Preoperatively elevated RDW-SD and RDW-CV predict favorable survival in intrahepatic cholangiocarcinoma patients after curative resection

Xingchen Li†, Qichen Chen†, Xinyu Bi, Jianjun Zhao, Zhiyu Li, Jianguo Zhou, Zhen Huang, Yefan Zhang, Rui Mao, Hong Zhao and Jianqiang Cai*

Abstract

Background: Recent studies suggest red blood cell distribution width (RDW) was a prognostic factor in various types of cancer patients, although the results are controversial. The objective of this study was to investigate the significance of RDW in patients with intrahepatic cholangiocarcinoma (ICC) after radical resection.

Method: The relationship between the preoperative serum RDW value and clinic pathological characteristics was analyzed in 157 ICC patients between January 2012 and June 2018 who underwent curative resection. X-tile software was used to determine 40.2 fl, 12.6% as the optimal cut-off value for RDW-SD and RDW-CV respectively. 153 patients were classified into the low RDW-SD (≤ 40.2, n = 53) group and the high RDW-SD (> 40.2, n = 104) group, low RDW-CV (≤ 12.6, n = 94) group and the high RDW-CV (> 12.6, n = 63). Based on the RDW-SD combined with RDW-CV (SCC), classified into SCC = 0, 1 and 2 group. Kaplan–Meier survival analysis and Cox proportional hazard models were used to examine the effect of RDW on survival.

Results: Kaplan–Meier curve analysis showed that Patients with RDW-SD > 40.2 were significantly associated with better OS (P = 0.004, median OS: 68.0 months versus 17.0 months). Patients with RDW-CV > 12.6 were significantly associated with better OS (p = 0.030, median OS: not reach versus 22.0 months). Compared with a SCC = 0 or SCC = 1, SCC = 2 was significantly associated with better OS (p < 0.001, median OS: not reach versus 33.0 months versus 16, respectively). In the multivariate analysis, RDW-SD > 40.2 fl (HR = 0.446, 95% CI: 0.262–0.760, p = 0.003), RDW-CV > 12.6% (HR = 0.425, 95%CI: 0.230–0.783, p = 0.006), SCC = 2 (HR = 0.270, 95%CI: 0.133–0.549, p < 0.001) were associated with favorable OS. The multivariate analysis showed RDW-SD, RDW-CV and SCC level were not independent prognostic factors for DFS.

Conclusions: Preoperative low levels of RDW are associated with poor survival in ICC after curative resection. This provides a new way for predicting the prognosis of ICC patients and more targeted intervention measures.

Keywords: Intrahepatic cholangiocarcinoma, Liver resection, RDW, Prognosis

Background

Intrahepatic cholangiocarcinoma (ICC) is a relatively rare type of primary liver cancer that arises from the intrahepatic bile duct epithelium and accounts for 75% of primary liver carcinomas, the incidence of which is increasing year by year [1]. The only curative treatment is...
surrounding the high recurrence rate in ICC patients has not been demonstrated. The purpose of this study was to evaluate the relationship between RDW and clinical outcomes in ICC patients.

Methods

Patients

The clinical date of 157 cases with ICC from our hospitals between January 2012 and June 2018 were collected and analyzed retrospectively. The inclusion criteria were as follows: (1) complete (R0) resection of liver cancer and histopathological diagnosis of ICC; and (2) none of these patients had previous malignant disease. The exclusion criteria were as follows: (1) patients with clinical or pathologic distant metastasis; (2) perioperative mortality; (3) no follow-up data; and (4) pretreatment diseases associated with RDW levels (thrombosis, sepsis, cardiovascular disease, etc.). The Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences approved the study, and the requirement for informed consent was waived.

Major resections were defined as a resection of more than two segments, and other resection was described as a minor resection. Serum red blood cell distribution width-standard deviation (RDW-SD) levels and red blood cell distribution width-coefficient of variation (RDW-CV) levels were measured within 1 week before surgery. Blood samples for the evaluation of serum RDW-SD levels (37.0–57.0 fl) and RDW-SD levels (111.6–14.6 fl) were obtained by using peripheral venous punctures. Red cell volume distribution width (RDW) is a conventional biomarker of erythrocyte volume variability and an indicator of homeostasis [13]. Recent evidence suggests that unequal erythrocyte action is involved in a variety of human cancers, such as cardiovascular disease [14, 15] and cancer [16, 17]. There is some evidence that high RDW levels are a negative prognostic indicator for these diseases, and inflammation is the mechanism leading to these high levels [13]. There is increasing evidence that elevated RDW levels are also associated with poor prognosis in a variety of cancers, including hepatocellular carcinoma (HCC) [18, 19], esophageal cancer [20, 21], lung cancer [22] and hematological malignancies [23]. However, a review of the previous related literature shows some research limitations. Multivariate analysis showed that preoperative RDW is not an independent prognostic indicator of OS in gastric adenocarcinoma patients [24]. Due to the inevitable heterogeneity of the study samples, the prognostic effects of RDW have not been fully investigated. The predictive value of RDW in ICC patients has not been demonstrated. The purpose of this study was to evaluate the relationship between RDW and clinical outcomes in ICC patients.
included assessments of pathological stage, microvascular invasion (MVI) and other high-risk relapse factors. During the follow-up review process, when recurrence was confirmed, salvage treatment including reoperation, percutaneous ablation or transarterial chemoembolization (TACE) was performed as needed. In this study, the examination data of the patients were extracted from the hospital medical records system, and the patients were followed up by telephone. The deadline for follow-up was the date of the last follow-up or death.

Statistical analysis
The clinicopathologic characteristics were compared using the X² and Mann–Whitney U tests, as appropriate. For testing markers (albumin [ALB], total bilirubin [TBIL], aspartate aminotransferase [AST], alanine aminotransferase [ALT], etc.), the upper limit of normal value was defined as cutoff value; for operation time and intraoperative blood loss, the median was defined as cutoff value. X-tile [25] analysis was implemented to investigate the optimal cut-off point of RDW-SD and RDW-CV. The X-tile plots are created by dividing marker data into two populations: low and large. All possible divisions of the marker data are assessed. Associations can be calculated at each division by a variety of standard statistical tests, including the log-rank test for survival and means tests for associations between other marker data. Alternatively, the program can select the optimal division of the data by selecting the highest X² value. OS was defined as the interval between the date of resection and the date of death or the last follow-up, and disease-free survival (DFS) was defined as the duration from resection to tumor progression or the last follow-up. This study used the Kaplan–Meier method to estimate DFS and OS and statistically compared the data by log-rank test. A forward LR Cox regression model was created to identify prognostic factors that influence OS and DFS. Variables with P < 0.10 in the univariable analysis were included in the multivariable analysis. The RDW-SD level and RDW-CV level exhibited collinearity (p < 0.001). To prevent collinearity, RDW-SD was included in the multivariate analysis of Model 1 (exclude of RDW-CV), and RDW-CV was included in the multivariate analysis of Model 2 (exclude of RDW-SD). Because the SCC score was based on RDW-SD and RDW-CV, the multivariate analysis of Model 3 included SCC score and factors with a p < 0.1 in the univariable analysis exclude of the RDW-SD and RDW-CV. All analyses were performed using SPSS, version 22 software (Armonk, NY, USA). p < 0.05 was considered statistically significant.

Results
Clinicopathological characteristics
The median age of all 157 patients was 58.00 (IQR: 51.50–64.00) years and most patients (55.4%) were male. The proportion of patients with positive serum hepatitis B surface antigen (HBsAg) was 21.7%. The proportion of patients with lesions in the central liver was 49.7%. The median diameter of the largest ICC lesion was 5.5 (IQR 3.8–7.0) cm, and 54.8% of patients had a lesion larger than 5 cm. A total of 19.1% of patients had multiple tumors and 26.8% of the patients had LNM. Ninety one patients (58.0%) were observed with poorly differentiated tumors. The preoperative clinical laboratory tests were as follows: tumor markers: preoperative CA19-9 > 27 U/mL (52.4%), preoperative CEA > 5 ng/mL (22.3%); liver function markers: ALB ≥ 40 g/L (79.0%), TBIL > 21 µmol/L (11.5%), AST > 40 U/L (9.6%), and ALT > 50 U/L (8.9%). The median RDW-SD level was 41.1 fl (IQR 39.7–43.3). The median RDW-CV level was 12.4% (IQR 12.0–13.1). A total of 58.6% (92/157) of the patients have postoperative complications, including 33 major complications and 59 minor complications. Seventy-nine patients had an operation time ≥ 230 min, and 49.0% patients had blood loss ≥ 300 mL. Ten patients (6.4%) received preoperative therapy and 66 patients (42.0%) received postoperative therapy. The detailed clinicopathologic parameters of patients are in Table 1.

Relationships among RDW-SD, RDW-CV, SCC and clinicopathological characteristics
X-tile software was used to determine 40.2 fl and 12.6% as the optimal cut-off values for RDW-SD and RDW-CV, respectively. Based on RDW-SD levels, 157 patients were classified into a low RDW-SD (< 40.2, n = 104) group and high RDW-SD (> 40.2, n = 53) group. Based on RDW-CV levels, 157 patients were classified into a low RDW-CV (< 12.6, n = 94) group and high RDW-CV (> 12.6, n = 63) group. Based on the RDW-SD combined with RDW-CV (SCC), 46 patients were classified into the SCC = 0 group, 55 patients were classified into the SCC = 1 group, and 56 patients were classified into the SCC = 2 group.

The high RDW-SD group had more patients with an ASA status of 1–2 (p = 0.027) and operation time < 230 min (p = 0.027) than the low RDW-SD group. The high RDW-CV group had more patients with non-liver cirrhosis (p = 0.020), T1-T2 stage disease (p = 0.005) and TBIL ≤ 21 µmol/L (p = 0.015). The patients with SCC = 0 was associated with an age < 60 years (p = 0.029) (Table 1).
The median follow-up time was 33.00 months. The median OS and median DFS were 28.00 months (95% CI: 12.9–43.1) and 10.00 months (95% CI: 7.2–12.8), respectively. One hundred and nine patients (69.4%) underwent recurrence, and 73 patients (46.5%) died. The 1-, 3- and 5-year progression-free survival rates were 41.8%, 29.5%, and 20.9%, respectively. The 1-, 3- and 5-year survival rates were 72.9%, 46.0% and 41.1%, respectively. Kaplan–Meier curve analysis revealed that patients with RDW-SD > 40.2 were significantly associated with better OS (p = 0.004, median OS: did not reach versus 33.0 months), and had an equivalent DFS (p = 0.047, median DFS: 11.0 months versus 7.0) than those with low RDW-SD values (Fig. 1). Patients with RDW-CV > 12.6 were significantly associated with better OS (p = 0.030, median OS: not reached versus 22.0 months) and had an equivalent DFS (p = 0.001, median DFS: 11.0 months versus 10.0) than those with low RDW-CV values (Fig. 2). Compared with patients with SCC = 0 or SCC = 1, patients with SCC = 2 were significantly associated with better OS (p < 0.001, median OS: did not reach versus 16, respectively), but all three SCC values had an equivalent DFS (p = 0.001, median DFS: 11.0 months versus 12.0 months versus 7.0 months, respectively) (Fig. 3).

OS analysis
In the univariate analysis, T3-T4 stage (p < 0.001), lymph node metastasis (p < 0.001), noncentral tumor (p = 0.027), poor differentiation (p = 0.044), preoperative CEA > 5 ng/mL (p = 0.001), RDW-SD ≤ 40.2 fl
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[p = 0.004], RDW-CV \leq 12.6\% \quad (p = 0.030), ALB < 40 \text{ g/L} \quad (p = 0.048), operation time \geq 230\text{ min} \quad (p = 0.015), blood loss \geq 300\text{ ml} \quad (p = 0.030) and decreased SCC score \quad (p = 0.007) were all associated with shorter OS (Table 2). In the multivariate analysis of model 1, RDW-SD > 40.2 fl (HR = 0.446, 95\% CI: 0.262–0.760, p = 0.003), central tumor (HR = 0.367, 95\% CI: 0.210–0.641, p < 0.001), and adjuvant therapy (HR = 0.423, 95\% CI: 0.232–0.774, p = 0.005) were significantly associated with favorable OS. In the
multivariate analysis of model 2, RDW-CV > 12.6% (HR = 0.425, 95% CI: 0.230–0.783, p = 0.006), central tumor (HR = 0.307, 95% CI: 0.171–0.552, p < 0.001), and adjuvant therapy (HR = 0.481, 95% CI: 0.264–0.876, p = 0.017) were significantly associated with favorable OS. In the multivariate analysis of model 3, the multivariate analysis showed that compared with SCC = 0, SCC = 1 (HR = 0.296, 95% CI: 0.153–0.571, p < 0.001) and SCC = 2 (HR = 0.270, 95% CI: 0.133–0.549, p < 0.001) were associated with favorable OS (Table 3).

**Discussion**

To the best of knowledge, this study is the first to use X-tile software to objectively identify the optimal cutoff point values of RDW-SD and RDW-CV for predicting survival. We discussed the relationship between preoperative RDW values and postoperative prognosis in ICC patients on the premise of excluding other diseases that affect RDW value. Our results indicated that patients with higher RDW values had better prognoses. RDW level is an marker of the degree of erythrocyte morphology imbalance in the blood, and it reflects the heterogeneity of erythrocyte volume [26]. RDW level may change as a result of blood diseases, infectious diseases, and even cancer [27, 28]. Additionally, studies have revealed that RDW level was an independent risk factor for survival in patients with colorectal cancer and bladder cancer [29–31]. RDW values are reflected in coefficient of variation of red cell volume distribution width (RDW-CV) and standard deviation of red cell volume distribution width (RDW-SD) levels. RDW-SD and RDW-CV were generally used to evaluate the RDW level in clinics. In our study, patients with high RDW-SD or RDW-CV were significantly associated with better OS. We used SCC as the combined index of RDW-SD and RDW-CV, and compared with SCC = 0 or SCC = 1, SCC = 2 was significantly associated with better OS and had an equivalent DFS. SCC is a combined indicator, so the differences between the three classifications further strengthen their

| Table 2 Prognostic factors for OS for ICC patients in univariate analysis |
|-----------------------------|-----------------------------|-----------------------------|
| **Factor**                  | **Univariate analysis**     | **Univariate analysis**     |
|                             | HR (95%CI)                  | Value p                     |
| Age ≥ 60 years              | 0.778 (0.483–1.251)         | 0.300                       |
| Male                        | 1.418 (0.887–2.267)         | 0.144                       |
| BMI ≥ 24 kg/m²              | 1.356 (0.843–2.182)         | 0.209                       |
| ASA score 3–4               | 0.970 (0.420–2.388)         | 0.943                       |
| Cirrhosis                   | 0.929 (0.575–1.500)         | 0.763                       |
| HBsAg (+)                   | 0.754 (0.420–1.351)         | 0.343                       |
| T3-T4 stage                 | 2.381 (1.431–3.962)         | 0.001                       |
| Lymphnode metastasis        | < 0.001                     |                             |
| Undissected lymph node      | Reference                   |                             |
| Negative lymph node         | 0.742 (0.414–1.331)         | 0.317                       |
| Positive lymph node         | 2.808 (1.554–5.072)         | 0.001                       |
| Tumor size ≥ 5 cm           | 1.529 (0.956–2.448)         | 0.077                       |
| Multiple tumors             | 1.657 (0.955–2.874)         | 0.173                       |
| Tumor location (central tumor) | 0.587 (0.366–0.941)     | 0.027                       |
| Tumor location (right lobe) | 0.858 (0.588–1.252)         | 0.427                       |
| Poor differentiation        | 1.667 (1.013–2.473)         | 0.044                       |
| Preoperative CA19-9 > 27 U/mL | 1.332 (0.763–2.327)     | 0.313                       |
| Preoperative CEA > 5 ng/mL  | 2.365 (1.429–3.913)         | 0.001                       |
| RDW-SD > 40.2 fl            | 0.503 (0.314–0.806)         | 0.004                       |
| RDW-CV > 12.6%              | 0.581 (0.356–0.949)         | 0.030                       |
| ALB ≥ 40 g/L                | 0.600 (0.361–0.996)         | 0.048                       |
| TBL > 21 umol/L             | 0.913 (0.438–1.904)         | 0.808                       |
| AST > 40 U/L                | 1.773 (0.909–3.458)         | 0.093                       |
| ALT > 50 U/L                | 1.814 (0.899–3.660)         | 0.096                       |
| Operation time > 230 min    | 1.785 (1.118–2.851)         | 0.015                       |
| Blood loss ≥ 300 ml         | 1.713 (1.053–2.788)         | 0.030                       |
| Major liver resection       | 1.419 (0.832–2.419)         | 0.198                       |
| Post-operative complications | 1.027 (0.640–1.647)       | 0.913                       |
| Preoperative therapy        | 0.648 (0.204–2.060)         | 0.462                       |
| Adjuvant therapy            | 0.663 (0.410–1.072)         | 0.094                       |
| The prognostic value on SCC score | 0.007                   |                             |
| SCC = 0                     | Reference                   |                             |
| SCC = 1                     | 0.554 (0.320–0.961)         | 0.035                       |
| SCC = 2                     | 0.411 (0.231–0.730)         | 0.002                       |

**DFS analysis**

In the univariate analysis, RDW-SD ≤ 40.2 fl (p = 0.047), T3-T4 stage (p = 0.017), lymph node metastasis (p < 0.001), multiple tumors (p = 0.018), preoperative CEA > 5 ng/mL (p < 0.001), ALT > 50 U/L (p = 0.019) and blood loss ≥ 300 mL (p = 0.008) were associated with worse DFS. RDW-CV (p = 0.579) and SCC score (p = 0.247) were not associated with DFS (Table 4). The multivariate analysis showed that RDW-SD level was not an independent prognostic factor, and positive lymph node (HR = 2.566, 95% CI: 1.388–4.746, p = 0.003), multiple tumors (HR = 2.181, 95% CI: 1.296–3.671, p = 0.003) and preoperative CEA > 5 ng/mL (HR = 1.750, 95% CI: 1.045–2.929, p = 0.033) were independent predictors for the unfavourable OS.
significance for predicting survival. In general, although RDW can predict the prognosis of ICC patients to some extent, its predictions seem to contradict the conclusions of mainstream studies that have shown that RDW value is an independent risk factor for overall survival in patients with HCC, endometrial cancer and prostate cancer in a multivariate analysis [18, 32, 33]. However, there are also studies that show that RDW was not an independent predictor of cancer-specific survival (CSS) or OS in other cancers [24, 34]. These controversial conclusions led us to re-examine the value of RDW in predicting tumor prognosis and reflecting the heterogeneity among different cancer species.

According to current research evidence, the mechanisms for the poor survival of cancers are not fully understood, are very likely multifactorial, and include inflammation, oxidative stress, and malnutrition [35–37]. However, the biological meaning of RDW increase remains largely unknown in spite of several explanations that might indicate the elevated RDW levels. RDW is

| Table 3 Prognostic factors for OS for ICC patients in multivariate analysis |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Factor                      | Multivariate analysisa      | Factor                      | Multivariate analysisa      |
|                             | Model 1                     |                             | Model 2                     |
|                             | HR (95%CI) Value p           |                             | HR (95%CI) Value p           |
| Age ≥ 60 years              | –                           | Age ≥ 60 years              | –                           |
| Male                        | –                           | Male                        | –                           |
| BMI ≥ 24 kg/m²              | –                           | BMI ≥ 24 kg/m²              | –                           |
| ASA score 3–4               | –                           | ASA score 3–4               | –                           |
| Cirrhosis                   | –                           | Cirrhosis                   | –                           |
| HBsAg (+)                   | –                           | HBsAg (+)                   | –                           |
| T3–T4 stage                 | –                           | T3–T4 stage                 | –                           |
| Lymphnode metastasis        | –                             | <0.001                      | <0.001                      |
| Undissected lymph node      | Reference                    | Reference                   | Reference                   |
| Negative lymph node         | 1.160 (0.581–2.318)         | 0.674                       | 1.226 (0.595–2.526)         |
| Positive lymph node         | 3.715 (1.721–8.019)         | 0.001                       | 4.394 (1.950–9.900)         |
| Tumor size ≥ 5 cm           | –                             | 2.041 (1.134–3.673)         | 0.017                       |
| Multiple tumors             | –                             | –                           | The prognostic value on SCC scorec |
| Tumor location (central tumor) | 0.367 (0.210–0.641)     | <0.001                      | 0.307 (0.171–0.552)         |
| Poor differentiation         | –                             | –                           | SCC = 0                     |
| Preoperative CA19-9 > 27 U/mL | –                           | –                           | SCC = 1                     |
| Preoperative CEA > 5 ng/mL   | 2.486 (1.305–4.734)         | 0.006                       | 2.234 (1.164–4.287)         |

  
aTo prevent colinearity, RDW-SD was included in the multivariate analysis of Model 1, and RDW-CV was included in the multivariate analysis of Model 2, respectively.

bThe median operation time and the median blood loss were chosen as the cut-off point.

cBecause the SCC score was based on the RDW-SD and RDW-CV, the multivariate analysis of prognostic value of SCC score included factors with a P < 0.1 in univariate analysis exclude of the RDW-SD and RDW-CV.
positively correlated with widely used plasma inflammatory markers, such as C-reactive protein (CRP) [38, 39] and blood sedimentation rate (ESR) [40], and is considered to be an inflammatory marker in cancer patients. Various inflammatory factors affect erythropoiesis through the production of erythropoietin (EPO), the inhibition of erythro-progenitor cells, and the reduction of iron release. In conclusion, the hypothesis that RDW can reflect the inflammatory state of cancer is reasonable.

Second, malnutrition is another characteristic of cancer due to loss of appetite and weight loss and can lead to deficiencies in minerals and vitamins such as iron, folic acid and vitamin B12, which can also lead to changes in RDW values. In summary, high RDW levels are a good indicator of chronic inflammation and malnutrition in cancer patients. However, it is still controversial whether the prognosis of tumor patients can be predicted in a real-world setting. Studies point to evidence that tumors mainly occur in middle-aged and elderly populations, and the prevalence of anemia and malnutrition in elderly patients is relatively high, which may lead to elevated RDW values due to other aspects, thereby reducing the prognostic significance of this parameter for tumors [20]. Similarly, the investigators demonstrated that RDW was no longer associated with OS or DFS in patients with esophageal squamous cells after adjusting the correlation index [41]. Another study of esophageal cancer reached the same conclusion [42]. Such differences in outcome may be related to the selected population. The inclusion criteria for patients in this study included no association with chronic pneumonia or other diseases that affect RDW value, thus excluding the influence of these diseases on RDW and the analysis results. Most of the patients in this study had RDW values within the normal range, while other studies, especially those investigating blood-related diseases, did not exclude patients with a large number of RDW abnormalities, so different results may appear. In addition, there was heterogeneity among different cancer species, and the predictive value of RDW may not be applicable to all disease species. Among the differences in statistical methods, the heterogeneity of RDW in different studies led to different methods for selecting cut-off values. The majority of the studies used ROC analysis to define the cut-off values. In some studies, the median was used as the cut-off point, and the above two methods were used to select a cut-off point value of 90% with an applied cut-off value between 13 and 15% [43]. In this study, X-tile analysis was used for the first time to obtain a cut-off point value of 12.6% by fitting the relationship between prognosis and RDW. The differences in statistical methods led to different research results.

There are also limitations in this study. First, only preoperative RDW values were included in this study, but the clinical value of postoperative RDW remains unclear and may dynamically represent changes in the balance between systemic inflammatory responses and immune responses after treatment. Second, this study

| Table 4 Prognostic factors for DFS for ICC patients in Univariate analysis |
|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Factor | HR (95%CI) | Value p | Factor | HR (95%CI) | Value p |
| Age ≥ 60 years | 0.797 (0.541–1.174) | 0.251 | Preoperative CEA > 5 ng/mL | 2.210 (1.442–3.386) | < 0.001 |
| Male | 1.119 (0.764–1.640) | 0.563 | RDW-SD > 40.2 fl | 0.681 (0.459–1.011) | 0.047 |
| BMI ≥ 24 kg/m² | 1.014 (0.689–1.492) | 0.945 | RDW-CV > 12.6% | 0.896 (0.608–1.230) | 0.579 |
| ASA score 3–4 | 1.352 (0.703–2.599) | 0.366 | ALB ≥ 40 g/L | 0.744 (0.478–1.159) | 0.191 |
| Cirrhosis | 1.101 (0.743–1.632) | 0.630 | TBIL > 21 umol/L | 0.912 (0.488–1.703) | 0.772 |
| HBsAg (+) | 1.193 (0.765–1.858) | 0.436 | AST > 40 U/L | 1.606 (0.898–2.873) | 0.111 |
| T3–T4 stage | 1.711 (1.100–2.662) | 0.017 | ALT > 50 U/L | 2.018 (1.120–3.634) | 0.019 |
| Lymphnode metastasis | < 0.001 | | Operation time ≥ 230 min | 1.380 (0.941–2.022) | 0.099 |
| Undissected lymph node | Reference | | Blood loss ≥ 300 ml | 1.710 (1.149–2.546) | 0.008 |
| Negative lymph node | 1.114 (0.685–1.811) | 0.664 | Major liver resection | 1.402 (0.906–2.171) | 0.129 |
| Positive lymph node | 2.713 (1.591–4.627) | < 0.001 | Post-operative Complications | 0.998 (0.674–1.477) | 0.991 |
| Tumor size ≥ 5 cm | 1.285 (0.877–1.884) | 0.199 | Preoperative therapy | 1.207 (0.587–2.484) | 0.609 |
| Multiple tumors | 1.738 (1.099–2.751) | 0.018 | Adjutant therapy | 0.887 (0.602–1.306) | 0.544 |
| Tumor location (central tumor) | 0.702 (0.480–1.028) | 0.069 | The prognostic value on SCC score | 0.247 |
| Tumor location (right lobe) | 0.906 (0.672–1.222) | 0.518 | SCC = 0 | Reference |
| Poor differentiation | 1.443 (0.965–2.158) | 0.074 | SCC = 1 | 0.716 (0.447–1.146) | 0.164 |
| Preoperative CA19-9 > 27 U/mL | 1.364 (0.875–2.124) | 0.170 | SCC = 2 | 0.698 (0.438–1.113) | 0.131 |

* The median operation time and the median blood loss were chosen as the cut-off point.
revealed that pre-operative CA19-9 level was not significantly associated with survival, the reason of which was that some patients with concomitant cholangitis (complicated by symptoms such as epigastric pain, hyperleukocytosis, or fever) were included in this study. Some studies have shown that preoperative cholangitis may affect on the value of CA19-9 [44, 45]. In future studies, in order to remove the influence of cholangitis on CA19-9 or other markers, we would strictly include the criteria and exclude this subset of patients. Finally, the data were collected retrospectively from a single center; therefore, our results may be potentially biased and inaccurate.

Conclusions

In conclusion, our results indicated that elevated preoperative RDW values within a certain range do not indicate a worse prognosis; more meaningful results were obtained: we obtained the opposite conclusion as that in the literature. However, the significance of RDW in predicting the prognosis of ICC needs to be confirmed by larger, prospective, randomized studies.

Abbreviations

ICC: Intrahepatic cholangiocarcinoma; OS: Overall survival; PLT: Platelet count; NLR: Neutrophil–lymphocyte ratio; PLR: Platelet–lymphocyte ratio; RDW: Red blood cell distribution width; RDW-SD: Red blood cell distribution width–standard deviation; RDW-CV: Red blood cell distribution width–coefficient of variation; SCC: RDW-SD combined with RDW-CV; HCC: Hepatocellular carcinoma; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; AFP: Alpha fetoprotein; MRI: Magnetic resonance imaging; CT: Computed tomography; MVI: Microvascular invasion; ALB: Albumin; TBL: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TACE: Transarterial chemoembolization; HBsAg: Hepatitis B surface antigen; DFS: Disease-free survival; CRP: C-reactive protein; ESR: Blood sedimentation rate; EPO: Erythropoietin.

Acknowledgements

We gratefully acknowledge all staff members of Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, for their help and cooperation.

Authors’ contributions

XL and QC are the main authors of manuscript and have made substantial contributions to the conception and design of study. XB, JZ, ZL, JZ, ZH, YZ and RM have been involved in collection and analysis of the data. HZ and JC gave final approval and revised of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the National Capital Health Research and Development of Special (No. 2018-1-4021) and the National Science and Technology Major Project (No. 2018ZX10723204). Principal Investigator: Jianqiang Cai. Members of the funding body participated in the design of the study and data analysis. And the funding body will cover the publication charge.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. Emails could be sent to the address below to obtain the shared data: lxc_pumc@126.com.

Ethics approval and consent to participate

The research was in compliance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of the Cancer Hospital, Chinese Academy of Medical Sciences (ID: NCC2019C-016) and the necessity for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 18 June 2020 Accepted: 9 February 2021

Published online: 01 March 2021

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