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ORIGINAL RESEARCH

Prognostic Value of Red Blood Cell Distribution Width (RDW) in the Recurrence of Hepatocellular Carcinoma Following Curative Resection

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Purpose: Although surgery is associated with an acceptable cure rate, tumor recurrence is still a challenging issue in hepatocellular carcinoma (HCC) patients. Red blood cell distribution width (RDW) is considered an inflammatory marker for predicting overall mortality in a wide spectrum of malignancies. In the current study, the prognostic role of pre- and postoperative RDW in HCC recurrence after liver resection (LRx) is investigated.

Patients and Methods: In 395 patients, RDW levels were evaluated preoperatively as well as six and twelve months after curative LRx. The RDW cutoff values were determined using receiver operating characteristic curves (ROCs) according to the recurrence-free survival (RFS). Survival analyses were performed using the Kaplan–Meier, and differences were compared using the Log rank test.

Results: The RFS was significantly higher among patients with low RDW at the 6th month and 12th month, postoperatively ($P < 0.001$ and $P = 0.028$). RDW levels of higher than 16.15% at the 6th (HR: 2.047, $P < 0.001$) and higher than 15.85% at 12th (HR: 3.105, $P < 0.002$) months after liver resection were independent predictors of RFS.

Conclusion: Postoperative RDW values seem to be predictive of tumor recurrence in HCC patients. RDW levels at the 6th and 12th months postoperatively were independent predictors of recurrence after LRx.

Keywords: hepatectomy, hepatocellular carcinoma, liver resection, red blood cell distribution width

Introduction

Hepatocellular carcinoma (HCC) is one of the most common types of solid organ cancers worldwide with poor prognosis and is the second leading cause of cancer-related death.[1] In recent decades, the incidence and prevalence of HCC has been increasing considerably, especially in high-risk patients.[1,2] Moreover, the advances in clinical therapeutics and management have led to prolonged survival of the patients, whereas no significant contribution has been made over the past four decades to increase the survival rates, in solid malignancies such as HCC. Although surgical resection is associated with an acceptable cure rate, tumor recurrence is still a challenging issue, and the underlying etiology has yet to be fully elucidated.[3] Therefore, different biomarkers have been suggested to predict recurrence after resection, among which red blood cell distribution width (RDW) is one of the most easily available markers.[4,5]

RDW is a hematological parameter for volume variability of erythrocytes in peripheral blood. Some studies have shown a strong association between RDW and age of the patients, however, its correlation with gender remains still unclear.[6] Besides, other investigations have criticized the overestimated effect of the aging over RDW levels, due to

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neglection of habitual marrow stimulations in healthy individuals. Nonetheless, several studies have considered the RDW as an inflammation-associated marker for predicting overall mortality in a wide spectrum of malignancies.[7–10] The possible mechanism may be inflammation-associated impairment in erythrocyte maturation, oxidative stress, deranged nutrition, and cancer-driven cytokine release.[11–14] Specifically, for HCC, preoperative RDW has been shown to be able to predict the post resection recurrence of the tumor and mortality of patients.[4,15] However, these studies focused only on preoperative RDW levels. To the best of our knowledge, there is no study evaluating the significance of pre- and postoperative RDW levels in the prognosis of HCC recurrence in the long term.

The aim of this study was to evaluate the prognostic role of pre- and postoperative RDW in the recurrence of HCC after curative resection.

Methods

Study Design

From 2001, all data of the patients who underwent liver resection at the University Hospital in Heidelberg were prospectively gathered in our data bank. Up to 2020, a total of 3870 liver resections were documented in our database. Among these, 417 patients underwent liver resection with HCC. After excluding patients with (1) inflammatory disorders influencing the level of RDW, such as rheumatoid arthritis, systemic lupus erythematosus, and spondyloarthritis; (2) hematological diseases, such as anemia or malignancies; (3) recent iron supplementation therapy or blood transfusion; (4) status after splenectomy; (5) infection; (6) autoimmune diseases; and (7) neoadjuvant or adjuvant chemotherapy or immunotherapy, 395 HCC cases were included in this study. The study protocol was approved by the independent ethics committee of the University of Heidelberg (approval number: S-754/2018). All procedures were performed according to the most recent revision of the Declaration of Helsinki. Informed consent to participate in the study was obtained from all patients before their data were entered into the database.

Patient Evaluation

Preoperative Evaluations

Treatment decisions were made by an interdisciplinary institutional tumor board that included surgeons, hepatologists, oncologists, radiologists, radio-oncologists, and pathologists. Patient demographic and clinical data were prospectively recorded, including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) class, and underlying liver disease (eg, hepatitis and cirrhosis). During preoperative workups, hepatitis serology was controlled in all patients, including hepatitis B surface (HBs) antigen, HBs antibody and hepatitis B core antibody as well as hepatitis C virus antibody. The liver cirrhosis was diagnosed preoperatively through imaging modalities or liver biopsies, in indicated patients. Barcelona clinic liver cancer (BCLC) staging was used to categorize the severity of the HCC among the included patients.

Intraoperative Evaluations

Intraoperative data, including the type of liver resection, blood loss, and operation time, were collected. Major liver resection was defined as resection of four or more segments, according to the Brisbane classification, and the remainder of resection were considered as minor liver resection.

Postoperative Evaluations

All patients were followed postoperatively every 6 months, including clinical evaluation, blood sampling, CT and/or MRI imaging. Postoperative morbidities were classified as grade I to V based on the Clavien–Dindo classification.[16] Major morbidity was defined as grade III or IV. Post hepatectomy liver failure (PHLF) was diagnosed and reported according to the International Study Group of Liver Surgery (ISGLS).[17] PHLF was graded as A, B, or C. The tumor TNM staging and grading, as well as resection margin (R0/1) were reported. Postoperative mortality was defined as all-cause death occurring within the first 90 days after surgery. Overall survival (OS) and recurrence-free survival (RFS) were monitored for three years.

RDW Measurement

Blood samples were obtained from peripheral veins 24–48 hours before the surgery as well as 6 and 12 months postoperatively. The blood tests were assessed on EDTA anticoagulated whole blood using an automatic blood cell analyzer with fresh samples. No difference has been considered in the central laboratory of the clinic, between the normal ranges of the RDW between male and female individuals, according to the instruction of the analyzer's producer.

Statistical Analysis

IBM SPSS Statistics Version 27.0 (IBM Corp. Released 2017. Armonk, NY) was used for statistical analyses. Continuous data are presented as medians (ranges), and categorical data are presented as frequencies and proportions. Univariate analysis was performed using Student's *t*-test for continuous data and chi-square or Fisher's exact test for categorical data. The cutoff values of RDW were determined using receiver operating characteristic curves (ROCs) according to the recurrence-free survival of patients, by considering the level of RDW at highest sensitivity and specificity. Survival analyses were performed using the Kaplan-Meier method, and differences between groups were compared using the Log rank test. Patients diagnosed with recurrence before six and 12 months postoperatively, were excluded from these Kaplan-Meier analysis as well as curves. All variables with a p value of < 0.1 in the univariate analysis were included in the multivariate analysis. The results are reported as hazard ratios (HRs) and 95% confidence intervals (95% CIs). P values < 0.05 were considered statistically significant.

Furthermore, we carried out a propensity scoring method to match two cohorts in order to mitigate selection bias and to control for patient imbalances. The scoring was performed between patients with RDW rates higher and lower than cut-off, based on a multivariate logistic regression model accounting for age, gender, cirrhosis, tumor size, tumor number, and BCLC. Using 1-to-1-digit match, we paired each patients with RDW higher than cut-off with one patients with RDW level of lower than cut-off. The matching was carried out for patients at different time-points.

Results

Preoperative and Perioperative Data

Table 1 summarizes the demographic and baseline clinical characteristics of patients. The mean age of the patients was 63.4 ± 11.6 years, and 304 patients (77%) were males. One hundred and seventy-six patients (44.6%) had liver cirrhosis. Among patients with underlying hepatic pathologies, the most common etiologies associated with HCC were hepatitis (49.4%),

Table 1 Demographic and Baseline Clinical Characteristics

Variable	Mean±S.E. or N (%)
Preoperative Data	
Age (year)	63.4±11.6
BMI (kg/m^2)	28.7±1.3
Gender	
• Male	304 (77%)
• Female	91 (23%)
ASA classification	
• I	8 (2%)
• II	204 (51.6%)
• III	175 (44.4%)
• IV	8 (2%)

(*Continued*)

Table 1 (Continued).

Variable	Mean±S.E. or N (%)
Cirrhosis	176 (44.6%)
Etiology of cirrhosis	
• Hepatitis B/C	87 (49.4%)
• Alcoholic	51 (28.9%)
• Nonalcoholic hepatosteatosis	21 (11.8%)
• Metabolic diseases	17 (9.9%)
Child-Pugh score	
• A	170 (43%)
• B	6 (1.5%)
Number of tumors	
• I	313 (79.2%)
• II	52 (13.2%)
• Multiple	30 (7.6%)
BCLC stage	
• Very early	43 (10.9%)
• Early	300 (75.9%)
• Intermediate	52 (13.2%)
Intraoperative Data	
Liver resection	
• Minor	277 (70.1%)
• Hemi hepatectomies	92 (23.3%)
• Extended resection	26 (6.6%)
Blood loss (mL)	778.2±803.5
Operation time (min)	164±68.7

Abbreviations: S.E., Standard Error; BCLC, Barcelona Clinic Liver Classification; BMI, Body Mass Index; ASA, American Society of Anesthesiologists; mL, Milliliter; min, Minute, kg, Kilogram; m, Meter.

alcoholic liver diseases (28.9%), nonalcoholic hepatosteatosis (11.8%), and metabolic diseases (9.9%). Regarding the extent of liver resection, minor resections were the common procedures (277 patients (70.1%)). Hemihepatectomies and extended liver resections were the second (92 patients (23.3%)) and third (26 patients (6.6%)) most common procedures. The mean intraoperative blood loss was 778.2 ± 803.5 milliliters, with a mean operation time of 164 ± 68.7 minutes.

Major complications (defined using the Clavien–Dindo classification) occurred in 42 patients (10.6%). The most common complications after liver resection were posthepatectomy bile leakage (PHBL) (18 cases, 4.5%), renal failure (14 cases, 3.5%), and ascites (10 cases, 2.5%). Posthepatectomy hemorrhage (PHH) and posthepatectomy liver failure (PHLF) were reported in 10 (2.5%) and 9 cases (2%), respectively. Eighteen patients (18.6%) required percutaneous transhepatic cholangiodrainage (PTCD) or reoperation because of PHBL. Of all included patients, five patients

underwent extended liver resection, and three patients who underwent hemihepatectomy died within the first 30 days after liver resection. The postoperative 90-day mortality was reported to be 3% (12 patients).

Oncological Outcomes After Liver Resection

All resections were performed in R0 status. The mean follow-up duration is 27.9 ± 2.3 months. The 1- and 3-year RFS rates were 92.7% and 68.9%, respectively. The 1- and 3-year OS rates were 94.7% and 78.6%, respectively. Tumor recurrence was diagnosed in 32 of the 395 patients (81%) during the follow-up period.

Predictive Value of RDW in Patients with HCC Recurrence

The mean levels of RDW were calculated to be 13.9 ± 1.6% preoperatively. The mean levels of RDW at 6 and 12 months after surgery were 15.5 ± 3.5% and 15.2 ± 2.4%, respectively. Patients who developed recurrent tumors during follow-up had significantly higher preoperative, six-month, and 12-month RDW levels (P <0.001, P= 0.002 and P <0.001, respectively).

We used ROC curve analysis to verify the predictive power of RDW in predicting HCC recurrence after liver resection. The optimal cutoff of preoperative RDW was 14.25%, with a sensitivity of 83.3% and a specificity of 73.7%, as well as an AUC of 0.85 (95% CI = 0.751–0.966, P < 0.001) (Figure 1A). For the six-month postoperative period, the optimal RDW cutoff for the prediction of recurrent HCC was 16.15%, which showed a sensitivity of 91.3% and a specificity of 79.8% (95% CI = 0.853–0.989, P < 0.001) (Figure 1B). Finally, the optimal value of RDW at 12 months after liver resection for the prediction of recurrence was 15.85%, which presented a sensitivity and sensitivity of 87.5% and 79.9%, respectively (Figure 1C). The AUC of RDW at 12 months was 0.882 (95% CI = 0.793–0.971, P < 0.001).

The 3-year RFS rates were compared between patients considering the cutoff values defined for different time points. As shown in Figure 2, the patients with RDW levels of ≤14.25% and >14.25% had RFS rates of 72.2% and 60.8%, respectively, which was significantly different (P= 0.032). The RFS comparison regarding the 6th month RDW level showed a significantly higher RFS among patients with RDW ≤16.15% (76.2% vs 47.8%; P <0.001) (Figure 3). Similarly, patients with RDW levels of ≤15.85 at 12 months postoperatively had significantly higher RFS than patients with RDW >15.85 (71.6% vs 55.9%; P= 0.028) (Figure 4).

Propensity score matching was carried out between two groups of patients based on the RDW levels at different time points. The 3-year RFS was compared between patients considering the above-mentioned cutoff values defined for each checkpoint. Albeit non-significant, the rate of 3-year RFS was higher among patients with RDW levels of ≤14.25% compared to that of patients with RDW levels of >14.25% (P= 0.150). However, the RFS of patients with RDW ≤16.15% was still significantly higher than that of patients with higher RDW levels (P= 0.033). Also, at 12th month postoperative,

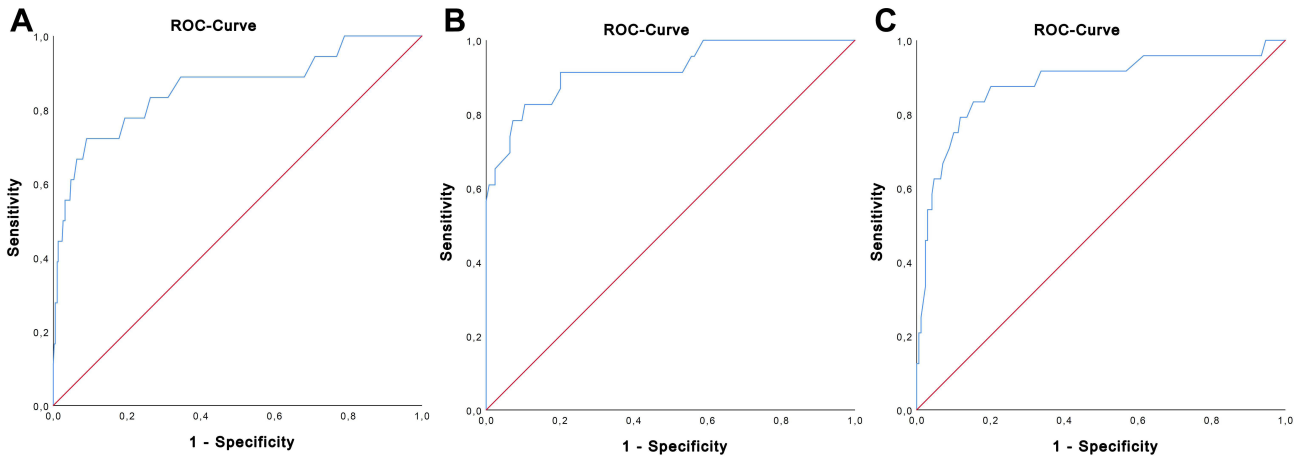

Figure 1 (**A**) Receiver-operator characteristics curves for red blood cell distribution width (RDW) preoperatively. (**B**) Receiver-operator characteristics curves for RDW at 6 months postoperatively. (**C**) Receiver-operator characteristics curves for RDW at 12 months postoperatively.

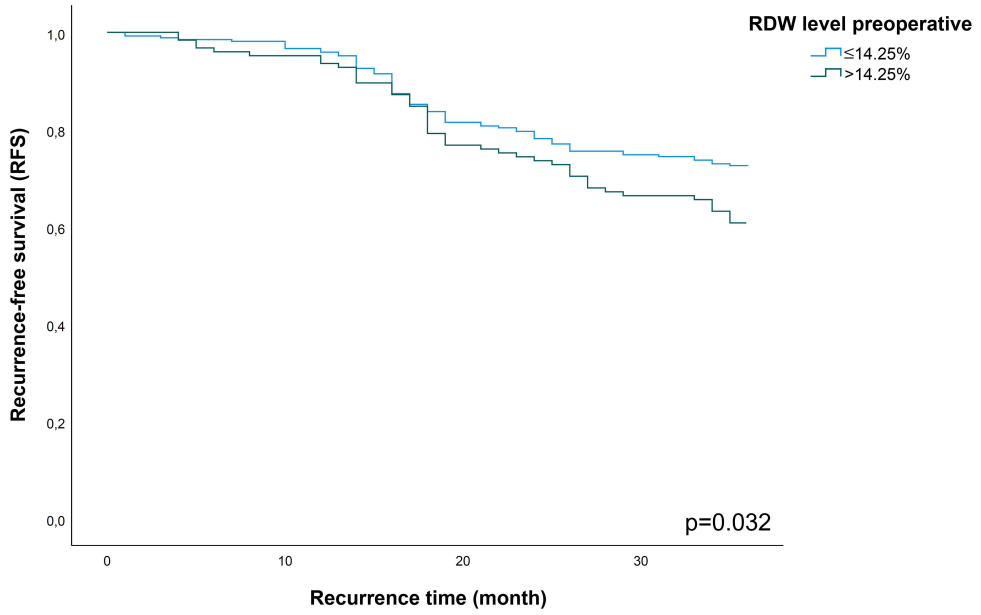

Figure 2 Kaplan–Meier recurrence-free survival curves of hepatocellular carcinoma (HCC) patients after liver resection. Patients were divided into two groups: preoperative level of red blood cell distribution width (RDW) ≤14.25% and preoperative level of RDW >14.25%.

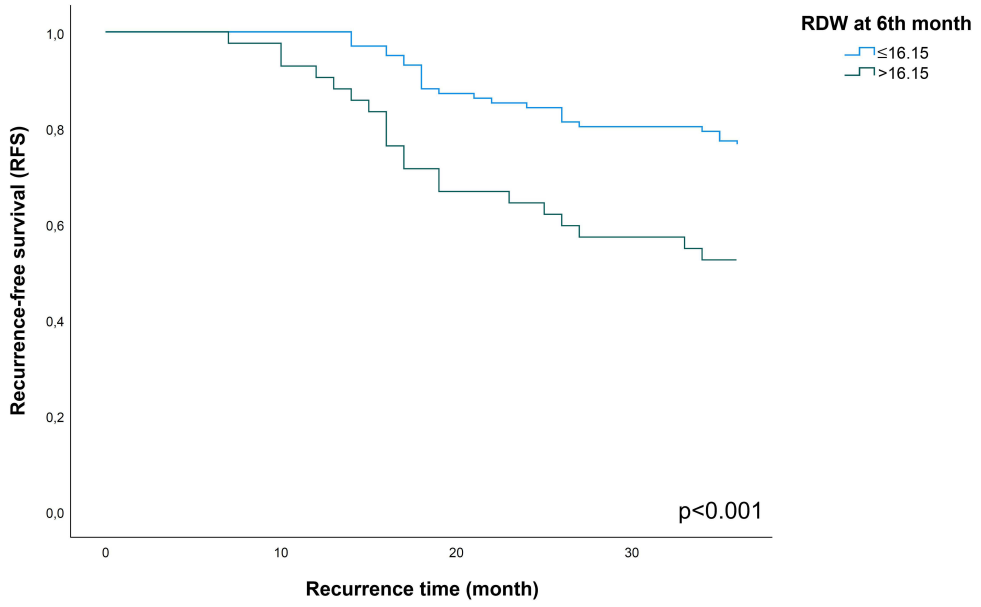

Figure 3 Kaplan–Meier recurrence-free survival curves of hepatocellular carcinoma (HCC) patients after liver resection. Patients were divided into two groups: red blood cell distribution width (RDW) at 6 months postoperatively ≤16.15% and RDW at 6 months postoperatively >16.15%.

patients with RDW levels of ≤15.85 had significantly higher rate of RFS compared to patients with RDW >15.85 (P= 0.005). The Kaplan-Meier analyses and curves have been provided in the Figures S1–S3.

Analysis of Factors Associated with HCC Recurrence

The results of the univariate analysis of pre- and postoperative factors associated with HCC recurrence are provided in Table 2. Patient sex, atypical liver resection, and RDW levels during preoperative and 6- and 12-month postoperative time points were all significantly associated with the RFS of the patients. The Cox proportional hazard analysis showed

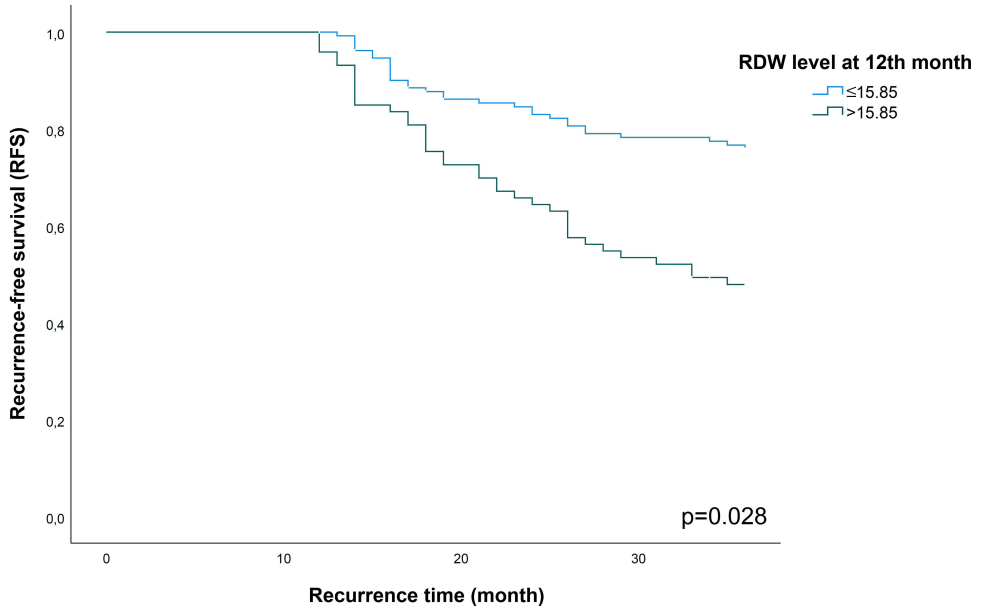

Figure 4 Kaplan–Meier recurrence-free survival curves of hepatocellular carcinoma (HCC) patients after liver resection. Patients were divided into two groups: red blood cell distribution width (RDW) at 12 months postoperatively ≤15.85% and RDW at 12 months postoperatively >15.85%.

that RDW levels at 6th (HR: 2.047, P <0.001) and 12 (HR: 3.105, P <0.002) months after liver resection were independent predictors of RFS (Figure 5).

Discussion

Hepatocellular carcinoma is the most common primary hepatic malignancy, with excessive global mortality. In addition, HCC has shown a remarkably high incidence of recurrence after curative liver resection.[1–3] Despite remarkable advancements, HCC is still amongst the malignancies with the most dismal prognosis with a five-year relative survival rate ranging between 7% and 28%. These dismal survival rates are due to lack of curative treatment for the intermediate or advanced stage of HCC. Nevertheless, curative treatments within the frame of surgical resection have been shown to be effective for early stage of HCC, even in patients with recurrent disease.[18,19] Several studies have been carried out to define the factors associated with disease recurrence after curative liver resection among HCC patients, mainly by focusing on molecular and genomic characteristics and manifestations of HCC tumors.[20–23] However, to date, no consensus has been met on the parameters that are capable of predicting the long-term oncological outcomes after liver resection for HCC tumors. On this basis, understanding the factors that might predict the prognosis and long-term oncological outcomes of patients with HCC to identify those with a possibly higher risk of recurrence and poor prognosis is critical and practical.

Cancer-related inflammation may help cancer cells present malignant reactions such as proliferation, infiltration, angiogenesis, and metastasis.[24,25] Chemokines, including interleukins and tumor necrosis factor, have considerable roles in the pathophysiological process of tumor formation and progression.[24] According to the literature, RDW is considered to be identical to acute-phase proteins and shows increased levels as a consequence of inflammatory events.[12,13] Elevated RDW levels have been shown to be a common phenomenon in cancers, and increased RDW levels have resembled tumor progression, invasion, and metastasis.[4,12,13,26] In addition, higher preoperative RDW levels played a predictive role in the development of poor outcomes in patients with malignancies.[4,12,13,26] Therefore, in the current study, we aimed to evaluate the role of RDW in the prediction of tumor recurrence in patients with HCC who underwent curative liver resection.

Our results showed that HCC recurrence subsequent to liver resection was significantly higher in patients with preoperative RDW levels >14.25%. The cutoff value of 14.25% for preoperative RDW levels showed promising

Table 2 Univariate and Multivariate Analysis of Pre- and Postoperative Factors Associated with HCC Recurrence

Variables	Univariate			Cox Regression		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (>60 years old)	0.533	0.281–1.010	0.053	1.678	0.905–3.110	0.100
Gender (female)	0.427	0.225–0.812	0.009	1.064	0.550–2.059	0.853
ASA (>II)	1.330	0.475–3.721	0.587			
Child–Pugh score B	2.076	0.148–28.975	0.586			
Cirrhosis (Yes)	0.595	0.298–1.187	0.140			
Hepatitis B/C	0.684	0.201–2.328	0.543			
Portal hypertension (Yes)	0.498	0.033–7.395	0.612			
Hepatosteatosis (Yes)	1.658	0.444–6.193	0.451			
Tumor size (largest node>3 cm)	1.277	0.661–2.467	0.728			
Number of tumors (more than 1)	1.271	0.599–2.696	0.626			
BCLC staging						
Very early (reference)	–	–	0.310			
Early	1.162	0.375–3.604	0.794			
Intermediate	1.628	1.254–3.547	0.312			
Resection extent (Minor resection)	0.695	0.232–2.574	0.672			
Hemihepatectomy (Yes)	0.323	0.101–1.033	0.056	3.138	0.406–24.250	0.273
Extended liver resection	0.448	0.063–3.145	0.419			
RDW						
Preoperative (RDW >14.25%)	1.970	1.034 – 3.736	0.038	1.383	0.684–3.594	0.746
6th month postoperative (RDW >16.15%)	2.305	1.038–3.739	<0.001	2.047	1.154–5.337	<0.001
12th month postoperative (RDW >15.85%)	15.898	4.932–51.241	<0.001	3.105	1.484–6.489	0.002

Abbreviations: HR, hazard ratio; CI, Confidence interval; ASA, American Society of Anesthesiologists; BCLC, Barcelona Clinic Liver Classification; RDW, Red blood cell distribution width; cm, Centimeter.

sensitivity and specificity in the prediction of tumor recurrence. Similarly, the cutoff values of 16.15% and 15.85% for RDW levels at the 6th and 12th postoperative months, respectively, had even higher accuracy in the prediction of HCC tumor recurrence. In addition, the comparison of the RFS with regard to the defined RDW cutoff values revealed significantly lower survival among patients with higher RDW levels. RDW levels at 6 and 12 months postoperatively were independent predictors of tumor recurrence during the three-year period after liver resection.

The exact mechanism of RDW increase in tumor cell growth or metastasis is not yet understood. Although the correlation between RDW levels and inflammation remains unclear, high RDW levels are thought to reflect inflammation.[27,28] Chronic inflammation in patients with malignancy is mediated through excess production of inflammatory cytokines such as IL-6, TNF-α, and CRP.[27,29,30] As a result, inflammatory reactions affect iron metabolism and inhibit the response to erythropoietin, which contributes to decreasing red blood cell survival through the production of inflammatory markers and leads to RDW levels.[31] It can be hypothesized that cancer progression, as a means of tumor recurrence, might direct or indirectly affect hematopoiesis and that RDW might also reflect cancer invasion. In an earlier survey, Zhao et al reported that the preoperative RDW value significantly correlates with tumor stage and vascular

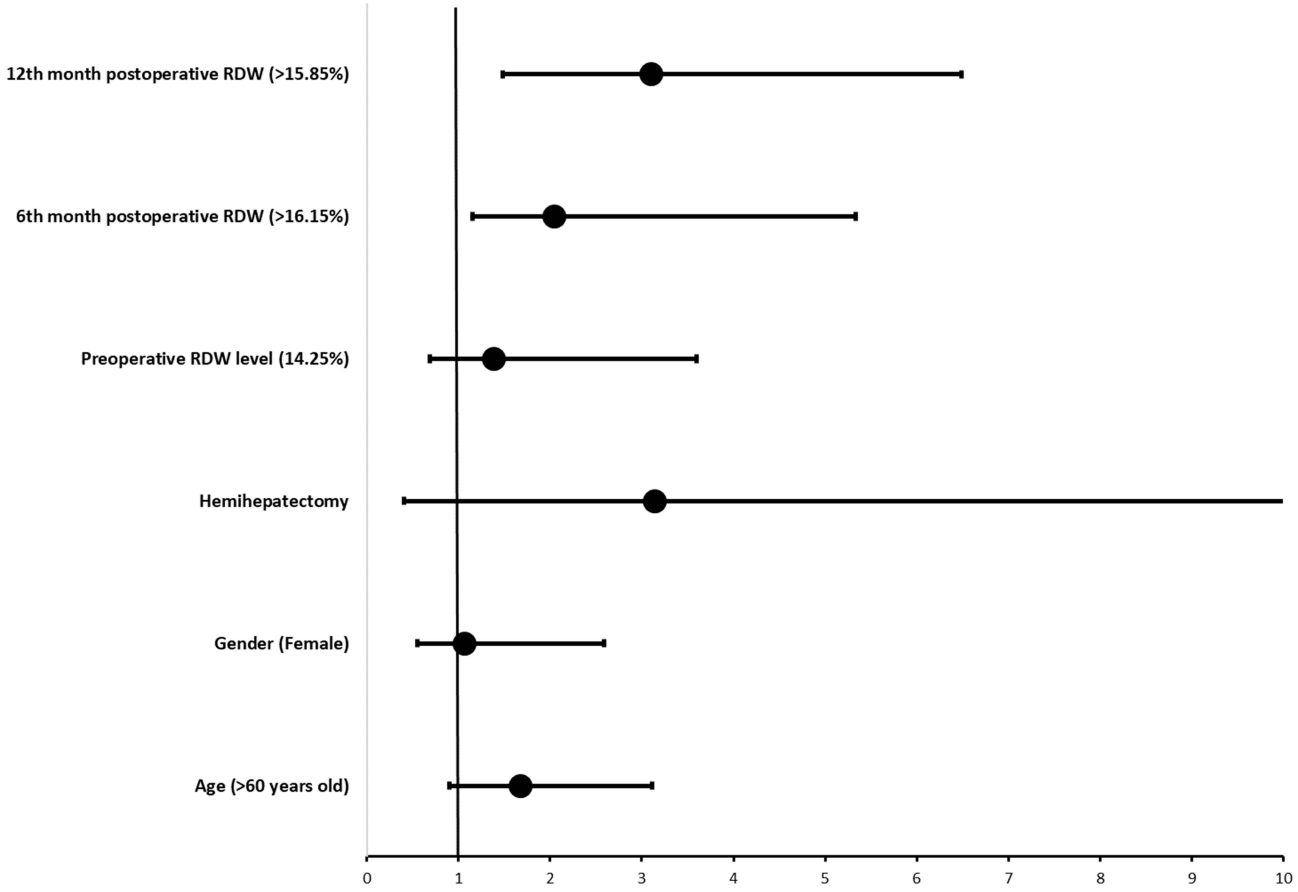

Figure 5 Forest plot of the multivariate cox-regression analysis.

invasion in patients with HCC.[15] In addition, their results have shown that an elevated preoperative RDW value is an independent risk factor for OS in patients with HCC after a multivariate analysis.[15] Zhu et al indicated that the RDW level and platelet-to-lymphocyte index were the only independent prognostic factors for overall survival in HCC patients among preoperative hematological components.[32] These studies were consistent with our findings, which reflect the correlation between elevated preoperative RDW levels and a higher incidence of recurrence. Although liver resection increases the levels of inflammatory mediators and markers, we hypothesized that tumor recurrence might also lead to inflammatory reactions that slow down the decrease in RDW levels. There are some limitations in this study. Although the data were gathered prospectively, the study had a retrospective design. Additionally, the results are from a single center experience.

Conclusion

Our findings indicated that preoperative and postoperative RDW values are closely related to tumor recurrence. RDW levels at 6 and 12 months postoperatively were independent predictors of tumor recurrence after liver resection. The comparison of RFS based on the defined RDW cutoff values revealed significantly lower RFS among patients with higher RDW levels. In the clinical setting, these findings can lead to long-term intensive follow-up of patients with high RDW.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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