (Fig. 1). In the resectable group, overall 185 (72.8%) patients experienced tumor recurrence after curative resection. The 1-, 3-, and 5-year recurrence rates were 36.2, 61.0, and 68.9%, respectively. Decision of the optimal cutoff point for early and late recurrence of type IV HC was made based on the recurrence rate calculated at 6-month time points. Recurrence was

Statistical Analysis

Data analysis was performed using the SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Comparisons between two groups were performed using the t test or Wilcoxon test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. Receiver operating characteristics (ROC) analysis was applied to the whole group and to the resectable subgroup separately to assess the ability of LMR to predict resectability and early recurrence, respectively. Survival was evaluated using Kaplan–Meier estimates, and differences in survival were analyzed by the log-rank test. To identify independent factors associated with resectability and early recurrence, variables were examined with univariate and multivariate logistic regression models. Two-tailed p-values < 0.05 were considered statistically significant.

Results

Characteristics of the Study Population

The patient characteristics are shown in Table 1. A total of 411 type IV HC patients were considered to be suitable for resection based on preoperative radiological examinations. Among them, 254 patients (61.8%) underwent curative-intent surgery, while the remaining 157 patients (38.2%) were determined to have unresectable tumors as the intraoperative findings were indicative of aggressive tumor progression. The curative resection strategies included extrahepatic bile duct resection and caudate lobectomy combined with left hemihepatectomy (n = 132, 52.0%), right hemihepatectomy (n = 89, 35.0%), extended left hemihepatectomy (n = 8, 3.1%), extended right hemihepatectomy (n = 7, 2.8%), left trisegmentectomy (n = 12, 4.7%), and right trisegmentectomy (n = 6, 2.4%). The median of bile ducts reconstructed and hepaticojunostomies performed was 2 (range, 1–3). Regional lymph node resection was routinely performed in all patients undergoing curative surgery. Of 370 patients with obstructive jaundice, 227 patients who had total bilirubin levels above 85 μmol/L underwent preoperative biliary drainage: 72 patients underwent ENBD and 155 patients underwent PTCD. PVE was performed in 24 patients.

The pre-LMR of patients who underwent PVE was higher than that of the patients who did not undergo PVE, but the difference was not statistically significant in the entire patient group (4.18 ± 0.96 vs 3.96 ± 0.96, p = 0.282) or in the resectable group (4.29 ± 0.85 vs 4.11 ± 0.77, p = 0.344). In total, 21 patients died within 90 days after surgery and were excluded from the analysis to reduce the impact of postoperative complications when assessing the recurrence rates and calculating the optimal cutoff point for early recurrence.19, 20
divided into two periods from 6 to 60 months according to the linear regression analysis. The two straight lines were Line A ($y = -0.9559x + 26.676$, $R^2 = 0.97$) and Line B ($y = -0.1913x + 11.544$, $R^2 = 0.90$). The intercept point of the two lines was C point (19.7, 7.8). Therefore, 20 months was defined as the cutoff point to distinguish early from late recurrence for resectable type IV HC (Fig. 2).

Patients with resectable type IV HC were stratified into two groups according to the dynamic changes in the LMR: the decreased LMRc group ($n = 129$) and the elevated LMRc group ($n = 125$). The 5-year disease-free survival rate of the decreased LMRc group was significantly lower than that of the elevated LMRc group (Fig. 3a), as was the 5-year overall survival rate (Fig. 3b).

### ROC Analysis

ROC analysis of pre-LMR for detecting resectability is shown in (Fig. 4a). The pre-LMR value for discriminating resectable type IV HC tumors from unresectable type IV HC patients was shown to be significant (area under the ROC curve [AUC] = 0.687, 95% confidence interval [CI] 0.631–0.744, $p < 0.001$). ROC curve analysis was used to calculate the ideal pre-LMR cutoff value for the prediction of resectability; it was found to be 3.67, with a sensitivity of 76.4%, and specificity of 66.9%. Furthermore, ROC analysis was applied in the resectable group to verify the value of post-LMR as an indicator of early recurrence (Fig. 4b). The optimal cutoff point for post-LMR was 4.10, with a sensitivity of 73.4% and a specificity of 53.6%.

| Variables | Overall ($n = 411$) | Resectable group ($n = 254$) | Unresectable group ($n = 157$) |
|-----------|---------------------|-----------------------------|-------------------------------|
| Age (years) | 60 (26–82) | 61 (26–82) | 58 (28–81) |
| Gender | | | |
| Male | 263 | 159 | 104 |
| Female | 147 | 94 | 53 |
| BMI | 22.3 (17.2–28.6) | 22.0 (17.2–28.6) | 23.0 (17.6–28.6) |
| ASA score | | | |
| 1 | 12 (2.9%) | 6 (2.4%) | 6 (3.8%) |
| 2 | 224 (54.5%) | 140 (5.5%) | 84 (53.5%) |
| 3 | 175 (42.6%) | 108 (42.5%) | 67 (42.7%) |
| Total bilirubin ($\mu$mol/L) | 224.74 ± 162.22 | 206.72 ± 172.04 | 253.90 ± 140.60 |
| CA-199 (U/mL) | 450.19 ± 369.53 | 414.38 ± 369.55 | 419.30 ± 363.23 |
| Albumin (g/L) | 37.05 ± 5.23 | 36.94 ± 5.18 | 37.19 ± 5.39 |
| Preoperative neutrophil count ($\times 10^9$/L) | 4.77 ± 2.52 | 4.61 ± 2.41 | 5.03 ± 2.68 |
| Preoperative monocyte count ($\times 10^9$/L) | 0.52 ± 0.19 | 0.52 ± 0.19 | 0.52 ± 0.19 |
| Preoperative lymphocyte count ($\times 10^9$/L) | 2.05 ± 0.79 | 2.13 ± 0.81 | 1.91 ± 0.75 |
| Postoperative neutrophil count ($\times 10^9$/L) | 4.40 ± 1.37 | 4.23 ± 1.22 | 4.68 ± 1.55 |
| Postoperative monocyte count ($\times 10^9$/L) | 0.51 ± 0.17 | 0.50 ± 0.17 | 0.52 ± 0.17 |
| Postoperative lymphocyte count ($\times 10^9$/L) | 2.29 ± 0.88 | 2.27 ± 0.76 | 2.34 ± 1.04 |
| Total lymph nodes evaluated | 4 (1–12) | 3 (1–9) | 5 (1–12) |
| Positive lymph node number | 2 (0–10) | 0 (0–7) | 4 (1–10) |
| Operative time (min) | 240.00 (80–720) | 250 (110–720) | 180 (80–500) |
| Blood loss (mL) | 500 (50–2000) | 600 (100–2000) | 300 (50–1000) |
| Blood transfusion | 123 (30.0%) | 84 (33.0%) | 39 (24.8%) |
| Any complication | 184 (44.8%) | 141 (55.5%) | 43 (27.3%) |
| Major complication (Clavien-Dindo II–IV) | 117 (28.5%) | 93 (36.6%) | 24 (15.3%) |
| Hospital stay (days) | 18 (5–113) | 18 (5–113) | 17 (5–43) |
| Preoperative hospital stay (days) | 7 (2–44) | 7 (2–44) | 7 (3–33) |
| Postoperative adjuvant therapy | 154 (37.3%) | 117 (46.1%) | 37 (23.6%) |

1 Parameters are presented as median and range
2 Parameters are presented as mean ± SD
A separate analysis was performed in the resectable group to identify predictors correlated with early recurrence (Table 3). In the univariate analysis, increased total bilirubin, CA19-9 > 200 U/mL, lower post-LMR, decreased LMRc, R1 resection, higher AJCC N stage, and positive lymphovascular invasion were associated with early recurrence. Multivariate analysis using the logistic regression model demonstrated that LMRc, R1 resection, AJCC N stage, and lymphovascular invasion were independent risk factors for early recurrence following curative-intent resection of type IV HC.

Discussion

Radical resection remains the only treatment option for HC patients to achieve long-term survival (Fig. 1), with resectability rate ranging from 32 to 80%. Considering the difficulty of curative-intent surgery for type IV HC, it was bracing to find that the radical resection rate is 61.8% in our institution. This encouraging result probably attributed to relatively strict criteria of resectability based on preoperative images: patients with tumor infiltration along the bile duct beyond both right side of the umbilicus of the left portal vein and the cranio-ventral side of the right portal vein or its anterior branch, and patients with unreconstructable vascular invasion with end-to-end anastomosis were deemed as unresectable. However, our criteria of resectability and operation may not be applicable in all institutions, which is a limitation of current research.

To our knowledge, no other report has ever revealed the significance of pre-LMR in predicting the resectability for type IV HC patients. Our study has for the first time indicated that pre-LMR was a useful predictor of resectability with an AUC of 0.687, at an optimal cutoff value of 3.67 (Fig. 4a). With increasing pre-LMR level, the resection rates raise from 37.1% in patients with pre-LMR ≤ 3.67 to 78.7% in those with pre-LMR > 3.67 (p < 0.001). Multivariate model has further verified pre-LMR ≤ 3.67 to be an unfavorable predictor of resectability. Previous research has revealed that pre-LMR is adversely correlated with tumor-related factors such as CA19-9, AJCC N stage, and distant metastasis. This inverse association of low pre-LMR with indicators of advanced disease stage may explain why low pre-LMR was associated with a low resection rate. PVE has been reported to significantly improve resection outcomes. In our cohort, the impact of PVE on pre-LMR and tumor resectability was found to be insignificant, this difference is probably attributed to a statistical bias caused by the limited sample size of patients with PVE in this study. Thus, despite this finding, pre-LMR could still act as a complementary tool for the preoperative assessment of resectability in patients with radiographically curative type IV HC.
CA19-9 is the most investigated tumor biomarker and is considered as a predictor of resectability in numerous cancers. In accordance with previous studies, the resectability rate of patients with CA19-9 > 200 U/mL was significantly lower than those with CA19-9 ≤ 200 U/mL (55.2 vs 74.1%, p < 0.001). However, two variables that might affect CA19-9 level were not taken into account in our study: First, previous studies excluded Lewis negative population due to their incapability to secrete CA19-9; second, former researches considered the impact of obstructive jaundice and cholangitis on CA19-9 by stratifying cohort according to hyperbilirubinemia. The present study neither excluded the Lewis negative population nor stratified patients based on bilirubin level. This might be a serious limitation of our study.

Tumor size > 3 cm is considered as a major risk factor for unresectability of HC. Hu et al. demonstrated that HC patients with tumor size > 3 cm were more likely to have unresectable tumors. Consistently, the resectability rate of type IV HC with tumor size > 3 cm was significantly lower than those with tumor size ≤ 3 cm in our cohort (43.0 vs 82.8%, p < 0.001). As the diameter of unresectable tumors could not be determined and measuring the size of only the resected tumors would introduce a bias, in our study, tumor size was determined on the basis of preoperative radiologic examination. According to the abovementioned results, we believe that patients with potentially curative type IV HC who have an pre-LMR ≤ 3.67, CA19-9 ≤ 200 U/mL, and radiologically diagnosed tumor size > 3 cm may be unsuitable for resection and should therefore be further evaluated with diagnostic laparoscopy.

Early recurrence after curative surgery has been associated with poor prognosis in hepatic carcinoma. Zhang et al. defined radiologically diagnosed recurrence within 2.5 years after curative surgery as early recurrence in HC patients. The difficulty to achieve negative resection margin for type IV HC renders relatively worse prognosis. For the present cohort, we determined that 20 months was the optimal cutoff point to define early recurrence for type IV HC after curative resection (Fig. 2). We also tried to identify the factors associated with early, as these could be useful for guiding surveillance, adjuvant therapy, and follow-up in patients who are likely to have early recurrence.

Fig. 3 a The 5-year disease-free survival rate of the low LMR group was significantly lower than that of the high LMR group; b the 5-year overall survival rate of the high LMR group was significantly higher than that of the low LMR group

Fig. 4 a ROC analysis of pre-LMR for determining the resectability for radiologically resectable type IV HC; b ROC analysis of post-LMR for determining early recurrence of resectable type IV HC after curative resection
The prognostic value of post-LMR and LMRc for type IV HC has never been reported in previous studies. ROC analysis indicated that post-LMR was not a useful predictor of early recurrence, with an AUC less than 0.60 (Fig. 4b). Multivariate analysis also demonstrated that LMRc, rather than pre-LMR or post-LMR, was a predictor of early recurrence. Decreased LMRc reflects relatively reduced lymphocyte counts or increased monocyte counts. Low lymphocyte count is known to be an indicator of weakened T lymphocyte-mediated anti-tumor ability. That is, the host immune response against tumor progression and metastasis is suppressed due to lymphocytopenia. On the other hand, circulating monocytes are recruited to the tumor microenvironment, where they subsequently promotes tumor progression. Moreover, monocytes within the tumor tissue differentiate into macrophages, which are capable of immunosuppression, metastasis promotion, and angiogenesis. In summary, a decreased LMRc in type IV HC patients after surgery reflects two aspects of tumor progression—the advancement of malignancy and suppression of the immune system, which explains why patients with decreased LMRc were more likely to develop early recurrence in our research. We also noted that decreased LMRc was

| Variables                  | Univariate analysis | Multivariate analysis |
|----------------------------|---------------------|-----------------------|
|                            | Resectable group    | Unresectable group    | $p$ value | HR (95% CI) | $p$ value |
| Gender                     |                     |                       | 0.486     |             |           |
| Male                       | 159                 | 104                   |           |             |           |
| Female                     | 94                  | 53                    |           |             |           |
| Age (years)                |                     |                       | 0.323     |             |           |
| $< 70$                     | 215                 | 127                   |           |             |           |
| $\geq 70$                  | 39                  | 30                    |           |             |           |
| CA-199 (U/mL)              |                     |                       | $< 0.001$ | 1.970 (1.149–3.378) | 0.014     |
| $\leq 200$                 | 106                 | 37                    |           |             |           |
| $> 200$                    | 148                 | 120                   |           |             |           |
| Total bilirubin (μmol/L)   | 206.72 ± 172.05     | 253.90 ± 140.60       | 0.004     | 1.001 (0.999–1.002) | 0.450     |
| Albumin (g/L)              |                     |                       | 0.754     |             |           |
| $\leq 40$                  | 188                 | 114                   |           |             |           |
| $> 40$                     | 66                  | 43                    |           |             |           |
| BMI                        |                     |                       | 0.038     | 1.584 (0.944–2.659) | 0.082     |
| $\leq 21$                  | 100                 | 46                    |           |             |           |
| $> 21$                     | 154                 | 111                   |           |             |           |
| ASA score                  |                     |                       | 0.686     |             |           |
| 1                          | 6                   | 6                     |           |             |           |
| 2                          | 140                 | 84                    |           |             |           |
| 3                          | 108                 | 67                    |           |             |           |
| Pre-NLR                    |                     |                       | 0.041     | 1.517 (0.900–2.556) | 0.117     |
| $< 3$                      | 183                 | 98                    |           |             |           |
| $\geq 3$                   | 71                  | 59                    |           |             |           |
| Pre-LMR                    |                     |                       | $< 0.001$ | 0.181 (0.111–0.296) | $< 0.001$ |
| $\leq 3.67$                | 62                  | 105                   |           |             |           |
| $> 3.67$                   | 192                 | 52                    |           |             |           |
| Tumor size (cm)            |                     |                       | $< 0.001$ | 6.218 (3.705–10.435) | $< 0.001$ |
| $\leq 3$                   | 212                 | 69                    |           |             |           |
| $> 3$                      | 42                  | 88                    |           |             |           |
| Portal vein embolization   |                     |                       |           |             |           |
| Yes                        | 17                  | 7                     | 0.348     |             |           |
| No                         | 237                 | 150                   |           |             |           |

The italic emphasis (originally boldfaced) in Tables 2 and 3 specified the variables that were statistically significant in the univariate and multivariate logistic regression analysis (two-tailed $p$ values < 0.05)
Table 3  Analysis of risk variables for early recurrence (≤20 months) of type IV HC after curative surgery

| Variables                          | Univariate analysis | Multivariate analysis |
|------------------------------------|---------------------|-----------------------|
|                                    | Early recurrence    | 20-month recurrence-free group |
|                                    | group \((n = 127)\) | group \((n = 126)\)   |
| **p value**                        |                     |  **HR (95% CI)**      |
| **HR (95% CI)**                    |                     | **p value**           |
| Gender                             | 0.407               |                       |
| Male                               | 83                  | 76                    | 1.001 (0.999–1.003) | 0.170 |
| Female                             | 44                  | 50                    |                       |       |
| Age                                | 0.203               |                       |
| < 70                               | 112                 | 103                   | 1.740 (0.986–3.107)  | 0.057 |
| ≥ 70                               | 16                  | 23                    |                       |       |
| Total bilirubin (μmol/L)           | 229.85 ± 189.53     | 183.23 ± 149.37       |                       |       |
| CA-199 (U/mL)                      | 0.031               | 0.032                 |                       |       |
| < 200                              | 45                  | 61                    |                       |       |
| ≥ 200                              | 83                  | 65                    |                       |       |
| Albumin (g/L)                      | 0.941               |                       |
| ≤ 40                               | 95                  | 93                    |                       |       |
| > 40                               | 33                  | 33                    |                       |       |
| Pre-NLR                            | 0.144               |                       |
| < 3                                | 87                  | 96                    |                       |       |
| ≥ 3                                | 41                  | 30                    |                       |       |
| Post-NLR                           | 0.139               |                       |
| < 3                                | 103                 | 110                   |                       |       |
| ≥ 3                                | 25                  | 16                    |                       |       |
| NLRc                               | 0.446               |                       |
| Elevated                           | 63                  | 56                    |                       |       |
| Decreased                          | 65                  | 70                    |                       |       |
| Pre-LMR                            | 0.421               |                       |
| ≤ 3.67                             | 34                  | 28                    |                       |       |
| > 3.67                             | 94                  | 98                    |                       |       |
| Post-LMR                           | < 0.001             | 0.591 (0.266–1.312)   | 0.196                 |
| ≤ 4.10                             | 94                  | 61                    |                       |       |
| > 4.10                             | 34                  | 65                    |                       |       |
| LMRc                               | < 0.001             | 0.421 (0.188–0.942)   | 0.035                 |
| Elevated                           | 48                  | 77                    |                       |       |
| Decreased                          | 80                  | 49                    |                       |       |
| Resection margin                   | 0.002               | 2.133 (1.112–4.091)   | 0.023                 |
| R0                                 | 75                  | 97                    |                       |       |
| R1                                 | 53                  | 29                    |                       |       |
| Tumor differentiation              | 0.065               |                       |
| Well                               | 25                  | 37                    |                       |       |
| Moderate                           | 85                  | 80                    |                       |       |
| Poor                               | 18                  | 9                     |                       |       |
| AJCC T stage                       | 0.151               |                       |
| T1                                 | 5                   | 12                    |                       |       |
| T2                                 | 77                  | 66                    |                       |       |
| T3                                 | 37                  | 43                    |                       |       |
| T4                                 | 9                   | 5                     |                       |       |
| AJCC N stage                       | 0.001               | 2.061 (1.344–3.162)   | 0.001                 |
| N0                                 | 63                  | 92                    |                       |       |
| N1                                 | 45                  | 24                    |                       |       |
| N2                                 | 20                  | 10                    |                       |       |
| AJCC stage                         | 0.094               |                       |
| I                                  | 4                   | 8                     |                       |       |
| II                                 | 40                  | 51                    |                       |       |
| III                                | 64                  | 57                    |                       |       |
| IV                                 | 20                  | 10                    |                       |       |
| Portal vein invasion               | 0.132               |                       |
| Positive                           | 28                  | 38                    |                       |       |
| Negative                           | 100                 | 88                    |                       |       |
| Hepatic artery invasion            | 0.119               |                       |
| Positive                           | 18                  | 10                    |                       |       |
| Negative                           | 110                 | 116                   |                       |       |
| Lymphovascular invasion            | < 0.001             | 2.744 (1.345–5.595)   | 0.006                 |
| Positive                           | 41                  | 15                    |                       |       |
| Negative                           | 87                  | 111                   |                       |       |
associated with shorter disease-free survival and overall survival. With regard to the impact of postoperative complications on post-LMR and consequently LMRc, the results demonstrated that, while patients with severe postoperative complication had lower post-LMR, those with infectious complication did not. Decreased post-LMR could be the result of lymphopenia triggered by complications such as hemorrhage and liver failure. It is possible that major postoperative complications impair cell-mediated immunity, which results in an early recurrence.

Other factors strongly associated with early recurrence in our cohort included AJCC N stage, lymphovascular invasion, and resection margin. In keeping with our results, a positive relationship has been shown between N stage and early recurrence for potentially resectable HC. While the pathologic classification of previous studies was mainly based on AJCC 7th edition, in which lymph node metastases were stratified according to the distribution of lymph nodes, our cohort followed the 8th edition of AJCC staging, which uses the number of positive lymph nodes for classification. Similar to our results, lymphovascular invasion has been strongly associated with poor oncological prognosis in type IV HC patients. Further, surgery-related factors such as the resection margin have also been shown to influence oncologic outcomes, as patients with an R0 margin had a decreased risk of early recurrence in our study. This finding further stresses on the importance of R0 resection to prevent early recurrence and that, to guarantee R0 resection, measurements such as intraoperative frozen section examination should be routinely performed if possible.

Several limitations of the current study should be considered. This was a retrospective and uncontrolled study that was conducted at a single center, which means that a selection bias was inevitable. Moreover, both monocyte counts and lymphocyte counts could have been affected by factors such as medications or postoperative complications, which were not sufficiently taken into account. Finally, our criteria of resectability and operation may not be shared by all centers. Despite these limitations, nomograms will be constructed on the basis of present research to predict resectability and early recurrence in patients with type IV HC in the future.

**Conclusion**

LMR is superior to NLR in predicting resectability and early recurrence for type IV HC. According to the above findings, decreased pre-LMR is associated with a poor resectability rate and may help identify patients who require further evaluation with diagnostic laparoscopy. Furthermore, patients with decreased LMRc are more likely to develop early recurrence and should be closely followed up. Still, it should be noted that it is not realistic to estimate resectability or early recurrence on the basis of a single biomarker. LMR estimation will be useful only if it is used along with comprehensive surveillances such as radiologic examinations and biological tests.

**Author Contributions**

DP: study conception and design, acquiring data, data analysis, and drafting article. JL: polishing and revision of article. HH: acquiring data. BL: statistical analysis. XY: statistical analysis and critical revision of article. NC: drafting article and critical revision of article. All authors read and approved the final manuscript.

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**Table 3**

| Variables | Early recurrence group (n = 127) | 20-month recurrence-free group (n = 126) | p value | HR (95% CI) | p value |
|-----------|---------------------------------|-----------------------------------------|---------|-------------|---------|
| Perineural invasion | Positive 86 | 91 | 0.383 | | |
| Negative 42 | 35 | | | | |
| Tumor size (cm) | ≤3 100 | 112 | 0.021 | 1.794 (0.826–3.897) | 0.140 |
| >3 28 | 14 | | | | |
| Adjuvant therapy  | Yes 54 | 63 | 0.212 | | |
| No 74 | 63 | | | | |

The Italic emphasis (originally boldfaced) in Tables 2 and 3 specified the variables that were statistically significant in the univariate and multivariate logistic regression analysis (two-tailed P values < 0.05).

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