The Association of Mean Platelet Volume and Red Cell Distribution Width with Disease Free Survival in Diffuse Large B Cell Lymphoma

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ABSTRACT

Background: The most frequent subtype of Non-Hodgkin Lymphoma (NHL) is diffuse large B cell lymphoma (DLBCL), which accounts for 25% to 30% of cases. The mean platelet volume (MPV) indicates the size, function, and activity of platelets in circulation. Red cell distribution width (RDW) is regarded an inflammatory related marker, both indicators are potential predictors of overall mortality in a variety of cancers. **Objective:** This study aimed to find out the association between MPV and RDW with disease free survival (DFS) in adults with DLBCL. **Patients and methods:** This observational retrospective study was conducted on 112 patients of a total of 140 DLBCL patients who achieved CR after receiving R-CHOP protocol to clarify the association of MPV and RDW with 2-year DFS outcome in a cohort of adults diagnosed as de novo DLBCL (NOS) who were treated at The Haematology Units of International Medical Centre, Zagazig and Menoufia University Hospitals. **Results:** A total of 140 patients with DLBCL were observed in this study of which 112 patients achieved CR after receiving R-CHOP protocol the remaining who didn't achieve CR were ruled out. The mean age for those 112 patients was 53.12 years and 70 (62.5%) were males. The cut-off value for detecting DFS in MPV was 9.1 with 82.6% sensitivity and 59.1% specificity ($P < 0.001$) indicating better DFS in DLBCL patients with higher MPV. The cut-off value for detecting DFS in RDW was 14.1 with 77% sensitivity and 63% specificity ($P=0.041$) indicating better DFS in DLBCL patients with lower RDW. **Conclusion:** Lower baseline MPV values, and higher baseline RDW values were associated with inferior DFS outcome in patients with Denovo DLBCL after achieving CR upon receiving standard R-CHOP protocol.
Keywords: DFS, DLBCL, Lymphoma, MPV, RDW.

INTRODUCTION

About 25% of all NHLs in the industrialized world are DLBCLs, the most prevalent lymphoma [1]. DLBCL makes up 49% of all NHLs in Egypt, whilst NHLs make up 76.6% of the total [2].

The volume of platelets in FL is known as the MPV, which is measured and examined as part of the CBC. Because it has been linked to platelet aggregation, thromboxane B2 release, and increased production of the platelet adhesion molecule glycoprotein (GP) IIb-IIIa, MPV is a reflection of platelet activity [3, 4]. Elevated MPV levels have been linked in a number of clinical trials to thromboembolic conditions, such as myocardial infarction and stroke in individuals who do not have cancer [5]. However, in cancer patients & hematological malignancy as multiple myeloma it was found that patients with a high MPV carried a favourable prognostic outcome [6].Red blood cell size heterogeneity is measured by RDW, which has been used to help differentiate between different forms of anemia [7]. An elevated risk of cardiovascular disease is linked to high RDW readings [8]. A recent research discovered a link between a high RDW and a bad prognosis for lung cancer patients [9]. Furthermore, greater RDW values were linked to a higher stage of the illness in individuals with symptomatic multiple myeloma [10]. This work's objective was to find the correlation between MPV & RDW and the disease-free survival among DLBCL patients.

PATIENTS AND METHODS

We conducted our study on 140 patients with Denovo DLBCL received R-CHOP protocol of which 112 patients achieved CR, on those 112 patients we conducted a retrospective study to elicit the association of MPV and RDW with DFS at the Haematology Units of International Medical Centre, Zagazig and Menoufia University Hospitals, from the beginning of 2020 until the end of 2022.

All patients were subjected to: Initial workup at diagnosis including full history, comprehensive clinical examination with special emphasis on Eastern Cooperative Oncology Group (ECOG) & BMI calculation (kg/m^2). Laboratory investigations [CBC (automated Sysmex XN-10 hematology analysis), peripheral blood film (smear was prepared and stained with Leishman stain), kidney & liver function tests, ESR, LDH, B2 microglobulin (all of these were done by automatic biochemical analyzer AU 680, Beckman Coulter, Danaher Cooperation, Washington DC, USA), CRP (was done by AQT90 FLEX analyzer, Radiometer Company, Copenhagen, Denmark), HCV Ab, HBsAg, HBcAb and HIV Ab (All were done by Architect i1000SR immunoassay, Abbott Architect, Illinois, USA). Revised International Prognostic Index (R-IPI) & Lugano staging (to assess response was done by PET-CT Omni Legend, GE Healthcare, USA).

Ethical approval: This study has been approved by The Ethics Committee of Faculty of Medicine, Menoufia University [11\ 2023 INTM 20]. Following informing all participants by details of the study, signed consent was provided by each participant. The study adhered to the Helsinki Declaration throughout its execution.

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Statistical analysis

SPSS of version 23.0 was used to tabulate and analyze the gathered data. To quantify the association between the categorical dependent variables and one or more independent variables, two sorts of statistics were performed: Descriptive statistics, such as percentage (%) and mean ± SD, and analytical statistics, such as multivariate Cox regression analysis were used. To define the prognostic indicators, DFS was used. To ascertain the threshold value, sensitivity, and specificity of the variables under study, a ROC curve was created. Additionally, DFS was examined using Kaplan-Meier curves. Any p-value that was equal to or less than 0.05 was regarded as significant.

RESULTS

In our study we observed 140 patients with DLBCL who received R-CHOP protocol of which 28 patients were refractory to the mentioned protocol and 112 patients achieved CR on it**.** Those 112 patients were followed up for events, which included death or relapse. The mean age of the patients in our research was 53.12 years, and 62.5% of the patients were males. According to Lugano staging, the majority of the patients (67.8%) were in stages III and IV. 51.8% of the patients in the study had extra nodal disease, 54.4% had concomitant comorbidities, and 41.1% had bone marrow involvement. The majority of the patients in the study had excellent R-IPI (63.4%), and only 38.3% had LDH above ULN [Table 1].

Table (1): Baseline characteristics of the studied DLBCL cohort. (No =112)

Parameter	Value
Age (Years)	53.12±12.68
Male sex (no. & %)	70 (62.5%)
Comorbidities (no. & %)	61 (54.4%)
Hypertension	40 (35.7%)
Diabetes mellitus	24 (21.4%)
Chronic kidney disease	3 (2.7%)
IHD	6 (5.4%)
BMI (Mean ± SD) (kg/m^2)	28.84±4.9
LDH >ULN (no. & %)	43 (38.3%)
Lugano staging (no. & %)	
Stage I & II	36 (32.2%)
Stage III & IV	76 (67.8%)
Extranodal involvement (no. & %)	58 (51.8%)
Bone marrow involvement (no. &%)	46 (41.1%)
ECOG <2 (no. & %)	103 (91.9%)
R-IPI (no. & %)	
Very good	25 (22.3%)
Good	71 (63.4%)
Poor	16 (14.3%)
MPV (Mean ± SD) in FL.	9.13±0.87
RDW (Mean ± SD)	14.14±1.14

DLBCL: diffuse large b cell lymphoma; **BMI:** body mass index, **ECOG:** eastern cooperative oncology group, **MPV:** Mean platelet volume, **RDW:** Red blood cell distribution width, **LDH:** lactate dehydrogenase, **ULN:** upper limit normal, **R-IPI:** Revised International Prognostic Index, **FL:** femtoliters.

The mean duration of DFS was statistically calculated as 12.75 months. A total of 58.93% of the studied patients were censored, while 41.07% had the event including 16.9% dead and 24.2% relapsed.

The cut-off point for MPV was estimated statistically as 9.1 with good sensitivity (82.6%) and specificity (59.1%) with a P-value of <0.001 according to ROC curve **[Figure 1A],** while the cut-off point for RDW was calculated as 14.1 with a good sensitivity (77%) and specificity (63%) with a P-value of 0.041 **[Figure 1B].**

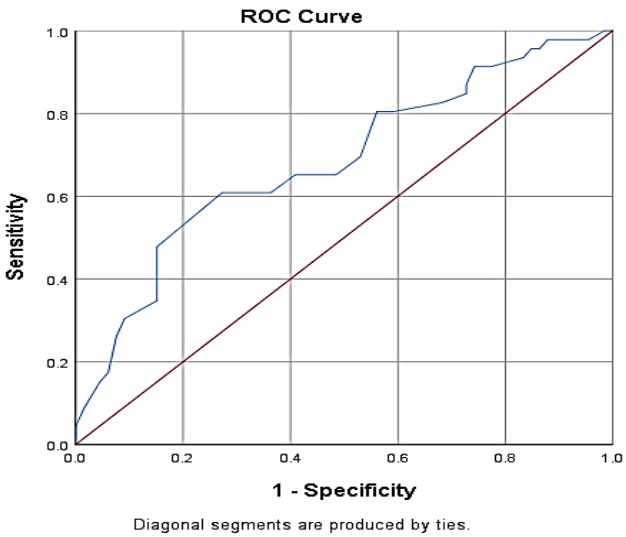

Figure [1A]: Receiver operating characteristic (ROC) curves analysis for MPV.

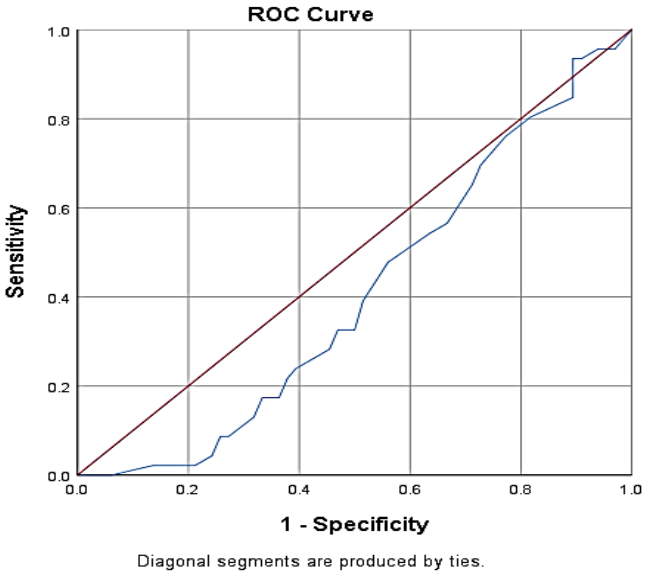

Figure [1B]: Receiver operating characteristic (ROC) curves analysis for RDW.

Based on Kaplan-Meier survival analysis of MPV, patients with a low MPV had a significantly lower DFS mean than those with a high MPV, with P-value 0.013 and log rank 6.202 **[Figure 2A],** while patients with a high RDW had a significantly lower DFS mean than those with a high RDW**,** with P-value 0.042 and log rank 3.112 **[Figure 2B].**

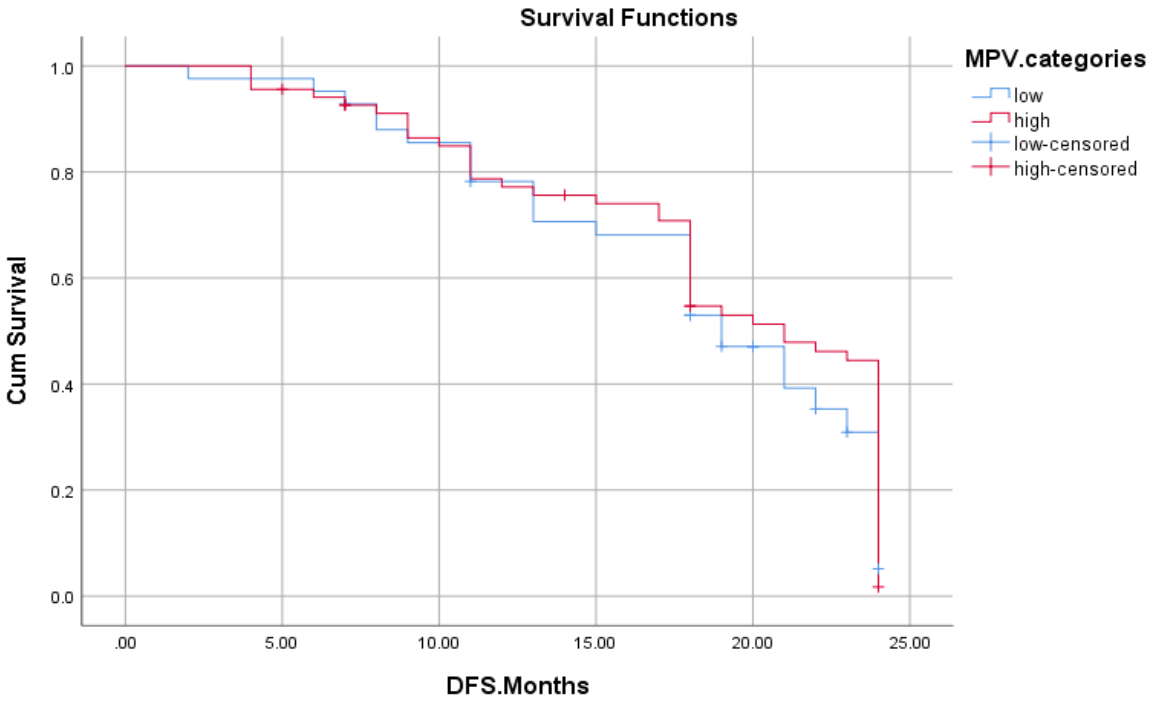

Figure [2A]: Kaplan-Meier analysis of DFS according to MPV in DLBCL patients.

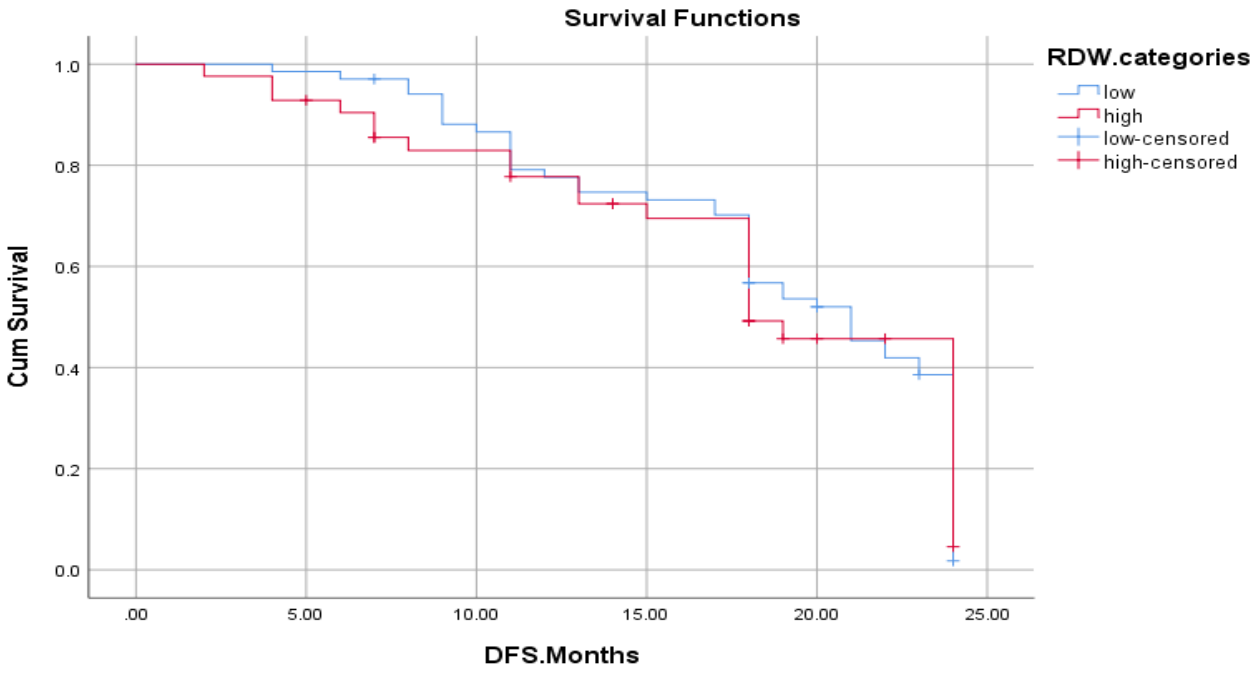

Figure [2B]: Kaplan-Meier analysis of DFS according to RDW in DLBCL patients.

Cox-regression analysis showed that independent prognostic factors for DFS were high R.IPI (P < 0.001), ECOG >1, (P = 0.008), elevated LDH (P = 0.001), high clinical stage (stage III and IV) (P = 0.024), bone marrow involvement (P = 0.049), MPV < 9.1 (P = 0.008), RDW >14.1 (p = 0.010), and presence of Extra nodal sites of disease (P = 0.003) [Table 2].

Table [2]: Multivariate Cox regression analysis of the predictors for DFS

Characteristics	DFS		
	HR	95%CI	*P* value
Male sex	1.023	0.613-1.800	0.944
Age (> 53)	1.245	0.720-2.147	0.435
R.IPI (>2)	2.889	1.633-5.154	**<0.001**
ECOG (>1)	2.278	1.241-4.192	**0.008***
B_2 microglobulin (>5.02)	1.618	0.879-1.723	0.965
LDH (>ULN)	2.529	1.461-4.404	**0.001***
Stage (III and IV)	1.894	1.092-3.301	**0.024***
Bone marrow involvement	2.363	1.113-5.570	**0.049***
RDW (>14.1)	1.461	1.262-1.814	**0.010***
MPV (< 9.1)	0.461	0.292-0.874	**0.008***
Presence of Extra nodal	2.434	1.360-4.418	**0.003***

DISCUSSION

DLBCL is the most prevalent lymphoma, and like the majority of NHLs, it is more common in males, with around 55% of cases occurring in men. The median age at presentation was 64 years. The incidence rises with age [11]. In the last era much research discussed the association between inflammatory markers and malignancy outcome. One of the most often utilized test indicators for platelet functioning is MPV [12]. It has been shown that platelets are crucial for the spread and metastasis of cancer [13].

According to **Zhang *et al.*** [14] preliminarily activated platelets have the ability to promote tumor growth. Given that MPV is a reflection of platelet activity. We anticipated that individuals with DLBCL will have high MPV as a poor prognostic indicator. Conversely, our results may actually support the idea that smaller platelets are more likely to die. Smaller platelets may have a greater prothrombotic propensity than bigger platelets in cancer patients, according to one idea put up to explain this occurrence. Data from a retrospective research that examined MPV levels in cancer patients who got VTE confirmed this theory [15]. Comparing MPV readings at the time of cancer diagnosis to those at the time of thrombus onset, it was discovered that the former were lower. Additionally, in their analysis of 308 NSCLC patients, **Kumagai *et al.*** [16] found that patients with low MPV had a worse overall survival (OS) and DFS than those with high MPV. **Zhuang *et al.*** [6] found MM patients with low MPV had a worse outcome, demonstrating the detrimental impact of low MPV on hemato-oncology patients.

Poor dietary condition and chronic inflammation are reflected in high RDW levels. Malnutrition and persistent inflammation are caused by malignant tumors [17]. The majority of symptoms and indicators described by cancer patients, such as tiredness, anorexia, weight loss, and cancer-related anemia, may be explained by this systemic inflammatory response, which reflects both disease activity and the host's intrinsic reaction to the tumor [18]. While, the exact mechanism underlying the correlations between RDW and disease activity or survival has not been determined. It is possible that elevated RDW levels are a reflection of an underlying inflammatory state that hinders erythrocyte maturation and results in insufficient production of the hormone erythropoietin, undernutrition (i.e., deficiencies of iron, vitamin B12, and folate), oxidative damage, and age-related diseases through alterations in erythropoiesis [19].

Additionally, individuals with solid tumors who had significant RDW did not respond well to therapy. It has also been shown that persistent inflammation might result in an adverse reaction to chemotherapy. The predictive usefulness of RDW in individuals with malignant illness has been the subject of several recent research. Patients with breast cancer had a considerably greater RDW than those with fibroadenomas [20]. In patients with multiple myeloma, lung cancer, and malignant mesothelioma, RDW was a significant predictive factor [9, 10]. These findings are consistent with our observations. RDW could be a common prognostic indicator across a range of illnesses [21].

In our study 112 patients out of 140 DLBCL patients achieved CR after receiving R-CHOP protocol. We followed up those 112 patients to find up the relation between MPV, and RDW values and DFS of the selected patients. According to our study the cut-off point for MPV was 9.1 with good sensitivity (82.6%) and specificity (59.1%) with a P-value of <0.001, while the cut-off point for RDW was 14.1 with a good sensitivity (77%) and specificity (63%) with a P-value of 0.041

Regarding MPV our results are compatible with **Zhou *et al.*** [22] who demonstrated that in patients with DLBCL, a low MPV before treatment was an independent unfavourable prognosis factor. **Kumagai *et al.*** [16] similarly showed that in patients who had total resection of NSCLC, a low MPV before surgery was an independent unfavourable prognostic factor. However, in contrast to our research, **Li *et al.*** [23] discovered that a high MPV number indicates a bad prognosis for colorectal cancer. According to estimation of **Periša *et al.*** [24], high baseline RDW is an independent predictor of poor prognosis in patients with DLBCL, which is similar to our findings.

Also, **Lee *et al.*** [25] concluded that patients with symptomatic multiple myeloma who had elevated RDW upon diagnosis had a worse prognosis and progressed disease status. As like in solid malignancy results were, **Albayrak *et al.*** [26] found that in prostate cancer, compared to patients with low RDW values, those with greater RDW values are more likely to experience the advancement of their cancer.

CONCLUSION

In this study, we concluded that lower baseline MPV values, and higher baseline RDW values were associated with inferior DFS outcome in patients with Denovo DLBCL after achieving Complete Remission upon receiving standard R-CHOP protocol. We conclude by acknowledging the limitations of our study, which included its retrospective design, short length, and small patient population. We advocate a prospective study design, which would have a larger patient population and a longer duration.

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