Red blood cell distribution width and platelet counts are independent prognostic factors and improve the predictive ability of IPI score in diffuse large B-cell lymphoma patients

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Research article

Keywords: prognosis, diffuse large B-cell lymphoma (DLBCL), red blood cell distribution width (RDW), platelet count (PLT)

Posted Date: October 12th, 2019

DOI: https://doi.org/10.21203/rs.2.11461/v2

Version of Record: A version of this preprint was published on November 11th, 2019. See the published version at https://doi.org/10.1186/s12885-019-6281-1.

Abstract

Background: Elevated red blood cell distribution width (RDW) and decreased platelet count (PLT) can be clinically relevant to the prognosis in cancer patients . However, their prognostic values in patients with diffuse large B-cell lymphoma (DLBCL) need to be further explored. Methods: Healthy donors (n=130) and patients with DLBCL (n=349) were included and evaluated retrospectively in this study. The prognostic influence of clinical and pathological factors including RDW and PLT on overall survival (OS) and progression-free survival (PFS) were studied by Kaplan-Meier curves . To evaluate the independent prognostic relevance of RDW and PLT, univariate and multivariate Cox proportional hazards regression models were applied. The adjusted IPI model was established based on the results of multivariate analysis, and verified by Harrell's C statistical analysis. Results: Kaplan-Meier curves indicated that an elevated RDW value and thrombocytopenia are poor factors for OS (P<0.001, P=0.006) and PFS (P=0.003, P<0.001) in DLBCL patients. Multivariate analysis confirmed that elevated RDW value (HR=2.026, 95%CI= 1.263-3.250, P=0.003) and decreased PLT count (HR =1.749, 95%CI=1.010-3.028, P=0.046) were both independent prognostic factors. The c-index of IPI and NCCN-IPI were increased when RDW level and PLT were supplemented in our cohort. Conclusions: Our study shows that elevated RDW level and decreased PLT are independent poor prognostic factors in newly diagnosed DLBCL patients. Adding RDW and PLT to the IPI score may improve its predictive ability, and the adjusted IPI may be more powerful in predicting the survival of DLBCL patients in the rituximab era. Keywords : prognosis, diffuse large B-cell lymphoma (DLBCL), red blood cell distribution width (RDW), platelet count (PLT)

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive lymphomas in hematological malignancies. In the newly diagnosed non-Hodgkin's lymphomas (NHL), about 30% to 40% are DLBCL[1]. Although the survival of DLBCL patients has been greatly improved with the administration of CHOP chemotherapies (cyclophosphamide, doxorubicin, vincristine and prednisolone) with rituximab, there are still about 10-15% of patients suffered from primary refractory disease, and about 20-30% relapsed[2].

Recently, some of the prognostic significance of biochemical markers, molecular genetic markers and immunohistochemical characteristics have gradually been identified[2]. But these markers are usually associated with high cost, great laboratory labored effort, high technical skill requirements and time-consuming procedures, which are not feasible to conduct in most laboratories. Thus, identifying cheaper and easily available prognostic surrogate markers may contribute greatly to improve the risk assessment for patients with various cancers including DLBCL.

It is well-known that tumor-associated inflammatory response can promote tumorigenesis and progression[5]. Accumulating studies have confirmed that inflammation-related clinical parameters are related to tumor biology and prognosis. These clinical parameters include red blood cell distribution width (RDW)[6], neutrophil/lymphocyte ratio (NLR)[7], lymphocyte/monocyte ratio (LMR)[8] and PLT[9]. There are few reports for the prognostic value of RDW and PLT in patients with DLBCL. Neither of the recently developed R-IPI nor NCCN-IPI prognostic score including the two factors and the role of RDW and PLT level as independent prognostic factors in DLBCL has never been explored. Therefore, in this study, we evaluated the prognostic significance of RDW and PLT in a large cohort of DLBCL patients, and tested whether they significantly improved the predictive power of the IPI score in DLBCL patients.

Materials And Methods

Patients and healthy donor participants

Total 349 patients with DLBCL were analyzed for retrospective studies, who were diagnosed according to the 2016 World Health Organization criteria[10] at the First and Second Affiliated Hospitals of Anhui Medical University, from July 2006 to April 2017, respectively. The study ethic approval was granted from the local ethical committee of Anhui Medical University, and was performed in accordance with the principles of the Declaration of Helsinki.

Patients were excluded if they were found to be HIV-positive. Other exclusion criteria included transformed indolent lymphoma and primary DLBCL of the central nervous systems (CNS). The rest of DLBCL patients (n=349) were treated with standard CHOP chemotherapy with or without rituximab. In addition, age and sex-matched 130 healthy donors (HDs) from the Second Affiliated Hospital of Anhui Medical University were recruited as normal control group.

Of the 349 DLBCL patients, we randomly selected 200 patients as the training set, while the remaining patients were assigned to the testing set (n=149)[11]. The demographic characteristics, clinical features, and laboratory parameters were obtained from medical records of any institution. Acquired clinical-pathological parameters included gender, age, lactate dehydrogenase (LDH) level, Ann Arbor stage, number of extra nodal sites involvement, Eastern Cooperative Oncology Group performance status (ECOG PS), B symptoms, physical examinations, computed tomography (CT) scans of the thorax, abdomen and pelvic cavity, along with whole-body positron emission tomography (PET/CT) scans and the process of treatment. Laboratory parameters such as complete blood count, biochemical profiles were collected at the time of diagnosis. The date of death was obtained from the clinical records or by telephone calls to their relatives.

Statistical analyses

The primary end point of the study was overall survival (OS), and the secondary end point was progression-free survival (PFS). OS was defined as the time from the date of diagnosis to the date of death due to any causes within the follow-up period or the date of the last follow-up observation. PFS was defined as the time from the date of diagnosis to the date of tumor progression, recurrence or death due to any causes.

Student's t-test was used to test the differences between the two groups in quantitative normal distribution variables and non-parametric Mann-Whitney U test for not normally distributed variables. Correlation was assessed using Spearman rank test. The optimal cutoff value of training set (n=200) for RDW and PLT were determined by applying receiver operating characteristic curve (ROC) analysis based on previously published reports[12]. Pearson’s Chi-square or Fisher’s exact test was used to assess the associations between RDW, PLT and clinical pathological parameters. The associations between RDW and PLT levels with OS and PFS respectively were estimated by Kaplan–Meier curves, and log-rank test was used for comparison between different groups.

Multivariate analyses of independent clinical factors for OS and PFS were conducted using the Cox analysis with the forward selection method. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). C-index was calculated using the individual IPI value followed by the addition of the RDW and PLT levels[13]. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 19.0, USA) and R version 3.4.3 (https://www.r-project.org/). $P<0.05$ was considered statistically significant and P-values were two-tailed.

Results

The characteristics of DLBCL patients and healthy donors

Healthy donors (n=130) and patients with DLBCL (n=349) confirmed by previous histopathological analysis were included in the study. A full list of clinical characteristics of healthy donors and DLBCL patients were listed in Supplementary Table 1. It showed that DLBCL patients and healthy donors had similar age, gender percentage, white blood cell count (WBC), absolute neutrophil count (ANC), platelet count (PLT) and albumin/globulin ratio (AGR). However, the absolute monocyte count (AMC) and RDW in DLBCL patients were significantly higher than that in healthy controls; and the absolute lymphocyte count (ALC), hemoglobin (Hb), albumin (ALB) and globulin (GLB) in DLBCL patients were significantly lower than healthy donors. There were 174 patients (49.9%) treated with R-CHOP, and 175 patients (50.1%) treated with CHOP only. The subgroups of patients' Ann Arbor tumor stage were 89 (25.5%) in stage Ⅰ, 86 (24.6%) in stage Ⅱ, 61 (17.5%) in stage Ⅲ and 113 (32.4%) in stage Ⅳ. There were no statistical differences in the age, gender, and other clinicopathological parameters between the training set and the testing set (Supplementary Table 2).

Cut-off values of RDW and PLT at diagnosis for survival analysis

RDW, PLT and Hb are three common parameters in blood routine test. Our initial purpose was to investigate their differences and significances for prognosis in patients with DLBCL, but eventually we only studied the prognosis value of RDW and PLT because of the Hb difference between male and female.

Using ROC analysis and calculating the Youden index (specificity+sensitivity−1), the optimal cutoff values chosen for RDW and PLT were 14.35% and 126.5×10^9/L respectively in the training set (Supplementary Figure 1). After applying the values on analysis of the whole cohort, DLBCL patients were able to be classified into high-level and low-level groups, where 93 (26.64%) patients fell in with higher RDW group and 44 (14.43%) patients with lower PLT group.

Association of RDW and PLT with other clinical pathological factors

Linear correlation analysis showed that higher RDW level was associated with higher NLR, lower ALB and lower Hb; while lower PLT was correlated directly with lower WBC, but was not correlated with NLR, ALB or Hb (Supplementary Figure 2)

Further analysis showed that, the value of RDW>14.35% was significantly correlated with a poorer ECOG-PS (P<0.001), more extranodal sites of disease (P=0.002), presence of B symptoms (P=0.011), and higher Ann Arbor stage (P<0.001) as well as higher LDH level(P<0.001) and IPI score (P<0.001). However, we found no statistical significance between age and gender with RDW level. We then found that, patients with PLT≦126.5×10^9/L were significantly correlated with higher Ann Arbor stage (P=0.003), more extranodal sites of disease(P=0.021), higher LDH (P=0.013) level and presence of B symptoms (P=0.033). There were no statistical correlation observed between low PLT with age (P = 0.602) and gender (P =0.726). In addition, ECOG PS (P=0.096) and IPI (P=0.061) had only borderline significance (Table 1).

Levels of RDW and PLT at diagnosis and clinical outcomes

At the time of statistics and analysis in our study, the median follow-up time was 21.3 months (range: 0.80-126.93). During follow-up, there were 134 (38.4%) patients presented disease recurrence, progress or death, of which 79 (22.6%) died. In the training set, the survival rate of patients with higher RDW was significantly worse than patients with lower RDW (5-year OS: 43%vs 69%; 5-year PFS: 29%vs 53%)(Supplementary Figure 3a,3b), and the patients with lower PLT showed significant worse PFS than the patients with higher levels (5-year PFS: 30% *vs* 49%)(Supplementary Figure 3d), but the overall survival wasn't significantly different (P=0.074) (Supplementary Figure 3c). Similar results were observed in the testing set and the whole cohort set (Supplementary Figure 3e-3l). In addition, in order to explore whether different chemotherapy regimens affect the evaluation efficacy of the level of RDW and PLT, we divided the patients into two groups, one group treated with R-CHOP regimen and the other group treated with CHOP regimen. Kaplan-Meier analysis showed poor OS and PFS in patients with high RDW (P=0.021 for OS and P=0.039 for PFS) and low PLT (P=0.001 for OS, P<0.001 for PFS) levels in the R-CHOP cohort. Patients with higher RDW and lower PLT in CHOP treated cohort had poorer OS (P=0.001 for RDW, P=0.045 for PLT), but the results of PFS were not statistically significant (Figure1).

We further assessed the prognostic value of RDW and PLT in the IPI subgroup. Kaplan-Meier analysis showed that, for patients with IPI score of 0-2, the RDW and PLT levels may not distinguish those with favorable outcomes from those with adverse outcomes (data not shown). However, in patients with IPI scores 3-5, the RDW and PLT levels were able to further risk-stratify patients into high-risk and low-risk groups. In R-CHOP cohort, the patients with lower PLT had significantly poorer OS (P=0.003) and PFS (P=0.013); and in high level of RDW patients, OS (P=0.014) was significantly reduced (Figure 2), similar results were also showed in the whole cohort and CHOP cohort (Supplementary Figure 4).

High RDW and Low PLT at diagnosis showed poor prognostic factors

To investigate the association between RDW and PLT levels with patients' clinical outcomes, we performed the Cox proportional risk model. Table 2 and Table 3 summarized the results of univariate and multivariate analysis for factors influencing OS and PFS in all DLBCL patients. Univariate Cox proportional analysis revealed that old age, advanced Ann Arbor stage, poor ECOG PS, elevated LDH, B symptoms, more extranodal sites of disease, higher IPI score, higher RDW and lower PLT were all predictors of DLBCL patients for OS and PFS (Table 2). To explore whether RDW and PLT were independent prognostic factors of DLBCL patients, we performed a multivariate analysis, including age, tumor Ann Arbor stage, ECOG PS, LDH, extranodal sites, B symptoms, IPI, RDW and PLT. Interestingly, our results showed that older age (P<0.001), advanced Ann Arbor stage (P=0.037), higher RDW (P=0.003) and lower PLT (P=0.046) were independent prognostic factors for OS. In another hand for PFS, only older age (P<0.001), advanced Ann Arbor stage (P=0.002) and higher RDW (P=0.002) were independent prognostic factors (Table 3).

We further performed multivariate analysis by applying above indicators to R-CHOP cohort and CHOP cohort. Surprisingly, we found that elevated RDW was an independent prognostic factor (P=0.012) in CHOP cohort, and depressed PLT was an independent prognostic factor (P=0.003) in R-CHOP cohort for OS. However, RDW wasn't an independent prognostic factor for PFS either in R-CHOP cohort or in CHOP cohort, whereas PLT was an independent prognostic factor (P=0.003) in R-CHOP cohort but not in CHOP cohort (Table 4).

Development of a modified IPI by adding both RDW and PLT

From multivariate analysis, there are clearly four independent prognostic factors for OS in all patients cohort. We then used the four clinical parameters to construct a new adjusted IPI model, age equaled to two points; RDW, PLT and Ann Arbor stage equaled to one point respectively[14]. Three risk categories were generated: low (0-1 points), intermediate (2-3 points) and high (4-5 points).

Based on the risk stratification model, the results showed that patients assigned to the low-risk group had good outcomes (5-year OS: 83%, 5-year PFS: 62%) and high-risk patients had very poor outcomes (5-year OS: 9%, 5-year PFS: 0%, Figure 3a,b) in all patients cohort. The similar results were observed in the R-CHOP (n =174) cohort (Figure 3c,d) and CHOP cohort(n =175)(Figure 3e,f). To strengthen the results from the multivariate analysis, we conducted a Harrell's C statistics analysis. The c-index of the IPI prognostic model for OS was 0.744 for patients treated with CHOP, 0.709 for patients treated with R-CHOP, 0.725 for all DLBCL patients, and 0.763, 0.718, 0,743 in NCCN-IPI prognostic model. When the factors of RDW and PLT values were added, the predictive power was increased in both IPI and NCCN-IPI prognostic model. And the c-index of the adjusted IPI in the three cohorts was 0.753, 0.732 and 0.748 (Table 5).

Discussion

Our results indicate clearly that RDW and PLT levels are independent risk factors for patients with DLBCL. In addition, for patients who are treated with R-CHOP like regimens, PLT is a significant prognostic factor for OS. Similarly for patients who are treated with CHOP like regimens, RDW is a more important prognostic factor. In addition, we first discovered that the combination of RDW and PLT with IPI can further improve the prognostic value and clinical significance of IPI and NCCN-IPI.

As a commonly used indicator for tumor-associated inflammatory responses, RDW has been widely studied and proved to be associated with the prognosis of a variety of diseases[6]. There is growing evidence demonstrating elevated RDW as a prognosis factor in various malignancies, such as lung cancer[15], prostate cancer[16], chronic lymphocytic leukemia[17], ovarian cancer[18], hilar cholangiocarcinoma[19] and Esophageal carcinoma[20]. Some reports have confirmed that high RDW is closely related to cancer stage[21,22].

The exact mechanism of RDW elevation in the blood of DLBCL patients is not clear. Lippi et al[6] demonstrated that short telomeres length, oxidative stress, inflammation, erythrocyte fragmentation, poor nutritional status, hypertension, dyslipidemia and abnormality of erythropoietin function may be the causes. These factors may lead to a profound deregulation of erythrocyte homeostasis including impaired erythropoiesis, abnormal erythrocyte metabolism and survival which resulted in elevated RDW. Lymphoma is a malignant tumor that originates from the lymphatic hematopoietic system. The patients with malignant disease often have chronic inflammation and poor nutritional status. Some studies reported that elevated RDW was correlated with higher IL-6[23] and erythrocyte sedimentation rate (ESR), as well as high-sensitivities of C-reactive protein (CRP), leukocytes, neutrophils, fibrinogen, and lower Hb[24,25]. Further research supports RDW being associated with erythropoietin (EPO)[26], ALB[27]{Vayá, 2015 #36;G, 2009 #37;Periša, 2015 #13}, iron, folate and vitamin B12[28]. In our study, however, we found that patients with elevated RDW were associated with poorer ECOG-PS, more extranodal sites of disease, B symptoms, higher Ann Arbor stage, higher LDH, higher IPI, higher NLR, lower ALB and lower Hb. In consideration of previous studies with our findings, it is rational to conclude that RDW is associated with tumor burden, chronic inflammation and malnutrition in DLBCL patients. All of the factors are well-known to lead to poor prognosis in cancer patients. Cancer related inflammation is considered a landmark feature of cancer development and progression [29]. Inflammatory medium and cytokines are important components of the tumor

microenvironment, which sustains the progression of the tumor [30]. Poor nutritional status was another hallmark of cancer [31]. Inflammation and malnutrition might damage erythropoiesis, thus result in an increased RDW.

How PLT level affects the outcome of DLBCL remains speculative, which probably attributes to the reduction of platelets in lymphoma patients. Reduction of platelets may be resulted from multi-factorial origins, such as drug, malignant infiltration of bone marrow, infection consumption, splenic sequestration, pre-existing viral hepatitis, myelodysplasia, and immune-mediated destruction[32]. Some studies reported that lymphoma patients with thrombocytopenia presented poor survival if the patients had bone marrow involvement[33,34]. However, it has been found that the prognosis effect of platelet counts was not consistent. In solid tumors, e.g., the elevated platelet count is poor prognostic factor and plays an important role in the progression and metastasis. The potential mechanisms include protecting circulating tumor cells from attack of host's immune system as well as supporting proliferation of tumor cells[35]. But, contradictorily, in many hematological diseases, patients with low PLT have a poor prognosis, such as Ph-like acute lymphoblastic leukemia[36], hemophagocytic lymphohistiocytosis (HLH)[37], primary plasma cell leukemia (pPCL)[38] and DLBCL[39,40]. Our data demonstrated that PLT$\leqq 126.5\times10^9$/L was associated with higher Ann Arbor stage, more extranodal sites, higher LDH, lower WBC. These results suggested that patients with low levels of PLT may have a higher tumor burden; in addition, patients with low levels of PLT may associated with the expansion of myeloid lines such as myeloid derived suppressor cells(MDSCs), macrophages and DCs, as well as the reduction of mature red blood cells and platelets[41]. But the exact function of platelets in the tumor microenvironment remains unclear. In our study, we propose that immune disorders, high tumor burden and bone marrow involvement and low level of neutrophiles are associated with poor prognosis in patients with thrombocytopenia in DLBCL.

Previous small sample studies showed that RDW and PLT are independent predictive factor for survival in DLBCL[27,39,40,42]. However, no study further analyze the c-index that is important to calculate the discriminative degree between the predicted value and the value of the COX model in survival analysis[43], nor evaluated the significance of RDW and PLT for IPI. Therefore, our study further expanded the sample size, and validated the prognostic significance of RDW and PLT for patients with DLBCL, and to construct a simpler and more useful prognostic model for DLBCL patients.

Based on the results of the multivariate analysis, we have constructed a new prognostic model which includes four independent prognostic factors: age>60 years, Ann stage>2, PLT$\leqq 126.5\times10^9$/L and RDW>14.35%. The adjusted IPI is easy to use and effectively divides patients with DLBCL into three risk groups. And then, to confirm the prognostic value of RDW and PLT, we conducted a Harrell’s C statistics analysis for OS. Our results suggested that combined RDW and PLT with the IPI score have a good prognostic value for patients with DLBCL, especially in patients with CHOP regimen chemotherapy. Adding RDW and PLT to the well-established prognostic models such as the IPI score might improve their predictive ability.

The cutoff values of the parameters were obtained according to the Youden index from training set, and then it was used to measure the impact of RDW and PLT on OS and PFS in DLBCL for training set, testing set, whole patients set, CHOP cohort and R-CHOP cohort. The inclusion of validation steps in this study has greatly increased the reliability of our data, and the results demonstrated that our new prognostic models maybe generally applicable to DLBCL patients.

Although our results are consistent with those previously reported, our study has several limitations. Firstly, as a retrospective study of a relatively small number of patients, a regional or phenotypical selection bias is inevitable.

Secondly, due to the widespread use of rituximab, we can expand the sample size of the R-CHOP group and further explore the effects of RDW and PLT on NCCN-IPI. Despite these limitations, our research provides new ideas for establishing a simpler, more practical, and accurate risk model for the prognosis of patients with DLBCL.

Conclusions

In conclusion, RDW and PLT levels are simple and useful independent prognostic factors in DLBCL patients. The adjusted IPI by adding both RDW and PLT is an effective and valuable risk stratification model for DLBCL patients, and may be more potential to predict the survival of DLBCL patients in the rituximab era.

Abbreviations

DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin's lymphomas; R-CHOP: rituximab versus cyclophosphamide, doxorubicin, vincristine and prednisolone; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CNS: central nervous systems; c-index: Harrell’s concordance index; HDs: healthy donors; OS: overall survival; PFS: progression-free survival; HRs: Hazard ratios; WBC: white blood cell count; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; AMC: absolute monocyte count; PLT: platelet count; HB: hemoglobin; RDW: red blood distribution width; ALB: albumin; GLB: globulin; AGR: albumin/globulin ratio; NLR: neutrophil/lymphocyte ratio; LMR: lymphocyte/monocyte ratio; ESR: erythrocyte sedimentation rate; AGR: albumin/globulin ratio; CRP: C-reactive protein; EPO: erythropoietin; HLH: hemophagocytic lymphohistiocytosis; pPCL: primary plasma cell leukemia; IPI: International Prognostic Index; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase.

Declarations

Acknowledgements

We would like to thank Dr. Nan Yang (Institute of Neuron and Muscle Research, Children's Hospital at Westmead NSW2124 Australia) for his great assistance in the language revision. We thank all the medical and nursing staff in our hematology department for their valuable cooperation.

Funding

This work was partly supported by Key Research and Development Plan of Anhui Province, China (201904a07020058), Higher School of Anhui Provincial Natural Science Research Project (KJ2018A0198), National Science Foundation of China (81272259), Scientific Research Foundation of the Institute for Translational Medicine (SRFITMAP, 2017zhyx13) and the Foundation of Anhui Medical University (2015xkj115).

Authors' contributions

MML, HLX and HMZ performed analyses and drafted the manuscript. LHH, LFP and YJZ contributed to statistical analyses. YFL, JL, JRL, YYD and QLG collected and assembled clinical data. ZMZ provided clinical expertise. All authors contributed to writing the manuscript. SDX conceived and supervised the study and wrote the manuscript. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent to publication

Not applicable.

Ethics approval and consent to participate

The study ethic approval was granted from the local ethical committee of Anhui Medical University, and was performed in accordance with the principles of the Declaration of Helsinki. All patients provided informed consent.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on a reasonable request.

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Tables

Table 1. Patient's baseline characteristics at diagnosis of all patients.

Characteristics	RDW(%)		P value	PLT($\times 10^9$/L)		P value
	>14.35(n=93,%)	≦14.35(n=256,%)		>126.5(n=305,%)	≦126.5(n=44,%)	
Age>60	38(40.86)	108(42.19)	0.824	126(41.31)	20(45.45)	0.602
Gender (male)	43(46.23)	148(57.81)	0.055	168(55.08)	23(52.27)	0.726
B symptoms(present)	37(39.78)	66(25.78)	0.011	84(27.54)	19(43.18)	0.033
Ann Arbor stage III/IV	63(67.74)	111(43.36)	<0.001	143(46.89)	31(70.45)	0.003
ECOG PS≧2	51(54.83)	49(19.14)	<0.001	75(24.59)	16(36.36)	0.096
Serum LDH level≧246u/l	58(62.37)	88(34.38)	<0.001	122(40.00)	24(54.54)	0.013
Extranodal sites≧2	34(36.56)	52(20.31)	0.002	69(22.62)	17(38.64)	0.021
IPI>2	44(47.31)	57(22.27)	<0.001	83(27.21)	18(40.91)	0.061

Abbreviations: RDW, red blood distribution width; PLT, platelet count; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

Table 2. Univariate analysis of clinicopathological parameters for the prediction of OS and PFS in DLBCL patients(n=349).

Parameter	Number	%	Overall survival			Progression-free survival		
			HR	95%CI	P value	HR	95%CI	P value
Gender(male)	191	48.48	0.951	0.610-1.484	0.825	1.044	0.744-1.465	0.804
age>60	146	37.06	3.437	2.146-5.504	<0.001	2.42	1.715-3.414	<0.001
PLT≦126.5(×10^9/L)	305	77.41	2.100	1.227-3.594	0.007	2.164	1.409-3.324	<0.001
RDW>14.35%	93	23.60	2.652	1.695-4.151	<0.001	1.706	1.191-2.443	0.004
B symptoms(present)	103	29.51	2.142	1.365-3.360	0.001	1.613	1.131-2.300	0.008
Ann Arbor stage III/IV	174	44.16	2.985	1.844-4.832	<0.001	2.462	1.727-3.510	<0.001
ECOG PS>1	91	23.10	2.685	1.718-4.198	<0.001	1.908	1.337-2.724	<0.001
LDH>normal	146	37.06	2.159	1.381-3.375	0.001	1.844	1.312-2.590	<0.001
Extranodal sites>1	86	21.83	2.457	1.560-3.870	<0.001	2.313	1.621-3.301	<0.001
IPI>2	101	25.63	4.097	2.616-6.417	<0.001	2.727	1.932-3.849	<0.001

Abbreviations: PLT, platelet count; RDW, red blood distribution width; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index.

Table 3. Multivariate analysis of clinicopathological parameters for the prediction of OS and PFS in DLBCL patients(n=349).

Parameter	Overall survival		P value	Score	Progression-free survival		P value
	HR	95%CI			HR	95%CI	
age>60	3.012	1.817-4.994	0.000	2	2.199	1.529-3.163	0.000
Ann Arbor stage III/IV	1.887	1.040-3.423	0.037	1	1.936	1.263-2.966	0.002
PLT≦126.5(×10^9/L)	1.749	1.010-3.028	0.046	1	1.963	1.274-3.024	0.002
IPI>2	1.771	0.984-3.187	0.057		1.499	0.977-2.299	0.064
RDW>14.35%	2.026	1.263-3.250	0.003	1			0.293

Abbreviations: PLT, platelet count; IPI, International Prognostic Index; RDW, red blood distribution width.

Table 4. Multivariate analysis for OS and PFS of patients treated with or without rituximab.

Parameter	Overall survival		P value	Progression-free survival		P value
	HR	95%CI		HR	95%CI	
CHOP cohort(n=175)						
RDW>14.35%	2.123	1.183-3.812	0.012			0.502
age>60	3.449	1.777-6.692	0.000	3.434	2.093-5.634	0.000
Ann Arbor stage III/IV	3.155	1.702-5.847	0.000	2.814	1.785-4.436	0.000
R-CHOP cohort(n=174)						
PLT≦126.5($\times 10^9$/L)	3.344	1.491-7.504	0.003	3.076	1.653-5.723	0.000
age>60	2.344	1.090-5.039	0.029			0.333
IPI>2	2.304	1.061-5.002	0.035			0.322
Extranodal sites>1			0.772	2.347	1.371-4.020	0.002

Abbreviations: RDW, red blood distribution width; PLT, platelet count; IPI, International Prognostic Index.

Table 5. Harrell's C statistic for discriminatory values on survival.

Parameter	CHOP cohort	R-CHOP cohort	All Patients
IPI	0.744	0.709	0.725
NCCN-IPI	0.763	0.718	0.743
PLT	0.527	0.611	0.557
RDW	0.613	0.618	0.616
IPI+RDW	0.750	0.710	0.728
NCCN-IPI+RDW	0.769	0.718	0.743
IPI+PLT	0.745	0.726	0.729
NCCN-IPI+PLT	0.762	0.731	0.746
IPI+RDW+PLT	0.751	0.733	0.731
NCCN-IPI+RDW+PLT	0.767	0.732	0.747
adjusted IPI	0.753	0.732	0.748

Abbreviations: RDW, red blood distribution width; PLT, platelet count; IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network International Prognostic Index.

Figures

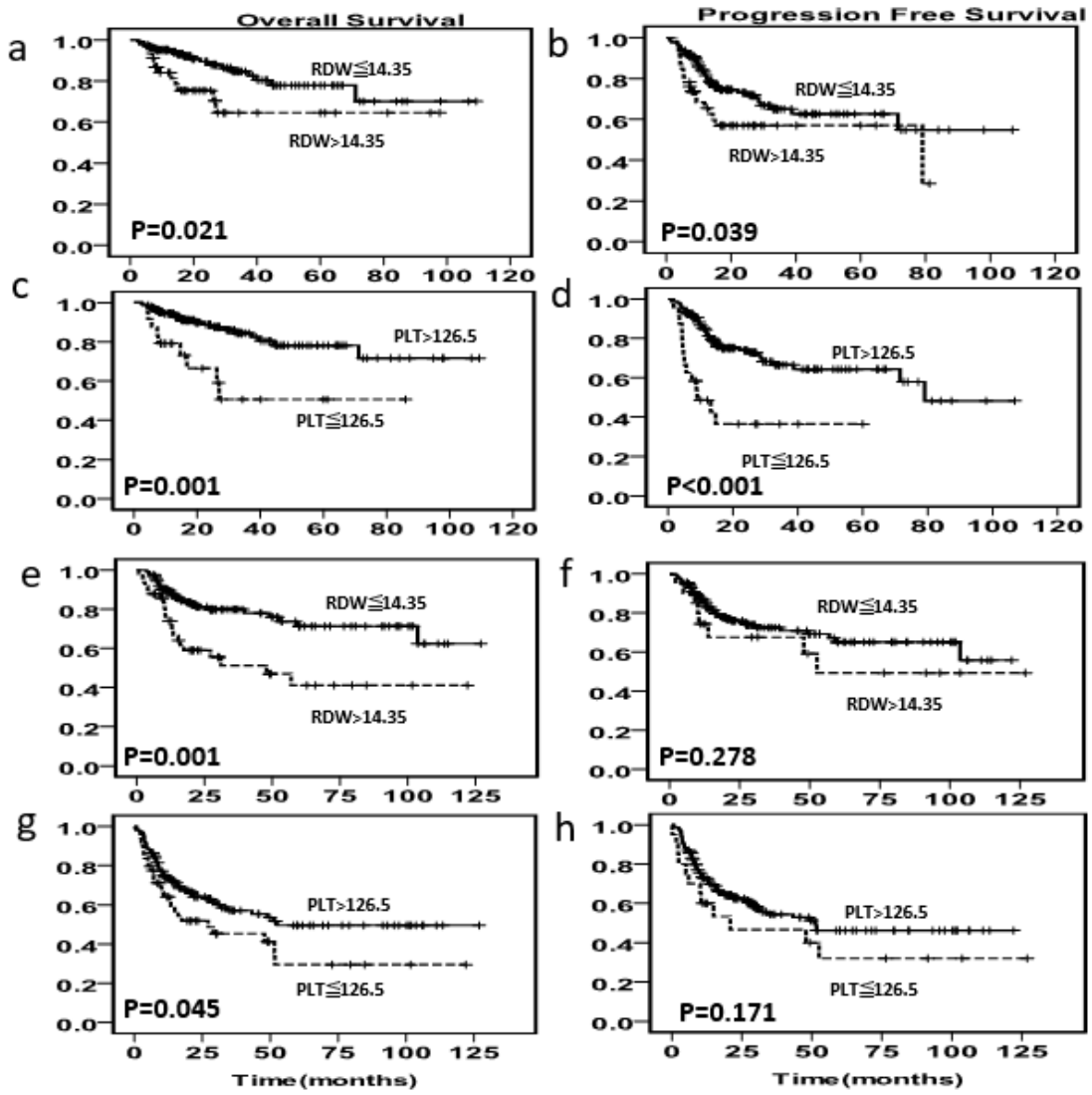

Figure 1

Survival curves according to RDW and PLT levels in the R-CHOP and CHOP cohort. (1) Overall survival(a) and progression free survival(b) according to RDW levels in the R-CHOP cohort.(2) Overall survival(c) and progression free survival(d) according to PLT counts in the R-CHOP cohort. (3) Overall survival(e) and progression free survival(f) according to RDW levels in the CHOP cohort.(4) Overall survival(g) and progression free survival(f) according to PLT counts in the CHOP cohort. Abbreviations: RDW, red blood distribution width; PLT, platelet count;

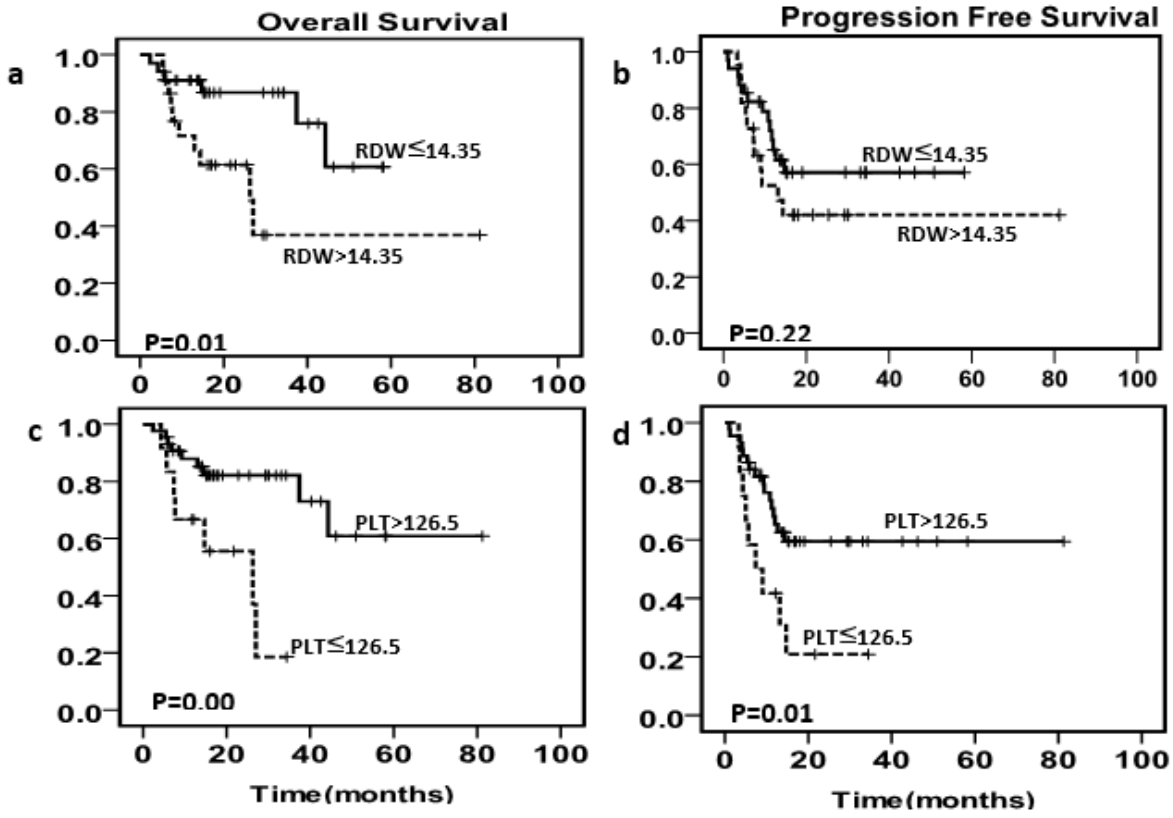

Figure 2

Survival curves according to RDW and PLT levels in IPI score 3-5 in R-CHOP cohort. (1) Overall survival(a) and progression free survival(b) according to RDW levels in IPI score 3-5 in R-CHOP cohort. (2) Overall survival(c) and progression free survival(d) according to PLT counts in IPI score 3-5 in R-CHOP cohort. Abbreviations: RDW, red blood distribution width; PLT, platelet count; IPI, International Prognostic Index.

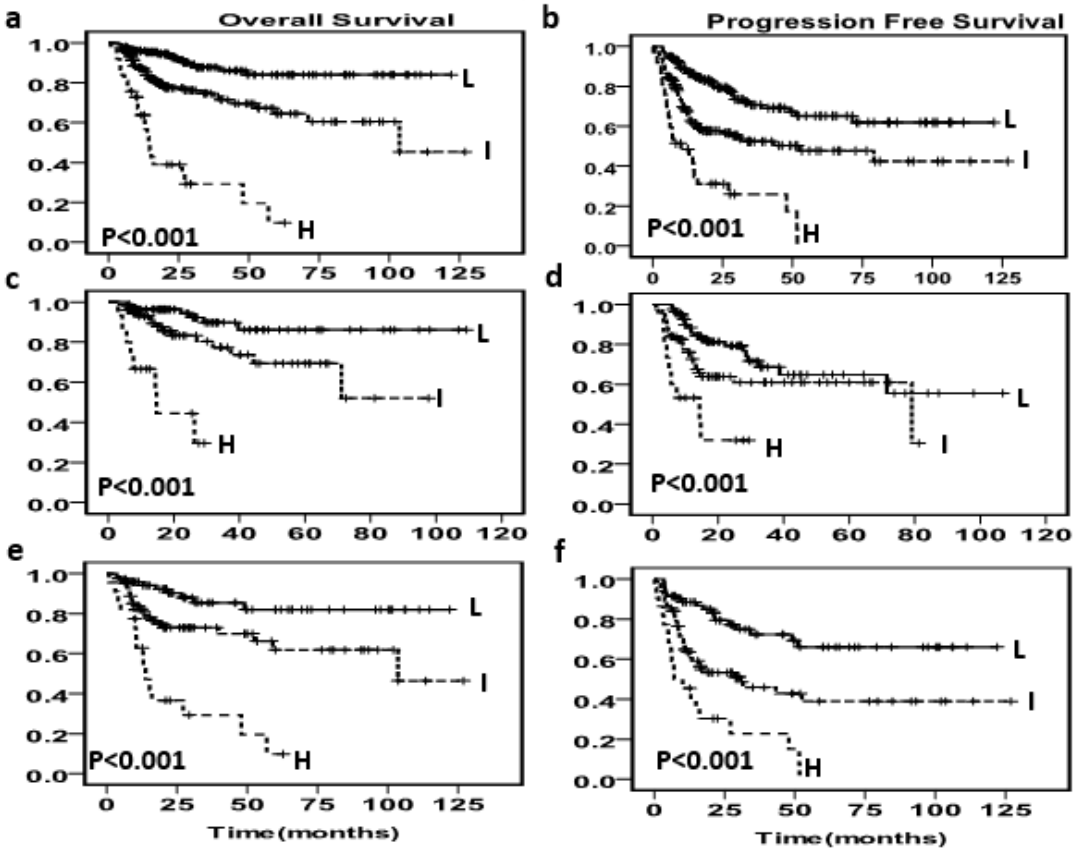

Figure 3

Adjusted IPI survival curves based on the addition of RDW and PLT. (1)Survival curves for OS(a) and PFS(b) according to adjusted IPI of adding RDW and PLT for risk stratification in the whole cohort. (2)Survival curves for OS(c) and PFS(d) according to adjusted IPI of adding RDW and PLT for risk stratification in R-CHOP cohort. (3)Survival curves for OS(e) and PFS(f) according to adjusted IPI of adding RDW and PLT for risk stratification in CHOP cohort. Abbreviations: RDW, red blood distribution width; PLT, platelet count; IPI, International Prognostic Index. OS ,Overall survival; PFS, Progression Free Survival; L, low risk; I, intermediate risk; H, high risk.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigureandTable823.pdf