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MEAN PLATELET VOLUME, RED CELL DISTRIBUTION WIDTH, AND LYMPHOCYTE RATIOS AS SURROGATE PREDICTORS OF SUBCLINICAL INFLAMMATION IN SCHIZOPHRENIA: A CROSS-SECTIONAL STUDY

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ABSTRACT

Inflammation is a key player in schizophrenia pathogenesis. Higher inflammatory indicators like erythrocyte distribution width (RDW), Mean Platelet Volume (MPV), Neutrophil-to-lymphocyte Ratio (NLR), monocyte lymphocyte Ratio (MLR) and Platelet-to-lymphocyte Ratio (PLR) were found in schizophrenic patients compared to healthy controls. This comparative cross-sectional study aimed to find the predictors of subclinical inflammatory process in schizophrenic compared to healthy controls. A consecutive sample of 90 individuals were prospectively enrolled in the study: 45 schizophrenic patients and 45 age- and sex-matched controls. The DSM-5 was used to diagnose schizophrenia. Socio-demographic data and blood samples were collected for both groups. The WBCs, absolute neutrophil count, absolute lymphocytic count, RDW%, MPV were significantly higher; Unlike hemoglobin, significantly lower in schizophrenic group ($P<0.05$). However, no significant differences between both groups regarding absolute monocyte and platelet Count. NLR was significantly higher while PLR and MLR were significantly lower in schizophrenic group ($p<0.05$). The MPV, RDW, PLR and NLR were independent predictors of subclinical inflammation in schizophrenic schizophrenia. Marked alteration of RDW, MPV, NLR and PLR reflecting the ongoing inflammatory process in schizophrenic patients and these changes during the course of the disease could be monitored to stand on the disease improvement.

1. Introduction

Schizophrenia (SZ) is a serious mental illness. Many hypotheses have been presented to explain its pathophysiology, the most notable of which are the serotonin (5-HT) theory and the inflammatory hypothesis (1).
The immune system may play an important role in the predisposition, onset, and progression of schizophrenia (2). Neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) and platelet to lymphocyte ratio (PLR) are innovative, low-cost, stable, reproducible, and suitable routine markers of the systemic immune response (3). Moreover, they have been investigated in schizophrenia, with higher inflammatory ratios seen in such patients when compared with healthy controls (4, 5).

Low-grade systemic inflammation is an ongoing process of the inflammatory response in attenuated form that has been discovered to be common in a variety of psychiatric diseases, including psychotic, mood, neurotic, and personality disorders (6). It is thought to be caused by neuroinflammation (7). Platelets also play a role in SZ pathogenesis via the serotonin pathway (8, 9, 10, 11) and the inflammation hypothesis (12). Platelets, interestingly, are also considered an inflammatory marker in SZ (12). Being stimulated in SZ, according to several researches (13, 14, 15). And become activated; create inflammatory mediators (16, 17, 18). Furthermore, higher platelets levels in SZ were linked to higher levels of proinflammatory cytokines. Platelets may play a key role in SZ pathogenesis, according to these findings (19, 20).

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It's well-known that stressful conditions, like inflammation, physiologically cause neutrophilia, lymphopenia and platelets changes with increasing in the MPV reflecting platelets activation (Zahorec 2001). Similar findings were observed in SZ patients (21, 22, 23).

Till now, there is no approved cut-off value for lymphocyte-ratios, RDW, and MPV that discriminate normal from abnormal values. So, The goal of this research was to find out optimal values defining inflammation status of these markers patients with SZ by comparing their hemogram parameters with age and sex-matched HC group.

2. Material and methods

A total of 90 subjects aged ≥ 16 were enrolled prospectively in this comparative cross-sectional study, conducted in the outpatient clinics of Psychiatric and Internal Medicine Departments, in a tertiary referral hospital, Sharika, Egypt, from March 2021 to April 2022: 45 known SZ patients diagnosed based on DSM-5 (24), and 45 apparently HCs without any psychiatric or medical disorder matched in age and sex, selected from the preoperative elective surgery consultation referred to the Internal Medicine clinic.

Venous Blood samples of all enrolled subjects were collected upon admission. Complete blood count (CBC) was measured by Sysmex XN-1000 automatic hematology analyzer (Sysmex Corporation, Kobe, Japan), after obtaining of a written informed consent from them or from the guardian of the patient.

Personal information was collected using a structured questionnaire for socio-demographic data after exclusion of comorbid mental disorders, intellectual disability, serious somatic disease that might change the blood count like (hematologic disease, recent transfusion, pregnancy, lactation and acute or chronic infection).

Finally, everyone who tested positive for blood dyscrasia was referred to a hematologist for further treatment.

Statistical analysis

The data was entered into a computer and statistically evaluated using the SPSS program (Statistical Package for Social Science) version 24 was used for data analysis. The Shapiro-Walk test was used to determine if the data had a normal distribution. The Chi square test ($\chi 2$) and Fisher exact were used as indicated to compare qualitative data, which were represented as frequencies and relative percentages. For normally distributed data, mean±SD (standard deviation) was used, and for non-normally distributed data, median and range were used. Also, to determine the difference between two groups' quantitative variables for normally and non-normally distributed variables, the independent T test and Mann Whitney *U* test were utilized respectively. In addition, Receiver operating characteristic (ROC) curve analysis was used to select CBC parameter threshold values. To find the independent predictors_of inflammation in SZ, a univariate and three different multivariate logistic regression analysis were applied because of the multicollinearity between dependent variables including PLR, NLR and MLR. were constructed. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05

3. Results

General characteristics

A total of 90 individuals were enrolled in the study: 45 SZ patients (mean age: 32.4±7.7), and 45 HCs (mean age: 33.0±4.2). The SZ group comprised 14 (31.1%) women and 31 (68.9%) men. The HCs group comprised 8 (17.8%) women and 37 (82.2%) men. No significant difference was detected in age and sex between the two groups (P = 0.868 and 0.141, respectively). The median duration of illness of SZ patients was 5.0 (0.1-21.0) months, 27 (60%) received atypical anti-psychotic while only 18 patients (40%) received combined typical and atypical antipsychotics. Regarding CBC parameters WBC, ANC, ALC, RDW%, MPV were significantly higher, Unlike HB was significantly lower in SZ group ($p < 0.05$). However no significant differences were detected between both groups regarding AMC and platelets. NLR was significantly higher while PLR and MLR were significantly lower in SZ group ($p<0.05$) (Table 1, Figure 1)

		Group				Total N=90		P
		Schizophrenia N=45		Healthy Control N=45				
Age, years		32.4±7.7		33.0±4.2		32.7±6.2		0.868
Sex	Female	14	31.1%	8	17.8%	22	24.4%	0.141
	Male	31	68.9%	37	82.2%	68	75.6%	
Duration of illness, Months		5.0 (0.1-21.0)						
Type of Anti-Psychotic	Atypical	27	60%					
	Combined	18	40%					
CBC Parameters								
WBC x10^9/L		9.3±2.7		6.4±1.3		7.8±2.5		**<0.001**
ANC x10^9/L		6.2±2.3		3.5±0.7		4.8±2.2		**<0.001**
ALC x10^9/L		2.4±0.8		2.0±0.5		2.2±0.7		**0.002**
AMC x10^9/L		0.5±0.2		0.6±0.2		0.5±0.2		0.627
Hb, g/dL		13.3 (10.0-15.9)		16.5 (14.2-19.1)		15.0 (10.0-19.1)		**<0.001**
RDW %		13.8 (12.1-17.9)		13.5 (12.1-15.3)		13.6 (12.1-17.9)		**0.016**
Platelets x10^9/L		233.4±61.9		249.8±44.7		241.6±54.3		0.15
MPV, fL		9.6 (8.0-11.7)		8.2 (6.7-9.7)		9.0 (6.7-11.7)		**<0.001**
Lymphocyte ratios								
NLR		1.9 (0.8-7.3)		1.3 (0.5-3.1)		1.6 (0.5-7.3)		**<0.001**
PLR		101.8 (41.2-247.3)		124.7 (73.8-275.0)		115.4 (41.2-275.0)		**0.001**
MLR		0.22 (0.05-0.77)		0.28 (0.11-0.83)		0.25 (0.05-0.83)		**0.013**

Table 1. Clinico-laboratory characteristics and systemic inflammatory markers of patients with schizophrenia and healthy controls ***(Qualitative variables were expressed as numbers and percentages and compared using Chi-square X^2 test, while, Continuous variables are described as mean± SD for normally disturbed variables and compared using Independent T test and median (range) for nonnormally disturbed variables and compared using Mann-Whitney test)***

ROC curve analysis of systemic inflammatory markers

The optimal cutoff value for the MPV, RDW, NLR, PLR, MLR were (>8.7, >13.5, >1.61, ≤87.03, ≤0.22) respectively, and had an AUC of (0.919, 0.647, 0.779, 0.699 and 0.652) respectively, with a sensitivity of (90.24%, 68.89%, 75.56%, 40% and 57.78%) respectively and a specificity of (82.22%, 60%, 77.78%, 97.78% and 68.89%); respectively.

The PPV was (82.2 %, 63.3%, 77.3%, 94.7%, and 65%); respectively. The NPV was (90.2%, 65.9%, 76.1%, 62% and 62%); respectively and P-value (P= <0.001, P=0.012, P<0.001, P<0.001 and P=0.008), respectively (Table 2; Figure 1).

Marker	Cut-off	Sensitivity % 95% CI	Specificity % 95% CI	PPV 95% CI	NPV 95% CI	AUC 95% CI	P
MPV, fL	>8.7	90.24 76.9 - 97.3	82.22 67.9 - 92.0	82.2 71.0 - 89.7	90.2 78.3 - 96.0	0.919 0.840 - 0.967	<0.001
RDW %	>13.5	68.89 53.4 - 81.8	60 44.3 - 74.3	63.3 53.4 - 72.1	65.9 54.0 - 76.0	0.647 0.540 - 0.745	0.012
NLR	>1.61	75.56 60.5 - 87.1	77.78 62.9 - 88.8	77.3 65.8 - 85.8	76.1 65.0 - 84.5	0.779 0.679 - 0.860	<0.001
PLR	≤87.03	40 25.7 - 55.7	97.78 88.2 - 99.9	94.7 71.5 - 99.2	62 56.1 - 67.5	0.699 0.593 - 0.791	<0.001
MLR	≤0.22	57.78 42.2 - 72.3	68.89 53.4 - 81.8	65 52.9 - 75.4	62 52.4 - 70.8	0.652 0.545 - 0.750	0.008

Table 2. Cross-tabulation between previous c-section history and mode of delivery

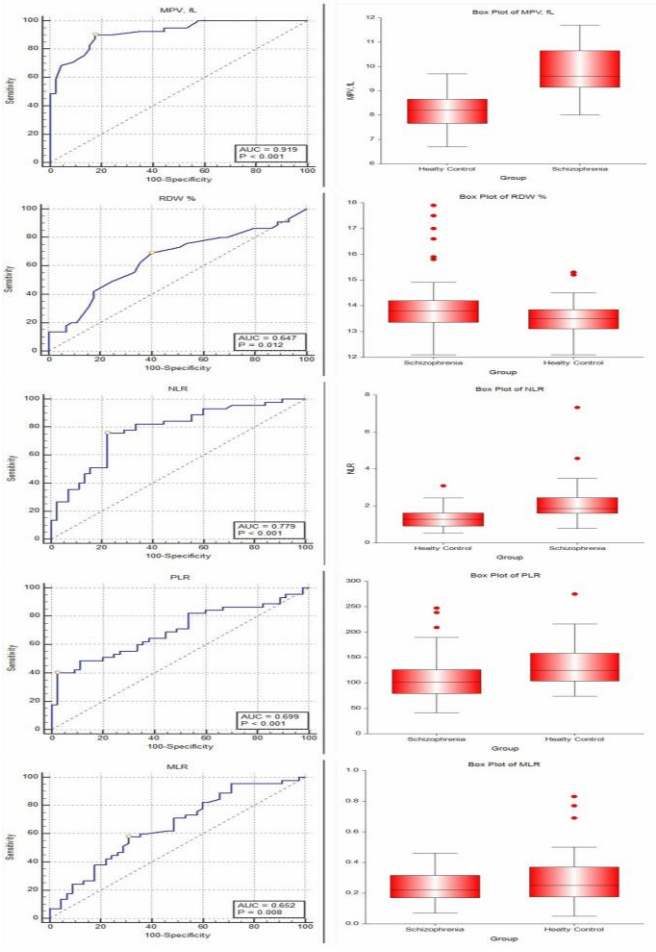

Figure 1. Receiver operating characteristic (ROC) curve of inflammatory markers; MPV, RDW, NLR, PLR and MLR to detect subclinical inflammation in schizophrenic patients [Left column], and Boxplot of their values in schizophrenic patients and healthy controls [Right column].

Uni- and multivariate logistic regression of systemic inflammatory markers

A binary logistic model was constructed to predict the ongoing subclinical inflammatory process in SZ patients compared to HCs using age, sex, MPV, RDW, NLR, PLR and MLR. The three different models were applied because of the multicollinearity between dependent variables including NLR, PLR and MLR. The MPV, RDW, PLR and NLR were independent predictors unlike and MLR (Table 3).

Logistic regression		Age	Sex Male vs Female	MPV Level >8.7	RDW Level >13.5	NLR Level >1.61	PLR Level ≤87.03	MLR Level ≤0.22
Univariate	P-value	0.657	0.145	<0.001	0.007	<0.001	0.002	0.021
	RR 95% C.I.	0.98 0.9-1.1	2.1 0.8-5.6	21.4 7.3-63.0	3.3 1.4-7.9	8.6 3.3-22.4	0.04 0.005-0.30	0.4 0.2-0.9
Multivariate Model 1*	P-value			<0.001	0.004	0.001		
	RR 95% C.I.			29.7 7.0-126.8	8.9 2.0-38.6	8.9 2.4-33.1		
Multivariate Model 2*	P-value			<0.001	0.017		0.01	
	RR 95% C.I.			34.9 8.0-151.5	5.7 1.4-24.0		0.04 0.003-0.45	
Multivariate Model 3*	P-value			<0.001	0.007			0.296
	RR 95% C.I.			31.7 8.2-122.1	6.4 1.6-24.9			0.54 0.17-1.72

Table 3. Logistic regression models analyzing the association between patients with schizophrenia and RDW, MPV, NLR, PLR, and MLR ***(RR: Relative Risk, 95% C.I.: 95% Confidence Interval * Three different models were applied because of the multicollinearity between dependent variables including NLR and MLR.)***

4. Discussion

In this study, we evaluated the subclinical inflammation status using CBC-derived inflammatory response markers in patients with SZ by comparing their hemogram parameters with age and sex-matched HC group. Ratios better than separate CBC parameters being more accurate and reliable than traditional parameters in measuring chronic peripheral inflammation in SZ patients (25).

Lymphocyte ratios are innovative, low-cost, stable, reproducible, and suitable routine markers of the systemic immune response with higher values in schizophrenia when compared with healthy controls (4, 5). Also, platelets are regarded as an inflammatory marker and become activated in SZ (12, 13, 14, 15).

We found higher NLR, WBCs, ANC, ALC, RDW, and MPV levels in patients with SZ compared to the HCs. Unlike, PLR, MLR and Hb were significantly lower in SZ. On performing multiple logistic regression analysis, only the MPV, RDW, PLR and NLR were found to be independent predictors for inflammation unlike and MLR.

Higher NLR mostly due to marked increase of ANC, comes in line with (26, 23). Similarly, to previous studies, they found increased inflammatory response in schizophrenia (21, 23, 27, 28).

In a prior study, schizophrenia was found to have higher NLR levels, neutrophil numbers, and lower lymphocyte numbers than the control group (21). In schizophrenia, Pro-inflammatory markers are known to be higher (27) and anti-inflammatory biomarkers to be lower compared to control subjects (28).

Regarding our findings that SZ patients had significantly reduced MLR

and PLR due to significantly higher ALC, but no significant difference in AMC or platelets.

This in agree with serdarevic et al (29) and in contrast with (26, 23) who reported higher MLR and PLR in SZ patients.

Regarding PC we found that, there was no significant difference between SZ patients and HCs, this finding was in contrast with (26, 23) that found increase PC in SZ group.

In SZ, platelets have already been identified as an inflammatory marker (12). PLATELETS in first-episode schizophrenia (FES) patients were considerably higher than that in healthy controls (HCs) in the YU et al study, which contradicted prior findings (12). It is widely accepted that platelets store more than 99 percent of serotonin in the blood, with the remaining 1% being soluble in plasma (30, 31), and that platelet-associated 5-HT levels in SZ patients are higher than those in healthy people (32, 33). Furthermore, decreased PC was observed in SZ during hospitalization and for up to six months after outpatient treatment (29, 34).

Also, we found that MPV was significantly higher while HB was significantly lower in SZ patients than HCs. This is in line with (26). In our study the optimal cutoff value for the MPV was >8.7 had an AUC of 0.919 (95% CI:0.840 to 0.967) with a sensitivity of 90.24% (95% CI:76.9 - 97.3%) and a specificity of 82.22% (95% CI:67.9 - 92.0%) and ($p<0.001$). While in Almış and Eğilmez study, the optimal cutoff value for the MPV level was 8.17 fL, and its sensitivity and specificity for the diagnosis of SZ were 68 and 64%, respectively. The AUC of PCT levels for SZ was 0.632 (95% CI: 0.538-0.725, P=.008) (35).

Platelet volume is a feature that reflects activity. Platelets with a larger volume have more granules and are more metabolically and enzymatically active than those with a lower volume (36). Platelet a-granules store a variety of proteins that regulate neuroinflammation, including high-mobility Group Box-1, interleukin-1, and heat shock proteins. These proteins could be released from platelets after activation and engage in inflammatory responses (37, 38, 39). FES patients had significantly higher MPV levels than HCs (26).

Regarding RDW, it was significantly higher in SZ patients than HCs with median RDW% 13.8 (range; 12.1-17.9%). serdarevic et al and Ayyildiz et al, also reported higher RDW levels; 14.1±2.8 and 14.14±1.16%, respectively (29, 40). The proinflammatory cytokines downregulate erythropoietin receptor expression, suppress erythropoietin gene expression, inhibit proliferation of erythroid progenitor cells, and decrease erythrocyte lifespan. Therefore, inflammation may contribute to increased RDW values by inhibiting responses to erythropoietin or the production of erythropoietin and shortening red blood cell (RBC) survival. Therefore, increased RDW, which is an inflammatory marker, may be a significant finding in patients with schizophrenia (41).

Finally, our three different multiple logistic regressions models illustrated that increase of MPV, RDW, NLR and decrease of PLR were independent predictors of subclinical inflammatory process in schizophrenia. This could be due to the interplay between MPV, RDW, and the key component of these ratios; neutrophil, platelet and lymphocyte that plays an important role in inflammation.

Despite the strength of our study; having relatively reasonable prospectively collected sample that include all CBC-derived inflammatory parameters, we have certain limitations as the substance abuse and the antipsychotics effect could not be excluded. Moreover, other confounding factors that affect blood components like smoking, ethanity, obesity, diet and exercise weren't taken into account. Thus, further larger sample multicenter studies are needed to study the causal relationship between these confounding factors and subclinical inflammatory process in schizophrenia and focus on the possible role of anti-inflammatory drugs in improving the prognosis of these patients. In conclusion, Marked alteration of RDW, MPV, NLR and PLR reflecting the ongoing inflammatory process in schizophrenic patients and these changes during the course of the disease could be monitored to stand on the disease improvement.

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