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

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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 PFS.

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.

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 surgical resection. Even when

potentially curative resections are achieved, the 5-year survival rate after resection is only 8–47% because these tumors have a high degree of malignancy, insidious onset and early subclinical changes and are very difficult to discover. Clear margins during resection are emphasized as the most important factor for good local control and a favorable prognosis; in addition, lymph node metastasis is also one of the most significant prognostic factors for survival in ICC [2]. Surgery requires radical resection with appropriate lymph node resection. The prognosis of patients is closely related to whether radical resection can be performed, but the radical resection rate of ICC is only 15–20%, far lower than the surgical resection rate of 70% for distal cholangiocarcinoma. Even though patients with ICC who undergo extended resection still have a poor prognosis, this is closely related to the high incidence of local recurrence and distant metastasis [3]. To date, no systemic adjuvant therapy has improved overall survival (OS), despite the increased research effort and active clinical trials investigating a variety of drugs [4]. We should attach great importance to this kind of malignant disease in the clinic.

Although the reasons for the high recurrence rate in ICC are complicated, inflammation plays an important role in the malignant progression and metastasis of ICC [5–6]. In addition, there is substantial evidence that systemic inflammation predicts survival and recurrence of ICC after resection [7]. Some studies have shown that systemic inflammatory markers of serum parameters, including platelet count (PLT), hemoglobin, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), can predict the survival of a variety of human cancers [8–12]. 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 diseases, 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.

Methods

Patients

The clinical date of 157 cases with ICC from our hospital 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. The RDW-SD combined with RDW-CV (SCC) was established to analyses the prognostic value of survival. The SCC was scored as 0 (decreased RDW-SD levels with decreased RDW-CV), 2 (elevated RDW-SD levels with elevated RDW-SD levels), or 1 (all other combinations).

Follow-up

Patients first underwent postoperative serum CA19-9, CEA and AFP measurements and magnetic resonance imaging (MRI) or computed tomography (CT) 1 month after surgery. Then, the patients were required to visit the clinics every 3 months for the next 2 years, every 6 months for the following 3 years, and once annually thereafter. The patients' follow-up adjuvant treatment was chosen based on the first review, which 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 X^2 and Mann-Whitney U tests, as appropriate. X-tile analysis was implemented to investigate the optimal cut-off point of RDW-SD and RDW-CV. This study used the Kaplan-Meier method to estimate PFS 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 PFS. 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). All analyses were performed using SPSS, version 22 software (Armonk, NY, USA). $P < 0.05$ was considered 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%) was 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% of the patients have postoperative 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 = 53) group and high RDW-SD (> 40.2, n = 104) 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**).

Prognostic value of RDW-SD, RDW-CV and SCC for survival

The median follow-up time was 33.00 months. The median OS and median PFS 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: 68.0 months versus 17.0 months) and better PFS (P = 0.047, median PFS: 11.0 months versus 7.0) than those with low RDW-SD values (Figure 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 PFS (P = 0.579, median PFS: 11.0 months versus 10.0) than those with low RDW-CV values (Figure 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 33.0 months versus 16, respectively), but all three SCC values had an equivalent PFS (P = 0.247, median PFS: 11.0 months versus 12.0 months versus 7.0 months, respectively) (Figure 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 (P = 0.004), RDW-CV≤12.6% (P = 0.030), ALB < 40 g/L (P = 0.048), operation time ≥ 230 min (P = 0.015), blood loss ≥ 300 ml (P = 0.030) and decreased SCC score (P = 0.007) were all associated with shorter OS (**Table 2**). The RDW-SD level and RDW-CV level exhibited collinearity (P < 0.001). To 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. 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. Because the SCC score was based on RDW-SD and RDW-CV, the multivariate analysis of the prognostic value of the SCC score included factors with a P < 0.1 in the univariate analysis, excluding RDW-SD and RDW-CV. 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.

PFS 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 PFS. RDW-CV (P = 0.579) and SCC score (P = 0.247) were not associated with PFS. The multivariate analysis showed that RDW-SD level was not an independent prognostic factor (**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.

In our study, patients with high RDW-SD (RDW-SD > 40.2) were significantly associated with better OS (P = 0.003) and better PFS (P = 0.047). Patients with high RDW-CV (RDW-CV≥12.6) were significantly associated with better OS (P = 0.026) and had an equivalent PFS (P = 0.567) to those with low RDW-CV. 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 (P = 0.005) and had an equivalent PFS (P = 0.221). SCC is a combined indicator, so the differences between the three classifications further strengthen their 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 [18,25–26]. 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, 27]. 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 [28–30]. However, the biological meaning of RDW increase remains largely unknown in spite of several explanations that might indicate the elevated RDW levels. RDW is positively correlated with widely used plasma inflammatory markers, such as C-reactive protein (CRP) [31–32] and blood sedimentation rate (ESR) [33], 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 [34]. 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 [35]. Another study of esophageal cancer reached the same conclusion [36]. 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% [37]. 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, the included patients who received curative surgery as the initial therapy and patients who received nonsurgical therapy were not included in the study, and the value of RDW in predicting ICC prognosis may vary from population to population. Finally, the data were collected retrospectively from a single center; therefore, our results may be potentially biased and inaccurate.

Conclusions

In conclusion, this study is the first to analyze the relationship between the preoperative RDW value and prognosis of ICC patients using a new method. 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. Evaluating the preoperative RDW status of patients is conducive to preoperatively predicting the survival of patients and formulating intervention measures and postoperative follow-up plans in advance. 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; HCC:hepatocellular carcinoma; MRI:magnetic resonance imaging; CT:computed tomography; MVI:microvascular invasion; TACE:transarterial chemoembolization; HBsAg:hepatitis B surface antigen; PFS:progression-free survival; CRP:C-reactive protein; ESR:blood sedimentation rate; EPO:erythropoietin

Declarations

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

The written consent is available for review by the Editor-in-Chief of this journal.

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.

Competing interests

The authors declare that they have no competing interests.

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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.

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References

1. EsnaolaNF MeyerJE. KarachristosA, et al. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma[J]. Cancer. 2016;122(9):1349–69.
2. Jarnagin WR, Shoup M. Surgical management of cholangiocarcinoma[J]. Semin Liver Dis. 2004;24(2):189–99.
3. Poultsides GA, Zhu AX, Choti MA, et al. Intrahepatic cholangiocarcinoma[J]. Surg Clin North Am. 2010;90(4):817–37.

4. LafaroKJ CosgroveD, GeschwindJF, et al. Multidisciplinary Care of Patients with Intrahepatic Cholangiocarcinoma: Updates in Management[J]. Gastroenterol Res Pract, 2015, 2015:860–861.
5. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer[J]. Cell. 2010;140(6):883–99.
6. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation[J]. Nature. 2008;454(7203):436–44.
7. Deans C, Wigmore SJ. Systemic inflammation, cachexia and prognosis in patients with cancer[J]. Current Opinion in Clinical Nutrition Metabolic Care. 2005;8(3):265–9.
8. Chen Y, Zhang L, Liu WX, et al. Prognostic Significance of Preoperative Anemia, Leukocytosis and Thrombocytosis in Chinese Women with Epithelial Ovarian Cancer[J]. Asian Pacific journal of cancer prevention: APJCP. 2015;16(3):933–9.
9. Obermair A, Petru E, Windbichler G, et al. Significance of pretreatment serum hemoglobin and survival in epithelial ovarian cancer[J]. Oncol Rep. 2000;7(3):639–44.
10. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis[J]. Cancer Epidemiol Biomarker Prev. 2014;23(7):1204–12.
11. Li J, Jiang R, Liu W-S, et al. A large cohort study reveals the association. of elevated peripheral. blood lymphocyte-to-monocyte ratio with favorable prognosis in nasopharyngeal carcinoma[J]. PLoS One. 2013;8(12):e83069.
12. Zhou X, Du Y, Huang Z, et al. Prognostic value of PLR in various cancers: a meta-analysis. PLoS One. 2014;9:e101119.
13. Salvagno GL, Sanchis-Gomar F, Picanza A, et al. Red blood cell distribution width: A simple parameter with multiple clinical applications[J]. Crit Rev Clin Lab Sci. 2015;52(2):86–105.
14. Felker GM, Allen LA, Pocock SJ, et al. Red Cell Distribution Width as a Novel Prognostic Marker in Heart Failure: Data From the CHARM Program and the Duke Databank[J]. J Am Coll Cardiol. 2007;50(1):40–7.
15. Montagnana M, Cervellin G, Meschi T, et al. The role of red blood cell distribution width in cardiovascular and thrombotic disorders[J]. Clin Chem Lab Med. 2012;50(4):635–41.
16. Tham T, Bardash Y, Teegala S, et al. The red cell distribution width as a prognostic indicator in upper aerodigestive tract (UADT) cancer: A systematic review and meta-analysis[J]. Am J Otolaryngol. 2018;39(4):453–8.
17. Hu L, Li M, Ding Y, et al. Prognostic value of RDW in cancers: a systematic review and meta-analysis[J]. Oncotarget. 2017;8(9):16027–35.
18. Zhao T, Cui L, Li A. The significance of RDW in patients with hepatocellular carcinoma after radical resection[J]. Cancer Biomarkers. 2016;16(4):507–12.
19. Zhu Y, Li JH, Yang J, et al. Inflammation-nutrition scope predicts prognosis of early-stage hepatocellular carcinoma after curative resection[J]. Medicine. 2017;96(39):e8056.

20. Hirahara N, Matsubara T, Kawahara D, et al. Prognostic value of hematological parameters in patients undergoing esophagectomy for esophageal squamous cell carcinoma[J]. International Journal of Clinical Oncology. 2016;21(5):909–19.
21. Zhang F, Chen Z, Wang P, et al. Combination of platelet count and mean platelet volume (COP-MPV) predicts postoperative prognosis in both resectable early and advanced stage esophageal squamous cell cancer patients[J]. Tumour Biol. 2016;37(7):9323–31.
22. Ichinose J, Murakawa T, Kawashima M, et al. Prognostic significance of red cell distribution width in elderly patients undergoing resection for non-small cell lung cancer[J]. Journal of Thoracic Disease. 2016;8(12):3658–66.
23. Wang J, Xie X, Cheng F, et al. Evaluation of pretreatment red cell distribution width in patients with multiple myeloma[J]. Cancer Biomarkers. 2017;20(3):267–72.
24. Shota S, Saito H, Kono Y, et al. Prognostic Significance of Pre- and Post-operative Red-Cell Distribution Width in Patients with Gastric Cancer[J]. Journal of Gastrointestinal Surgery, 2019(2).:1–8.
25. Kemal Y, Demirag G, Bas B, et al. The value of red blood cell distribution width in endometrial cancer[J]. Clin Chem Lab Med. 2015;53(5):823–7.
26. Albayrak S, Zengin K, Tanik S, et al. Red Cell Distribution Width as a Predictor of Prostate Cancer Progression[J]. Asian Pacific journal of cancer prevention: APJCP. 2014;15(18):7781–4.
27. Lee A, Lee HJ, Huang HH, et al. Prognostic Significance of Inflammation-associated Blood Cell Markers in Nonmetastatic Clear Cell Renal Cell Carcinoma[J]. Genitourinary Cancer. 2019;12(11):1–10.
28. Ferrucci L, Guralnik JM, Woodman RC, et al. Proinflammatory state and circulating erythropoietin in persons with and without anemia[J]. The American Journal of Medicine, 2005, 118(11):1288.e11-1288.e19.
29. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation[J]. Cell. 2011;144(5):646–74.
30. Semba RD, Patel KV, Ferrucci L, et al. Serum antioxidants and inflammation predict red cell distribution width in older women: The Women's Health and Aging Study I[J]. Clin Nutr. 2010;29(5):600–4.
31. Wan GX, Chen P, Cai XJ, et al. Elevated red cell distribution width contributes to a poor prognosis in patients with esophageal carcinoma. Clin Chim Acta. 2016;452:199–203.
32. Perisa V, Zibar L, Sincic-Petricevic J, et al. Red blood cell distribution width as a simple negative prognostic factor in patients with diffuse large B-cell lymphoma: a retrospective study. Croatian Med J. 2015;56(4):334–43.
33. Meng S, Ma Z, Lu C, Liu H, Tu H, Zhang W, et al. Prognostic Value of. Elevated Red. Blood Cell Distribution Width in Chinese Patients with Multiple. Myeloma[J]. Ann Clin Lab Sci. 2017;47(3):282–90.
34. Hirahara N, Matsubara T, Kawahara D, et al. Prognostic value of hematological parameters in patients undergoing esophagectomy for esophageal squamous cell carcinoma[J]. International

Journal of Clinical Oncology. 2016;21(5):909–19.
35. Zhang F, Chen Z, Wang P, et al. Combination of platelet count and mean platelet volume (COP-MPV) predicts postoperative prognosis in both resectable early and advanced stage esophageal squamous cell cancer patients[J]. Tumor Biology, 2016.
36. Sun P, Zhang F, Chen C, et al. The ratio of hemoglobin to red cell distribution width as a novel prognostic parameter in esophageal squamous cell carcinoma: a retrospective study from southern China[J]. Oncotarget. 2016;7(27):42650–60.
37. Wang P-F, Song S-Y, Guo H, et al. Prognostic role of pretreatment red blood cell distribution width in patients with cancer: A meta-analysis of 49 studies[J]. J Cancer. 2019;10(18):4305–17.

Tables

Table 1. Patient and tumour characteristics

Item	All patients (n=157) (%)	RDW-SD≥40.2 fl VS RDW-SD≤ 40.2 fl	RDW-CV≥12.6 % VS RDW-CV≤12.6 %	SCC=0 VS SCC=1 VS SCC=2
		P	*P*	*P*
Age ≥60 years	70(44.6)	0.056	0.494	0.029
Male	87(55.4)	0.900	0.977	0.882
BMI ≥24kg/m^2	94(60.3)	0.355	0.187	0.392
ASA score 3-4	13(8.3)	0.027	0.190	0.099
Cirrhosis	57(36.3)	0.790	0.020	0.279
HBsAg (+)	34(21.7)	0.294	0.758	0.906
T3-T4 stage	33(21.0)	0.768	0.005	0.008
Lymphnode metastasis	42(26.8)	0.971	0.736	0.781
Tumor size ≥ 5 cm	86(54.8)	0.314	0.873	0.854
Multiple tumors	30(19.1)	0.357	0.213	0.067
Tumor location(Central tumor)	78(49.7)	0.573	0.580	0.994
Tumor location(right lobe)	77(49.0)	0.970	0.785	0.721
Poorly differentiation	91(58.0)	0.089	0.515	0.275
Preoperative CA19-9 ≥27 U/mL	82(52.2)	0.333	0.279	0.374
Preoperative CEA ≥ 5 ng/mL	35(22.3)	0.174	0.142	0.202
RDW-SD≥40.2 fl	104(66.2)	-	0.000	-
RDW-CV≥12.6 %	63(40.1)	0.000	-	-
SCC=0	46(29.3)	-	-	-
SCC=1	55(35.0)	-	-	-
SCC=2	56(35.7)	-	-	-

ALB≥40 g/L	124(79.0)	0.375	0.133	0.283
TBIL 21 umol/L	18(11.5)	0.968	0.015	0.169
AST 40 U/L	15(9.6)	0.591	0.587	0.179
ALT 50U/L	14(8.9)	0.053	0.724	0.024
Operation time ≥230 min	79(50.3)	0.027	0.896	0.052
Blood loss ≥300 ml	77(49.0)	0.921	0.297	0.827
Major liver resection	113(72.0)	0.667	0.548	0.812
Post-operative Complications	92(58.6)	0.164	0.720	0.353
Preoperative therapy	10(6.4)	0.101	0.008	0.010
Adjuvant therapy	66(42.0)	0.924	0.407	0.105

Table 2. Prognostic factors for OS for ICC patients after surgery

Factor	Univariate analysis		Multivariate analysis[a]			
			Model 1		Model 2	
	HR (95%CI)	Value P	HR (95%CI)	Value P	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 ≥24kg/m^2	1.356 (0.843-2.182)	0.209				
ASA score 3-4	0.970(0.420-2.238)	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(.431-3.962)	0.001				
Lymphnode metastasis		0.000		0.000		0.000
Undissected lymph node	Reference		Reference		Reference	
Negative lymph node	0.742(0.414-1.331)	0.317	1.160(0.581-2.318)	0.674	1.226(0.595-2.526)	0.580
Positive lymph node	2.808(1.554-5.072)	0.001	3.715(1.721-8.019)	0.001	4.394(1.950-9.900)	0.000
Tumor size ≥ 5 cm	1.529(0.956-2.448)	0.077			2.041(1.134-3.673)	0.017
Multiple tumors	1.657(0.955-2.874)	0.073				
Tumor location(Central tumor)	0.587(0.366-0.941)	0.027	0.367(0.210-0.641)	0.000	0.307(0.171-0.552)	0.000
Tumor location(right lobe)	0.858(0.588-1.252)	0.427				
Poor differentiation	1.667(1.013-2.743)	0.044				
Preoperative CA19-9 □27 U/mL	1.332(0.763-2.327)	0.313				
Preoperative CEA □ 5	2.365(1.429-	0.001	2.486(1.305-	0.006	2.234(1.164-	0.016

ng/mL	3.913)		4.734)		4.287)	
RDW-SD≥40.2 fl	0.503(0.314-0.806)	0.004	0.446(0.262-0.760)	0.003		
RDW-CV≥12.6 %	0.581(0.356-0.949)	0.030			0.425(0.230-0.783)	0.006
ALB≥40 g/L	0.600(0.361-0.996)	0.048	0.472(0.257-0.866)	0.015	0.511(0.269-0.974)	0.041
TBIL≥ 21 umol/L	0.913(0.438-1.904)	0.808				
AST ≥ 40 U/L	1.773(0.909-3.458)	0.093				
ALT≥ 50U/L	1.814(0.899-3.660)	0.096			2.332(0.984-5.528)	0.055
Operation time ≥230 min[b]	1.785(1.118-2.851)	0.015	1.894(1.097-3.270)	0.019	1.804(1.030-3.161)	0.039
Blood loss ≥300 ml[b]	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	0.423(0.232-0.774)	0.005	0.481(0.264-0.876)	0.017
The prognostic value on SCC score[c]		0.007		< 0.001		
SCC=0	Reference		Reference			
SCC=1	0.554(0.320-0.961)	0.035	0.296 (0.153-0.571)	< 0.001		
SCC=2	0.411(0.231-0.730)	0.002	0.270 (0.133-0.549)	< 0.001		

a: To 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.

b: The median operation time and the median blood loss were chosen as the cut-off point.

c: Because 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.

Table 3. Prognostic factors for PFS for ICC patients after surgery

Factor	Univariate analysis		Multivariate analysis	
	HR (95%CI)	Value P	HR (95%CI)	Value P
Age ≥60 years	0.797(0.541-1.174)	0.251		
Male	1.119(0.764-1.640)	0.563		
BMI ≥24kg/m^2	1.014 (0.689-1.492)	0.945		
ASA score 3-4	1.352 (0.703-2.599)	0.366		
Cirrhosis	1.101 (0.743-1.632)	0.630		
HBsAg (+)	1.193(0.765-1.858)	0.436		
T3-T4 stage	1.711(1.100-2.662)	0.017		
Lymphnode metastasis		0.000		0.007
Undissected lymph node	Reference		Reference	
Negative lymph node	1.114(0.685-1.811)	0.664	1.355(0.792-2.318)	0.268
Positive lymph node	2.713(1.591-4.627)	0.000	2.566(1.388-4.746)	0.003
Tumor size ≥ 5 cm	1.285(0.877-1.884)	0.199		
Multiple tumors	1.738(1.099-2.751)	0.018	2.181(1.296-3.671)	0.003
Tumor location(Central tumor)	0.702(0.480-1.028)	0.069		
Tumor location(right lobe)	0.906(0.672-1.222)	0.518		
Poor differentiation	1.443(0.965-2.158)	0.074		
Preoperative CA19-9 ≥27 U/mL	1.364(0.875-2.124)	0.170		
Preoperative CEA ≥ 5 ng/mL	2.210(1.442-3.386)	0.000	1.750(1.045-2.929)	0.033
RDW-SD≥40.2 fl	0.681(0.459-1.011)	0.047		
RDW-CV≥12.6 %	0.896(0.608-1.320)	0.579		
ALB≥40 g/L	0.744(0.478-1.159)	0.191		
TBIL≥ 21 umol/L	0.912(0.488-1.703)	0.772		
AST ≥ 40 U/L	1.606(0.898-2.873)	0.111		

ALT□ 50U/L	2.018(1.120-3.634)	0.019
Operation time ≥230 min[a]	1.380(0.941-2.022)	0.099
Blood loss ≥300 ml[a]	1.710(1.149-2.546)	0.008
Major liver resection	1.402(0.906-2.171)	0.129
Post-operative Complications	0.998(0.674-1.477)	0.991
Preoperative therapy	1.207(0.587-2.484)	0.609
Adjuvant therapy	0.887(0.602-1.306)	0.544
the prognostic value on SCC score[b]		0.247
SCC=0	Reference	
SCC=1	0.716 (0.447-1.146)	0.164
SCC=2	0.698 (0.438-1.113)	0.131

a:The median operation time and the median blood loss were chosen as the cut-off point.

b: Because 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.

Figures

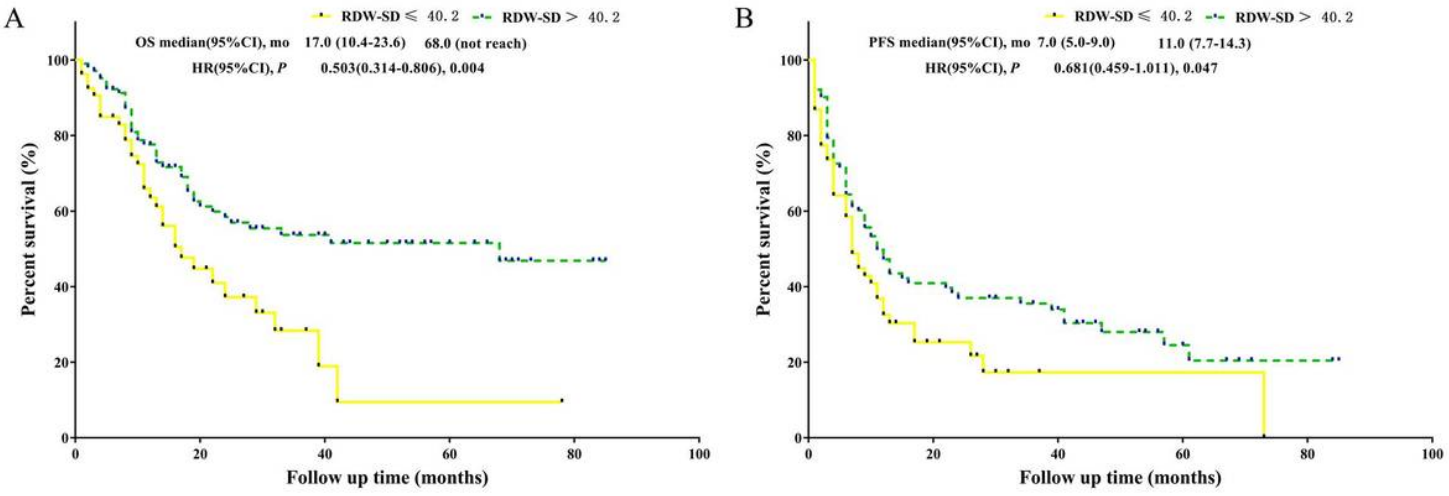

Figure 1

A. OS analysis of RDW-SD＞40.2 fl versus RDW-SD≤40.2 fl. B. PFS analysis of RDW-SD＞40.2 fl versus RDW-SD≤40.2 fl

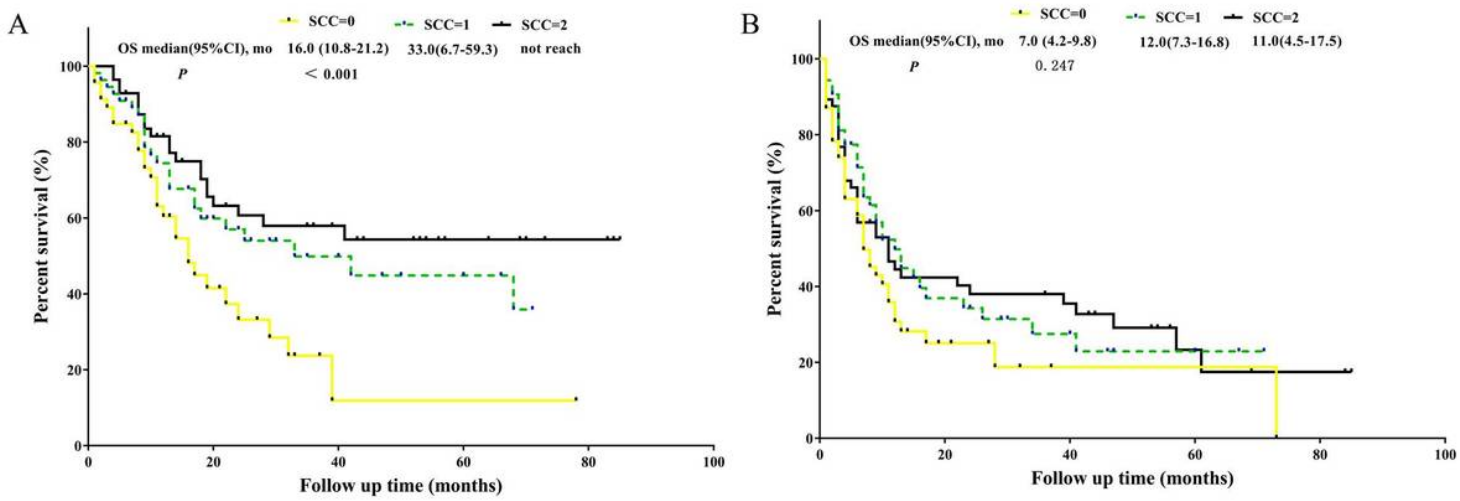

Figure 2

A. OS analysis of RDW-CV＞12.6 % versus RDW-CV≤12.6 % B. PFS analysis of RDW-CV＞12.6 % versus RDW-CV≤12.6 %

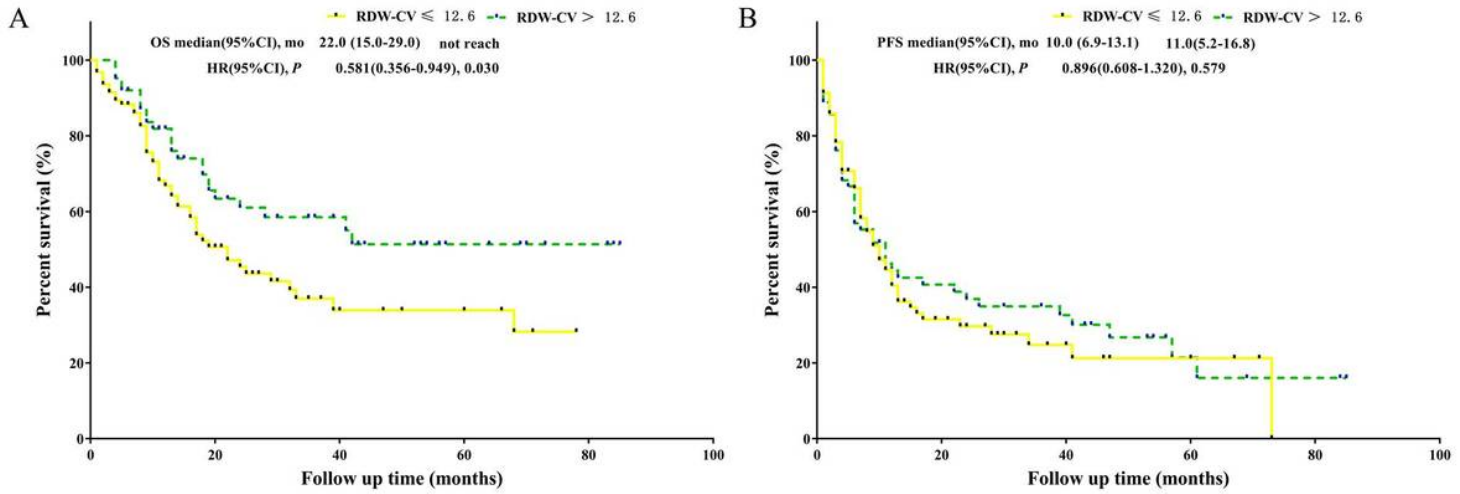

Figure 3

A. OS analysis of SCC = 0 versus SCC = 1 versus SCC = 2 B. PFS analysis of SCC = 0 versus SCC = 1 versus SCC = 2

Supplementary Files

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- HZDBQZDZ2E07F1C3EC401CD7DD09.pdf