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Clinical Study of the Role of Differential Blood Count as a Pretreatment Diagnosis for Patients With Diffuse Large B Cell Lymphoma (DLBCL)

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Abstract

The study employed simple differential blood count assessing clinical prognosis index at diagnosis of DLBCL patients. Each patient's prognostic performance status was computed using absolute neutrophils/absolute lymphocytes(ANC/ALC), absolute lymphocytes/absolute monocyte (ALC/AMC), and absolute platelet/absolute lymphocytes APC/ALC) respectively,

and then compared to preexisting parameters IPI, ECOG-PS, KI-67% protein expression, LDH, gender, bone marrow infiltration, and tumor location using ROC curves to determine the sensitivity and specificity threshold of each CBC performance index and survival analysis to estimate 5-year PFS and OS. The study showed that NLR compared to LDH at NLR ≥ 3.50 correlates to an increase in LDH >230UI/L, ECOG-PS score 2-4, increase in nodal tumor location, and elevation in cell proliferation at ki-67% protein expression (≥20%) at diagnosis exhibit poor prognosis to R-CHOP chemotherapy. Our results also demonstrated that LMR≤2.50 was associated with ECOG-PS score 2-4, increased number of extranodal tumor locations, in comparison with gender female participants had high sensitivity 60%, also low score LMR≤ 2.50 correspond to IPI score 3-5 among DLBCL patients. Our results further revealed that Pretreatment PLR≥150 at diagnosis correlates with LDH>230UI/L, and an ECOG-PS score of 2-4 in DLBCL patients.

Conclusion: This study confirmed that pretreatment differential blood index NLR, LMR, and PLR are strongly associated with clinicopathological characteristics and provide important clinical prognostics in the early detection of DLBCL to the rituximab combined regimen.

Abbreviations: CBC: complete blood count, ANC: absolute neutrophils count, ALC: absolute lymphocyte count, APC: absolute platelet count, AMC: absolutes monocyte count, PFS: progression-free survival, OS: overall survival

Keyswords: B-cell lymphoma, clinicopathological, lymphocyte, monocytes, neutrophils

1. Introduction

Diffuse large B cell lymphoma DLBCL: an intermediate grade lymphoma that is aggressive and heterogonous among the subtype of adult non-Hodgkin lymphoma (NHL) patients (Shehata et al, 2019). DLBCL is considered potentially treatable with the characteristic features of aggressiveness, however, with the advancement in treatment using rituximab combined chemotherapy (R-CHOP), DLBCL still has an approximation of 20- 30% relapse(M. Li et al, 2019).DLBCL originating from B cell causes dissemination into the normal lymph node structure. The disease may arise *de novo* or transform from an indolent lymphoma, such as small lymphocytic lymphoma or follicular lymphoma, patients with the disease present with fast enlarging symptomatic lymphatic masses usually confined in the neck or abdomen, B symptoms such as drenching night sweat, fever, and weight loss observed in about 30% of patients(Beltran et al, 2019). Approximately 50 to 60 percent of patients are affected by advanced-stage diffuse disease III and IV(Chang et al, 2015). The international prognosis index is subjected to the current standard prognostic system for lymphoma but it has been suggested that the international prognosis index (IPI) might not be perfect in risk classification, diagnosis, and early diagnosis in DLBCL patients(Marcheselli et al, 2020). Further evaluation in prior reports stated RBC and HB are internal signals that initiate an inflammatory response, tumor growth, and resistance to chemotherapy (Moses & Brandau, 2016). However, previous studies have been on positron emission tomography using early interim analysis, causing the prognostic effect that still increases after chemotherapy but does not highlight the significance of peripheral blood biomarkers at the diagnosis and pretreatment stage of DLBCL. Inflammatory markers have been assessed in

numerous studies for various malignancies as prognostic and predictive factors, NLR ratios have an advantage over absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) alone because it reflects both systematic inflammation (neutrophils) and immunity inflammation lymphocytes(Feng et al, 2019). Prior reports stated an elevated neutrophil count indicates the chance of inflammation (Hong et al, 2017). However, the prognostic effects of NLR, LMR, and PLR on DLBCL treatment response remain inconsistent among studies and, there is a need for further evaluation and confirmation of the clinical role of peripheral complete blood count biomarkers. Previous studies on prognosis remain inconsistent among DLBCL patients to R-CHOP, and do not confirm its relations to tumor burden and bone marrow infiltration in patients at diagnosis, this study herein discussed the role of differential blood count index, absolute neutrophils/absolute lymphocytes[ANC/ALC], absolute lymphocytes/absolute monocytes[LMR] and absolute platelet/ absolute lymphocytes[PLR] prognostic assessment in DLBCL at diagnosis to tumor burden, location, and cell proliferation (ki-67%) response to R-CHOP chemotherapy.

2. Materials and Methods

2.1 Materials

This retrospective cross-sectional study comprises DLBCL patients from the first affiliated hospital of Jinzhou medical university china Liaoning province. A non-random database of 94 DLBCL patients on Rituximab combined chemotherapy was analyzed. All the data used was taken from patients admitted to the hematology department of the first affiliated hospital of Jinzhou medical university who met the inclusion criteria of pathological diagnosis and had no previous history of treatment and malignancy involvement in the study group.

2.2 Methods

We analyzed pretreatment peripheral CBC blood data on each of the sample patients using Beckman Coulter's five-part differential blood count analyzer at the time of diagnosis. This includes absolute; neutrophils(ANC), monocyte(AMC), lymphocytes(ALC), and platelets (APC) .We further used the absolute values to compute their respective ratios comprising neutrophil lymphocytes ratio (NLR), lymphocytes mono ratio (LMR), platelet: lymphocytes ratio (PLR) of each participant in the study group respectively, clinicopathologic characteristics, and Demographic data of patients were collected from the medical history of each patient in the study, which include International Prognostic Index (IPI), serum lactate dehydrogenase levels (LDH). Pathology type, European cooperative oncology group performance status (ECOG-PS), ki-67% protein expression index, presence of B symptoms, and extranodal involvement sites.

The research approval was granted by the ethical and internal review board at the first affiliated hospital of Jinzhou medical university. Each of the sample patients was treated with R-CHOP regimen chemotherapy and written informed consent was sought from all participants.

2.3 Statistical Analysis

Disease diagnosis characteristics representing each categorical group were presented using both univariate and multivariate analysis tables, and each of the sample blood indexes was ascertained by computing corresponding absolute neutrophils/absolute lymphocyte (ANC/ALC), absolute lymphocyte/absolute monocytes (ALC/AMC), and absolute platelet/absolute lymphocytes (APC/ALC) respectively. The rationale for using ROC (receiver operating characteristics) used in previous studies by Ho et al., (2015) is to establish a cut-off threshold for NLR, LMR, and PLR to further evaluate progression-free survival (PFS) and overall survival(OS) on survival analysis using SPSS software version 20 (Inc. IL Chicago USA) to ascertained the sensitivity and specificity cut of levels and range of each calculated ratio of LMR, NLR and PLR against clinicopathological features prognosis to R-CHOP at 95% CI, indicating a statistically significant value of $P<0.05$.

3. Results

The median age at diagnosis was 65years. Out of the studied patients <60yrs were 33(35.10%) and >60yrs were 61(64.90%). Gender demographics at diagnosis, male 35(37.23%) and female 59(62.77%). We observed that 39 (41.49%) out of the total sample had LDH >230UI/L at diagnosis. The study participant IPI –PS put into 0-2 and 3-5 were 34(36.17%) and 60(63.83%) respectively. Out of the total sample, 36(38.29%) exhibited B-symptoms, ECOG-PS 0-1 and 2-4 were 44 (46.81%) and 50 (53.19%) at diagnosis respectively. ki-67% protein expression index expressing patients' magnitude of cell proliferation >20% was detected in 78 patients (82.98%) at diagnosis and bone marrow infiltration was observed in 11 cases (11.7%). However, 83(88.30%) had no marrow infiltration at diagnosis. In the distribution of patient characteristics and location of the tumor, 79 (84.04%) had nodal involvement at diagnosis, and 15(15.96%) presented extranodal tumor involvement. The study observed that 48(51.06%) patients expressed BCL2 positive, as seen in table *1.0*

Table 1. Descriptive features of 94 DLBCL patients' distribution to NLR, LMR, and PLR

n =94	NLR≥3.50		LMR≤2.50		PLR≥150	
VARIABLES	NO%	P	NO%	P	NO%	P
AGE						
<60	33(35.10)	0.090		0.722		0.129
>60	61(64.9)	0.014		0.089		0.093
GENDER						
MALE	35(37.23)	0.164		0.14		0.16
FEMALE	59(62.77)	0.093		0.096		0.092
LDH (U/L						
<230	55(58.51)	0.086	46(48.94)	0.231	54(57.45)	0.092
>230	39(41.49)	0.01	48(51.06)	0.095	40(42.55)	0.023
IPI						
0-2	34(36.17)	0.091	38(40.43)	0.282	37(39.36)	0.228
3-5	60(63.83)	0.093	56(59.57)	0.089	57(60.64)	0.089
B-SYMPTOMS						
YES	34(36.17)	0.094	32(34.04)	0.090	33(35.11)	0.089
NO	60(63.83)	0.477		0.722		0.409
ECOG-PS						

0-1	44((46.81)	0.091	40(42.55)	0.088	43(45.74)	0.091
2-4	50(53.19)	0.018	54(57.45	0.018	51(54.26)	0.065
KI-67%						
0-19%	16(17.02)	0.748		0.203		0.309
>20%	78(82.98)	0.0104		0.046		0.068
TUMOR LOCATION						
LYMPH NODE	79(84.04)	0.091		0.033		0.339
EXTRA NODAL	15(15.96)	0.085		0.023		0.056
BCL2 (POSITIVE)	48(51.06)	0.012		0.032		0.049
BCL2 (NEGATIVE)	46(48.94)	0.456		0.065		0.76

ECOG-PS: European cooperative oncology group performance Status, NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte monocyte ratio, PLR: platelet lymphocyte ratio, BCL2: B-cell lymphoma 2, IPI, International prognostic index, LDH, lactate dehydrogenase, NO%: number of patient and percentage out of the total, P; P-value.

Table 2. Distribution of peripheral blood count markers of 94 DLBCL patient's to pre-existing clinicopathology features at diagnosis

Variables		**NLR**	**P**	**AUC**	**LMR**	**P**	**AUC**	**PLR**	**P**	**AUC**
ECOG-PS		≥ 3.50 ECOG-PS 2-4	0.029	0.632	≤2.50 ECOG-PS 2-4	0.026	0.635	≥150 ECOG-PS 2-4	0.075	0.609
IPI		≥ 3.50 3-5	0.116	0.598	*≤2.50 3-5 score*	0.037	0.688	≥150	0.256	0.571
KI-67%		≥3.50 KI-67% ≥20%	0.13	0.753	≤2.50	0.518	0.365	≥150	0.342	0.437
LDH		≥3.50 LDH>230	0.04	0.676	≤2.50	0.229	0.574	≥150 >230UNL	0.026	0.638
Tumor location	*Nodal*	≥3.50	0.091	0.642	≤2.50	0.033	0.321	≥150	0.339	*0.76*
	Extranodal	≥ 3.50	0.091	0.358	≤2.50	0.033	0.679	≥150	0.339	0.419
BM infiltration		≥ 3.50 YES	0.780	0.527	≤2.50	0.067	0.52	≥150	0.935	0.492
Gender		≥ 3.50	0.561	0.345	≤2.50 Female	0.094	0.604	≥150	0.067	0.546
AGE		≥ 3.50	0.170	0.355	≤2.50	0.074	0.413	≥150	0.131	0.405
B symptom		≥ 3.50	0.542	0.495	≤2.50	0.346	0.322	≥150	0.433	0.549

IPI: international prognostic index, AUC: Area under the curve, UNL: Upper normal limit

NLR: Neutrophil lymphocyte ratio, LMR: Lymphocyte monocyte ratio, PLR: Platelet lymphocyte ratio, ECOG-PS: European cooperative oncology group performance status, LDH: lactate dehydrogenase, ROC: Receiver operating Characteristics, BM: bone marrow, P; P-value.

3.1 The Role of NLR ≥3.50 At Pretreatment Diagnosis to Clinicopathological Characteristics in DLBCL Patients

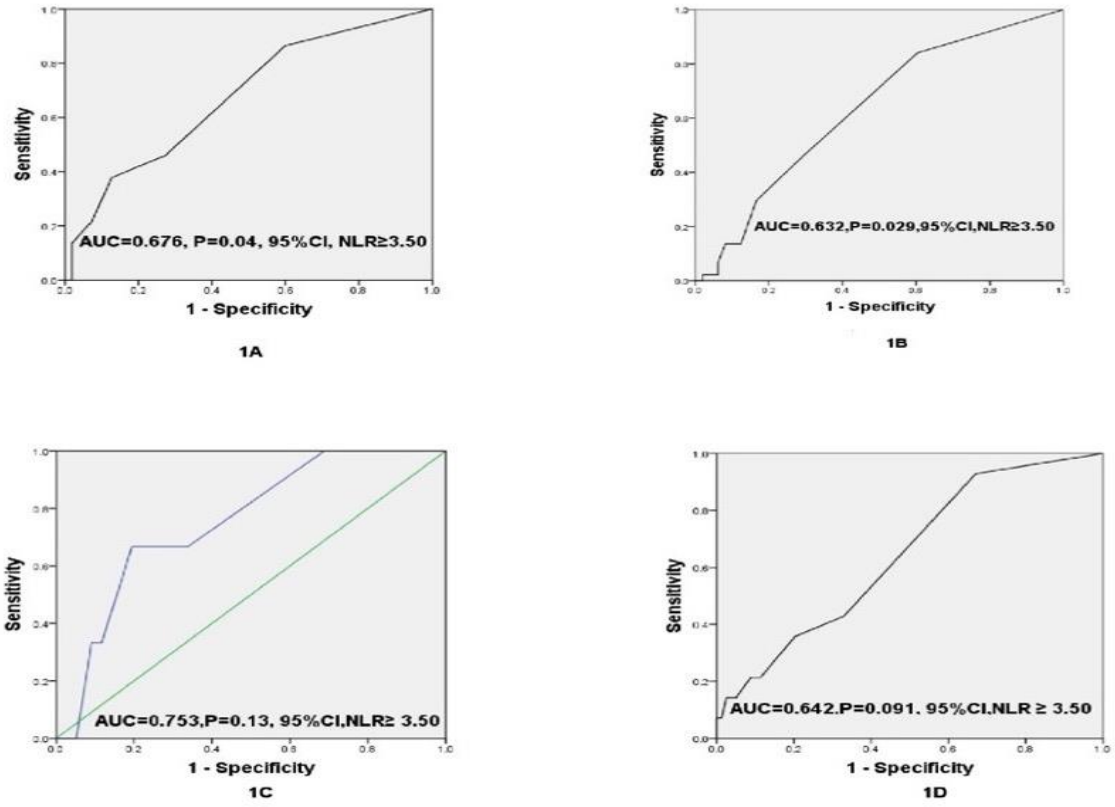


Figure 1.Computed threshold of NLR≥3.50 reactions to clinicopathological characteristics of 94 DLBCL patients at diagnosis

Where A, B, C, and D represent NLR-associated reactions with LDH, ECOG-PS, KI-67% protein expression, and tumor location respectively at 95%CI.

AUC: Area Under the Curve, NLR: Neutrophil Lymphocyte Ratio.

3.1.1 NLR /LDH

Absolute neutrophils/absolute lymphocytes [NLR ≥3.50] indicate neutrophilia and lymphopenia suggest high levels of NLR correspond to LDH>230 which leads to increased lymphoma cell proliferation and angiogenesis, our retrospective evaluation of peripheral blood count biomarkers showed NLR ≥3.50 strongly correlate to LDH≥230UI/L (P= 0.04, AU=0.676 95% CI) at pretreatment detective sensitivity 86% and specificity of 60% refer to Figure *1A.*

3.1.2 NLR/ECOG-PS

Patient clinical characteristics showed a high number of advanced stage III and IV disease stage DLBCL of 50 (53.19%). We further evaluated the level of NLR<3.50 and NLR≥3.50 using receiver operating characteristics in assessing the pretreatment diagnosis and prognosis significance. NLR≥3.50 is highly associated with ECOG-PS stage 2-4 (AUC=0.632, P=0.029, 95% CI) at a sensitivity of 71% and specificity level of 56% resulting in increased treatment failure with greater patients achieving partial remission (PR) 32(34%) and no remission NR 9(9.57%), suggesting a high relative risk of 5-year progression-free survival of 67% as seen from *Figure 1B and Table 3.10.*

3.1.3 NLR/ki-67%

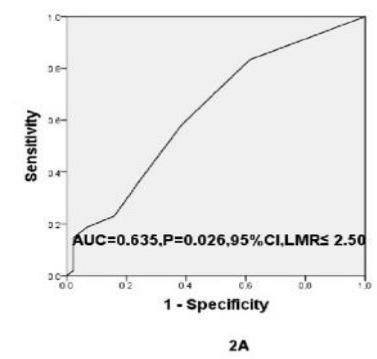
We evaluated DLBCL retrospective samples using immune histochemical staining report on their ki-67% protein expression assessment, patients were put into cohorts of 0-19% and ≥20% of 16(17.02%) and 78(82.98%) respectively. Ki-67% with high levels of protein expression showed BCL2 positive, with NLR ≥3.50 levels corresponding to ki-67% expression ≥20% (AUC=0.753, P=0.13,95% CI) at a sensitivity of 66% and specificity of 57% of the diagnosed patients seen from Figure 1C, exhibiting poor 5-year PFS and OS outcome response to R-CHOP detailed in Table 3.1.

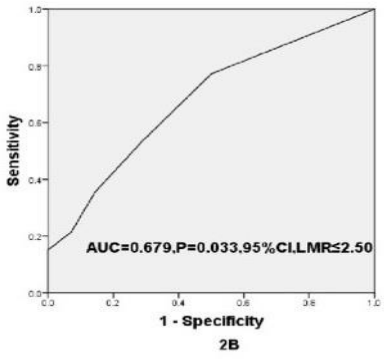
3.1.4 NLR/Tumor Location

The study's analysis of DLBCL participants reveals that out of the 94 patients, the nodal tumor location was 79(84.04) and the extra lymphoid tumor location was 15 (15.96%) patients. NLR≥3.50(AUC=0.642, P=0.091) expressed tumor location of lymph nodes regions at a significant diagnosis of 75% sensitivity rate and 68% specificity *Figure 1D.*

We evaluated neutrophilia and lymphopenia in DLBCL patient's pretreatment at diagnosis of the 94 participants' performance status to age, <60yrs and >60yrs of 33(35.10%) and 61(64.90%) respectively, NLR<3.50 and NLR≥3.50 diagnostics and prognosis characteristics of our data revealed high levels of NLR≥3.50 positively correlate with patients at old-age >60 years (AUC=0.355, P-value 0.017, 95% CI)

3.2 The Role of LMR≤2.50 at Pretreatment Diagnosis to Clinicopathological Characteristics in DLBCL Patients





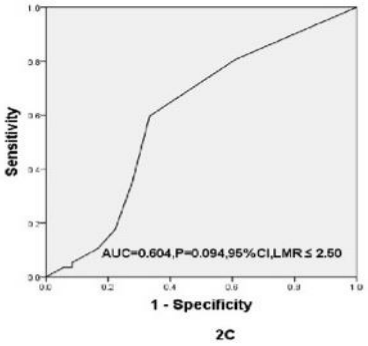


Figure 2. Threshold of LMR ≤2.50 reactions to clinicopathological characteristics of DLBCL patients at diagnosis

Where A, B, and C demonstrate ROC sensitivity and specificity reactions of LMR against ECOG-PS, extranodal tumor location, and gender respectively at 95%CI.

AUC: Area under the Curve, LMR: Lymphocyte's monocytes ratio.

3.2.1 LMR ≤ 2.50/ ECOG-PS

The evaluation of 94 diagnosed DLBCL patients in the study cohorts at diagnosis established heterogeneity among patients' status of ECOG-PS.

Patients with low LMR levels showed advanced stage ECOG-PS and IPI prognosis index at LMR≤2.50 (AUC=0.635, P=0.026, 95% CI) on ROC sensitivity and specificity of 74 and 62% respectively.

Patients with low LMR 54 (57.44%) exhibited poor prognostic status to R-CHOP seen in table 3.20 with few patients achieving complete remission *Figure* 2A.

3.2.2 LMR ≤ 2.50/Extra Lymphoid Tumor Location

The studied participants were divided into cohorts of lymphoid tumor involvement 79(84.04%) and extra lymphoid involvement 16(15.96%), heterogeneity to LMR levels on receiver operating characteristics, and DLBCL patients at diagnosis of low LMR levels expressed 2 or more extra lymphoid tumor locations (0.679, P=0.033 95% CI) with a positive expression at diagnostics sensitivity of 77% and specificity of 50% Figure *2B.*

3.2.3 LMR ≤ 2.50/Gender

The study participants of 94 DLBCL patients put into males 35(37.23%) and females 59(62.77%), we examined both cohort's performance at diagnosis on ROC at LMR ≤2.50, to a larger extent its revealed female cohort at the established threshold in the study correlated with *LMR ≤ 2.50* (AUC=0.604, P=0.094, 95% CI) sensitivity of 68% and specificity of 48% resulting into poor prognosis to R-CHOP in the female cohort than the male cohorts as seen in *Figure 2C.*

3.3 The Role of PLR≥ 150 at Pretreatment Diagnosis to Clinicopathological Characteristics in DLBCL Patients

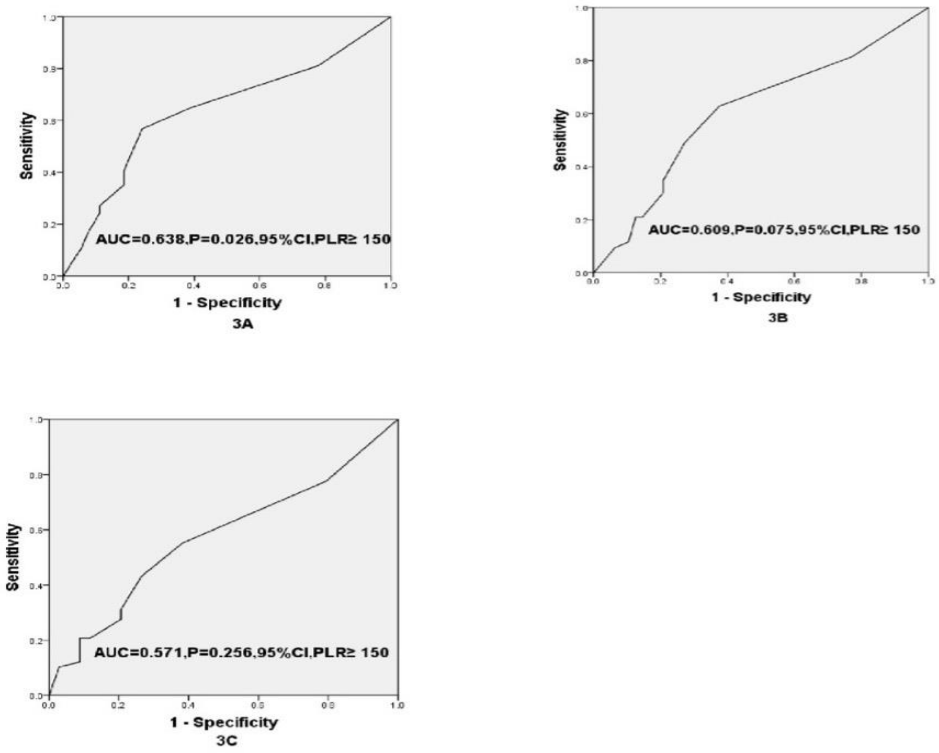


Figure 3. Threshold of PLR≥150 reactions to clinicopathological characteristics of 94 DLBCL patients at diagnosis

where A, B, and C represent PLR association with LDH, ECOG-PS, and IPI prognostic index respectively using the ROC curve at 95%CI.

3.3.1 PLR≥ 150 / LDH

The lactate dehydrogenase (LDH) level of each patient was estimated and stratified into two cohorts of <230UI/L 55(58.51%) and ≥230 UI/L 39 (41.49%) at diagnosis, increased levels of LDH were highly associated with increased PLR ≥150 (AUC=0.638, P=0.026, 95%CI) at a sensitivity of 75% and specificity of 51%.

The study's characteristics evaluation further suggested that patients with high PLR

39(41.48%) expressed BCL2 positive *Figure 3A.*

3.3.2 PLR≥ 150 / ECOG-PS

Investigating DLBCL patient's characteristics at diagnosis and after R-CHOP chemotherapy response revealed Platelet lymphocyte ratio (PLR) ≥150 associated with ECOG-PS stage 2-4 corresponding to DLBCL patients of advanced stage III & and IV (AUC =0.609 P= 0.075, 95% CI) at the sensitivity of 74% and specificity at 52% from Figure 3B.

3.3.3 PLR≥ 150 / IPI Prognostic Index

Contrary to other suggestions our retrospective evaluation of the diagnosis of DLBCL patients with increased peripheral platelet count and lymphopenia (PLR) threshold of ≥150 to association with the international prognostic index indicated no statistically significant association (AUC=0.571, P=0.256 95% CI) of sensitivity 45% and specificity 69% ***Figure 3C*** however cox regression on survival analysis seen in *table 3.30* show PLR≥150 expressed poor 5-year PFS and OS to rituximab combined therapy among DLBCL patients. Similarly, PLR associated with B-symptoms, ki-67% protein expression, age, location of the tumor, and bone marrow infiltration scored AUC <6.0 statistically no value given a high indicative of false-positive results see *table 2.0.*

4. Expression of 5-Year Progression-Free Survival [PFS] and 5-Year Overall Survival [OS] of 94 Dlbcl Patients on Survival Analysis

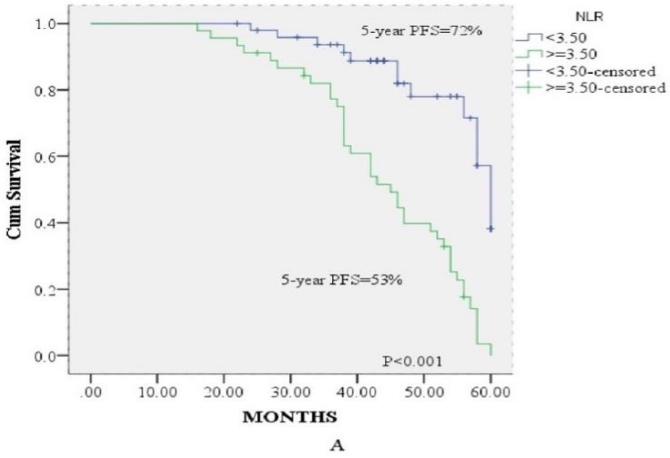
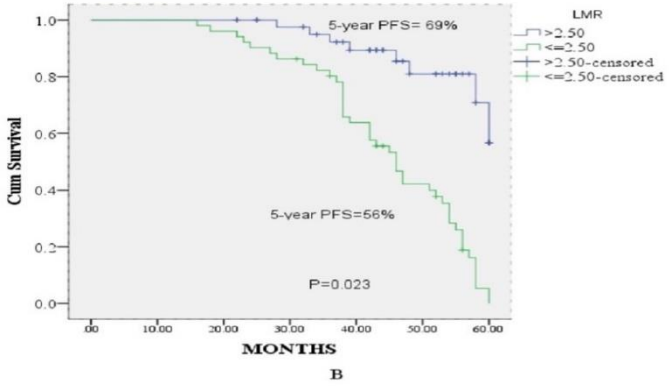


Table 3.1. Multivariate Cox Regression Analysis of 5-Year Progression-Free Survival and Overall-survival to NLR

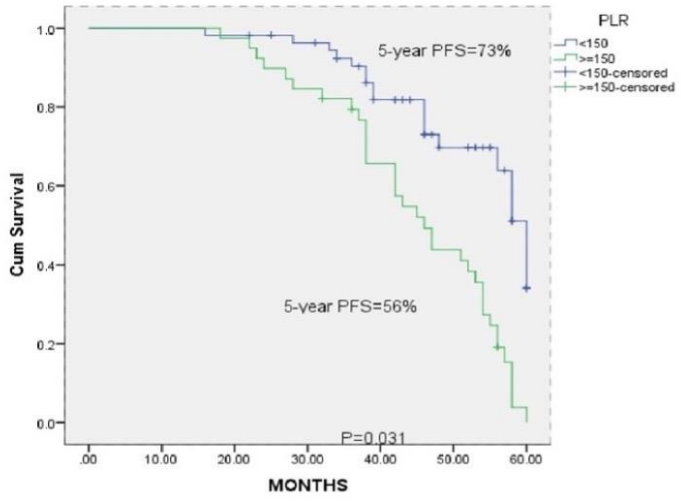
patient details	Progression-free survival (PFS)		OVERALL SURVIVAL (OS)	
	P-Value 95%	RR (95%CI)	P-VALUE	RR (95%CI)
AGE	0.02	1.092 [0.834-2.33]	0.042	0.539 [0.297-0.947]
B-SYMPTOMS	0.816	2.109 [1.87-2.84]	0.01	1.65 [1.522-4.913]
KI-67	0.001	1.312 [1.12-1.781]	0.484	1.213 [0.872-2.43]
OUTCOME	0.010	1.670 [1.240-3.712]	0.019	1.531 [1.018-1.704]



B

Table 3.2. Multivariate Cox Regression Analysis of 5-Year Progression-Free Survival and Overall To LMR

patient details	Progression-free survival (PFS)		OVERALL SURVIVAL (OS)	
	P-VALUE	RR (95%CI)	P-VALUE	RR (95%CI)
AGE	0.03	0.859 [1.052-4.530]	0.101	1.456 [1.096-4.509]
B-SYMPTOM	0.525	1.75 [0.723-3.950]	0.054	1.226 [1.030-2.439]
KI-67	0.01	2.062 [1.177-5.78]	0.005	2.134 [1.972-3.641]
OUTCOME	0.066	0.872 [0.708-3.493]	0.01	1.828 [1.216-5.543]



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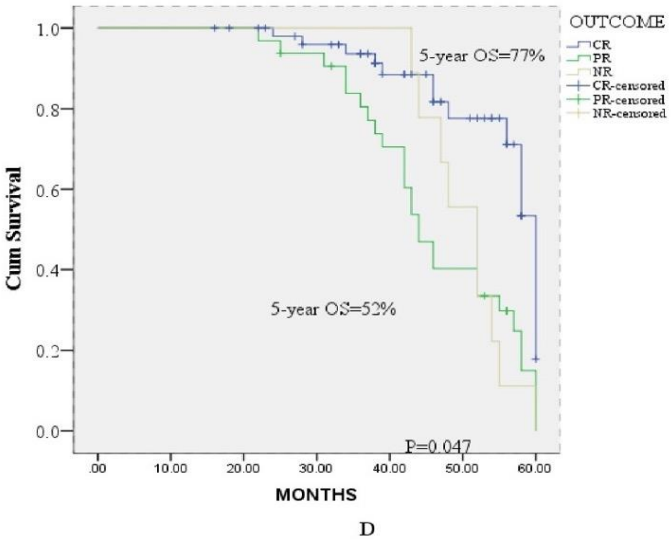

Figure 4. Survival analysis of patient's differential blood count parameters of 94 cases assessing the 5-year progression-free survival outcome to Rituximab combined chemotherapy

Whereas A, B, and C represent NLR, LMR, and PLR respectively

Figure 4D. Represent 5-year overall survival observation on 94 DLBCL patients to R-CHOP treatment outcome.

CR: complete Remission, PR: partial Remission, NR: No remission, OS: overall survival

Table 3.3. Multivariate Cox Regression Analysis of 5-Year Progression-Free Survival and Overall survival, To PLR

patient details	Progression-free survival (PFS)		OVERALL SURVIVAL (OS)	
	P-value	RR (95%CI)	P-VALUE	RR (95%CI)
age	0.072	0.652 [0.371-1.146]	0.012	0.689 [0.423-1.082]
b-symptoms	0.108	0.784[0.502-4.711]	0.166	1.587 [1.199-1.834]
Ki-67	0.027	1.250[0.537-2.176]	0.016	1.187 [1.009-2.270]
outcome	0.017	1.200[0.537-2.682]	0.048	1.842 [1.691-2.030]

In *figure 4A* NLR≥3.50 vs NLR<3.50 expressed a significant relation of P<0.001 demonstrated in 49(52.12%) and 45(47.88%) patients respectively, it appears patients with an increased level of NLR≥3.50 had a high relative risk (67%) 5-year outcome (remission) as seen in *table 3.10* indicating a 5-year Progression-free survival of 53% on NLR≥3.50 to R-CHOP.

A review of the 94 DLBCL pretreatment features at the established threshold LMR≤2.50 vs LMR>2.50 at diagnosis of 54(57.44%) and 40(42.56%) respectively indicates LMR≤2.50 had statistically significant (P =0.03, 95% CI). the study shows 57.44% of patients express poor prognosis to R-chop and a 5-year PFS of 56% of LMR≤2.50 seen in *figure 4B* and detailed RR expression in *table 3.20***.**

The study employed ROC established threshold level of Platelet/lymphocyte ratio (PLR) ≥150 vs PLR<150 at diagnosis of 39(41.48%) and 55(58.52%) patients respectively, (P=0.031, 95%CI) showed 5-year PFS of 73% at PLR<150 and PLR≥150 of 56% seen in *figure 4C, and table 3.3.*

More so, DLBCL patients' prognosis to R-CHOP treatment on 5-year overall survival showed that 54(57.45%), 32(34%), and 8(8.5%) achieve complete remission (CR), partial remission (PR), and no-remission (NR) respectively, with an estimate 5-year OS of 77% and 52% as seen in *figure 4D.*

5. Discussion

Despite the improvement in technology and clinical studies that underpin hematological malignancies diagnosis, and prognosis basis on cytogenetics, immunology, morphology, and molecular biology. This has limited underdeveloped facilities and clinical settings in acquiring basic knowledge and clinical guide on pretreatment prognosis evaluation at diagnosis stage challenges confronting DLBCL patients. Comparative reports of DLBCL patients to healthy cohort showed that DLBCL patients' immune had elevated neutrophils, monocytes, and suppressed lymphocytes compared to the healthy cohort(Hu et al, 2018). The study focuses on the use of cost-effective and favorable simple tools complete blood count (CBC) performance indexes to assess DLBCL pretreatment prognosis at diagnosis among 94 DLBCL patients to Rituximab combined therapy.

5.1 NLR≥3.50/Clinicopathological Characteristics

We analyzed 94 patients' CBC indexes and the study revealed NLR≥3.50 was associated with LDH>230UI/L (P= 0.04, AU=0.676 95%). In agreement, prior reports state that neutrophils initiate tumor cell spreading by capturing circulating tumor cells using extracellular traps and causing their movement to distant sites of the immune system in affected cells(Annibali et al, 2019, Ji et al, 2018& Wang et al, 2018).

It's affirmed neutrophilia and lymphopenia levels of NLR≥3.50 at diagnosis result in poor prognosis as seen in *table 3.1*, that exhibit 67% and 53.1% relative risk of 5-year PFS and OS outcome respectively, this conforms to a previous study that reports NLR>4.0 exhibit poor overall survival(OS) and event-free survival (EFS)(Mutz et al, 2015) although with a different threshold of sensitivity and sample number.

In agreement with the previous report, the findings of our study show that high levels of NLR≥3.50 at diagnosis, 49 of 52.12% had advanced stage III and IV DLBCL with ECOG-PS score 2-4(P=0.029, 95% CI) *see Figure 1B.* Furthermore, NLR≥3.50 correlates with KI-67% protein expression ≥20% (AUC=0.753, P=0.13) underpinning tumor cell proliferation within DLBCL patient's tumor microenvironment leading to poor prognosis to R-CHOP response consistent to prior reports (Cho et al, 2018 ,Huang et al, 2016 ,Song et al, 2015 & Tang et al, 2017).

An increased level of NLR observed in our study at diagnosis showed an increased number of nodal site tumor involvement, in agreement with (Annibali et al., 2019 & Wang et al., 2018).

Lymphocyte concentration using dog models confirmed NLR>3.50 was a worse prognostic indicator for survival (Park et al, 2017) consistent with our current study.

Elevated NLR levels in patients breed a positive immune microenvironment therefore early detection is associated with a bad prognosis for patients (Katoh et al, 2017&Stefaniuk et al., 2020). This current study unveiled NLR≥3.50 is an independent pretreatment prognostic performance index in assessing DLBCL patients' response to R-CHOP at diagnosis seen in *figure 4A* and table *3.10*.

5.2 LMR≤2.50/ Clinicopathological Characteristics

The study results demonstrated LMR≤ 2.50 detection at diagnosis in DLBCL patients is a good prognostic marker that corresponds to ECOG-PS score 2-4 (AUC=0.635, P=0.026, 95% CI) at diagnosis and a low level of LMR promotes poor prognosis in response to R-CHOP chemotherapy in agreement with (Li Y *et.al* (2014), Zhao P *et.al*.2017, Li Y. L, et al., 2014, &Zhao et al, 2017).

Our current study emerged that low LMR levels correspond to increasing extranodal tumor location (AUC=0.679, P=0.033 95%CI) consistent with similar findings in a previous study (Chen et al, 2020). Accordingly, a healthy volunteer sample and patients with DLBCL comparison revealed a low percentage of lymphocytes correlated with a poor prognosis to rituximab combined chemotherapy (Hu et al, 2018, Koh et al, 2014,& Yang et al, 2019).

In response to inflammation LMR actively predicts pro-tumor and anti-tumor of the host and decreases LMR proves a good biomarker in pretreatment diagnosis of DLBCL patients, with poor OS (Li M et al, 2019 , Markovic et al, 2014, & Sun HL.et al, 2016).

This study for the first time indicated that LMR≤ 2.50 concerning gender is highly sensitive in female DLBCL patients, however, the mechanism remains unclear, and this generates an argument calling for large multicenter studies on the impact of LMR on gender among DLBCL patients.

Comparing both NLR and LMR to Glasgow prognostic score (GPS) in prognosis determination, suggested it predicts prognosis in DLBCL(Sun F et al, 2018). There are challenges confronting the use of LMR in predicting DLBCL, that includes genetic mutations, type of pathology, and tumor size however, decreased LMR relates to elevated LDH and tumor burden, making it a good biomarker in detecting prognosis status of DLBCL patients(Sun H. L.et al, 2016).

Consistent with our results sensitivity biomarker LMR ≤ 2.50 at diagnosis and prior articles on its impact stated LMR (≤ 2.60)(Tse, 2006). The level of LMR≤ 2.7 proves a sensitive biomarker for early prognosis assessment of DLBCL in an increasing number of extranodal sites(Li YL et al., 2014, Sun F et al., 2018, & Lin et al., 2015). Monocytes are measured as immunologically relevant and described as alternate biomarkers of cancer microenvironment which makes an important prognostic marker in DLBCL patient's cell lines at diagnosis to R-CHOP chemotherapy refer to *table 3 .2*.

A meta-analysis conducted by (Lin et al, 2015) stated low LMR has the worst prognosis and is

significant to the R-CHOP arm regimen comparable to the CHOP regimen however, this study only evaluated the R-CHOP arm regimen and it emerged LMR≤2.50 at diagnosis had 54 (57.44%) of the cases. This recorded 56% and 69% of 5-year PFS and OS respectively as seen in *figure5B.*

5.3 PLR≥150/ Clinicopathological Characteristics

The current study demonstrated high levels of platelet in peripheral blood count analytics within the advanced stage III and IV DLBCL disease patients and showed a poor prognosis at diagnosis to R-CHOP regimen seen in *figure 5C*, we further evaluate increased platelet level and lymphopenia in DLBCL patients at diagnosis on multivariate analysis *table 4.3*.

The study showed that PLR≥150 in DLBCL cases at diagnosis correlates positively with increased LDH>230UI/L(AUC=0.638, P=0.026,95%CI).In agreement to prior findings(Chang et al, 2015) and ECOG-PS score 2-4(AUC =0.609 P = 0.075, 95% CI) *Figure 3B.* In agreement with the previous finding by (Marcheselli et al, 2020).

Prior publications report PLR value ≥200 after the first regimen of R-CHOP proves an inferior progression-free survival(PFS) and provide a predictive biomarker, this remains inconsistent throughout studies (Yin et al, 2015).

This study observed a PLR≥150 performance prognosis biomarker in the early diagnosis of DLBCL among patients with a subsequent increase in LDH>230UI/L. A review of 80 DLBCL patients showed PLR>95 associated with poor prognosis and 5-year OS in R-CHOP treated DLBCL patients(Seo et al, 2017).

The prognostic and detection marker of PLR remains inconsistent as this was suggested in other reports that thrombocytopenia and red cell distribution width [RDW] are both independent prognostic factors associated with poor OS (Belotti et al., 2015). Contrary to our study on PLR correlation to the location of the tumor, the previous report suggested PLR has a high correlation with lymph node metastasis rate. (Markovic et al., 2014)

PLR and systematic immune inflammation index(SII) replicate in enriched host immunity and elevated SII due to high-level Neutrophils, platelet, and low-level lymphocytes indicating a strong inflammatory response and a weak immune reaction, originating from invasion and metastasis of cancer cells (Mizuno et al., 2019).

6. R-Chop Stratification on Peripheral Blood Count Biomarker Pretreatment Prognosis Detection

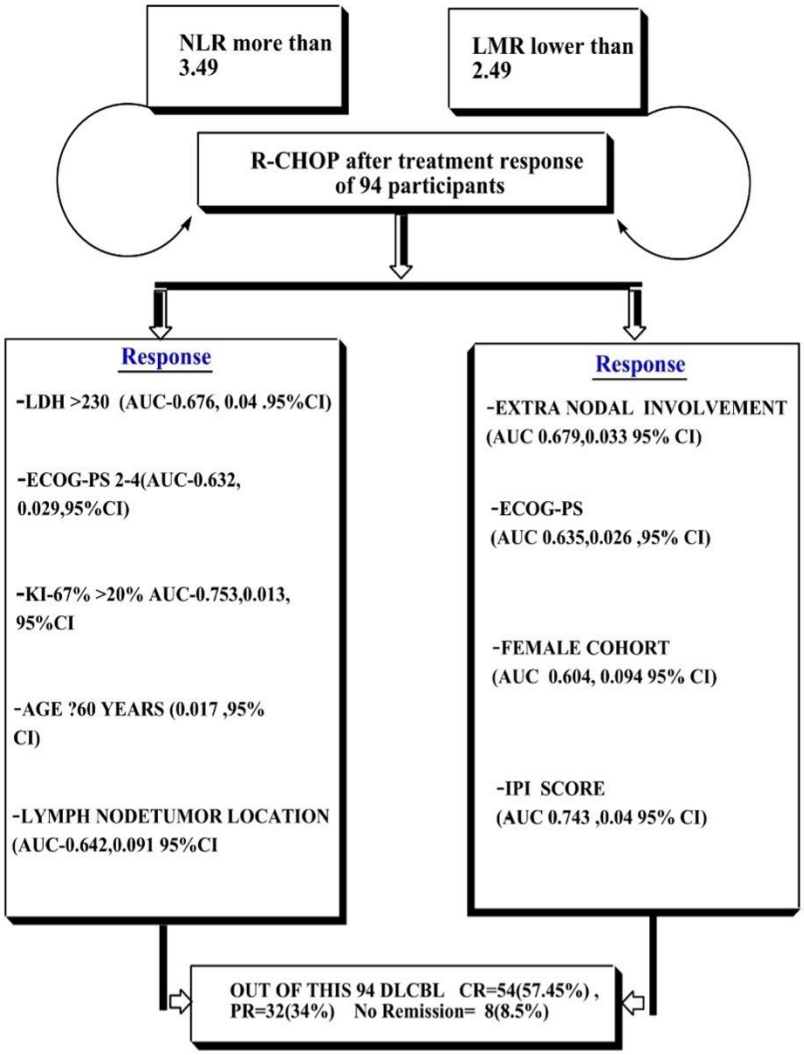

Figure 5. CR: complete remission, PR: partial remission

Post-treatment evaluation of R-CHOP regimen chemotherapy of 94 DLBCL diagnosed participants in the hematology department of the first affiliated hospital of Jinzhou medical university. Out of 94 evaluated patients on R-CHOP (rituximab 375mg/$m^{2,}$ cyclophosphamide 750mg/$m^{2,}$ doxorubicin 50mg/m^2 vincristine 1.5mg/m^2 prednisone 100mg/m^2.

Figure 5 detailed blood biomarkers for pretreatment and post-treatment outcomes on chemotherapy.

DLBCL patients who attained NLR≥3.50 and LMR≤2.50 at the diagnosis stage had worse 5-year PFS than other cohorts of low NLR and high LMR seen in Figures 4A and 4B. In a detailed fashion elevated levels of neutrophils accelerated by inflammatory activities errands tumor angiogenesis which probably affects the lymphocytes lineage.

Furthermore, lymphopenia demonstrates a depressed immune mechanism that effectively leads to poor prognosis in compromised immune body activity in the stages of lymphoma.

It's also confirmed that patients with high NLR≥3.50 and low LMR ≤2.50 level have advanced stage III and IV DLBCL this indicates a high association of cellular proliferation KI-67% protein expression of >20%. Increased neutrophils' extracellular traps and level of immunoglobulin somatic hypermutation during malignant transformation might be the associated increase in cell proliferation of ki-67% greater than 20% stage accordingly (Basso & Dalla-Favera, 2015).

7. Conclusion

The study suggested inexpensive and clinically significant tools NLR≥ 3.50, LMR≤2.50, and PLR ≥150 from simple automatic complete blood count readily accessible by many centers. These parameters specifically correlate with preexisting factors LDH, ECOG-PS, ki-67% protein expression, tumor location, gender, and IPI. The present study shows the index LMR≤2.50 and NLR≥3.50 at diagnosis synergistically exhibit independent worst prognostic performance tools to DLBCL patients on the R-CHOP regimen.

7.1 Clinical Practice Point

- In the study of 94 DLBCL patients, 82.98% exhibited elevated cellular proliferation expressing Ki-67% protein expression at diagnosis of ≥20%.
- Patients with elevated NLR≥3.50 at diagnosis were more prone to high tumor burden cells and cellular proliferation at a 2-fold increased risk to R-CHOP chemotherapy resistance than patients with low NLR ≤3.50
- Patients with LMR≤2.50 and PLR≥150 were more likely to have ECOG-PS 2-4 and NCCN IPI prognostic index score 3-5 at diagnosis and a 2-fold increased risk of R-CHOP chemotherapy treatment failure.
- LMR≤2.50 in DLBCL patients were associated with a poor prognosis of 68% sensitivity at diagnosis in achieving a complete remission to R-CHOP among female patients than a male cohort.
- Proposed threshold of NLR ≥3.50, LMR≤2.50 at diagnosis can discriminate between DLBCL patients with advanced-stage disease and low-stage, and poor 5-year PFS and OS to R-CHOP chemotherapy.

Declaration

Ethics approval and consent to participate

Ethical approval was granted by the internal review board of the first affiliated hospital of Jinzhou medical university with IRB NO: 202050 and all participant consent was rightfully ascertained following the ethical clearance approval.

Consent for publication

We declare that We contributed significantly towards the research study i.e., (a) conception, design, analysis, and interpretation of data, (b) drafting the article or revising it critically for important intellectual content, and (c) final approval of the version to be published.

We hereby acknowledge the journal of biology and life science conflict of interest policy requirement to scrupulously avoid direct and indirect conflicts of interest and, hereby agree to promptly inform the editor or editor's designee of any business, commercial, or other proprietary support, relationships, or interests that we may have which relate directly or indirectly to the subject of the work.

We also agree to the authorship of the article and approve publication in the following sequence:

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Availability of Data and Materials

All data of participants as stated in the manuscript are available and reported as stated in the manuscripts.

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Conflict of interest

The authors declare that they have no conflict of interest.

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