Original Article

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Relationship of PLR, NLR and LMR with Metabolic Syndrome in Schizophrenic Patients on Antipsychotics: A Longitudinal Case-control Study

Psychiatry/Mental Health Section

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ABSTRACT

Introduction: Cytokines are the small cell signalling proteins like granulocytes, lymphocytes, monocytes, etc. which may indirectly play a role in the pathophysiology of schizophrenia via inflammation. Neutrophil-to-Lymphocyte Ratio (NLR), Lymphocyte-to-Monocyte Ratio (LMR) and Platelet-to-Lymphocyte Ratio (PLR) are consistently used as a biomarkers for the innate immunity. Metabolic syndrome has been established as a serious public health concern over the last decade with increased morbidity associated with it. However, data regarding changes in LMR and PLR in metabolic syndrome is sparse. Therefore, the relationship between metabolic syndrome and raised inflammatory markers is not established.

Aim: To find out the relationship between inflammatory markers and metabolic syndrome in patients of schizophrenia and normal population.

Materials and Methods: A longitudinal case-control study was conducted in the Department of Psychiatry, Sanjay Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India, between February 2019 and January 2020. The study consisted of 84 schizophrenic patients from Inpatient and Outpatient Departments and 100 healthy controls from the general population, and data were collected using semi-structured proforma. Participants were evaluated for Complete Blood Count (CBC), parameters of metabolic syndrome (systolic and diastolic blood pressure; high density lipoprotein; triglycerides; fasting blood glucose; waist circumference) and severity of symptoms using Brief Psychiatric Rating Scale (BPRS). Data was analysed using IBM Statistical Package for the Social Sciences (SPSS) version 22.0 by Student's t-test, one way Analysis of Variance (ANOVA), repeated measure ANOVA, Spearman's rho correlation and linear regression analysis.

Results: The mean age of cases and controls was 31.4±11.9 years and 35.4±14.1 years, respectively. There were 54 (64.3%) males and 30 (35.7%) females in cases and 62 (62%) males and 38 (38%) females in controls. There was a significant difference between cases and controls for LMR, and NLR at baseline and four months (p-value <0.01). There a was significant difference between two antipsychotics group for NLR and PLR at baseline, two months, and four months (p-value <0.01) with moderate to large effect size. There was a significant correlation between metabolic syndrome and LMR, NLR and PLR for cases as well as controls (p-value <0.05).

Conclusion: The study established the alteration of NLR, LMR and PLR in patients of schizophrenia, and also established a relationship between MetS and inflammatory markers which suggested some common pathway between inflammation, metabolic syndrome and schizophrenia.

Keywords: Blood parameters, Lymphocyte-to-monocyte ratio, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Risk factor

INTRODUCTION

Various hypothesis have been proposed to explain the pathophysiology of schizophrenia, but still, not closer to the finish, including abnormalities in dopaminergic, glutamatergic, GABAergic, and cholinergic neurotransmitter systems [1-4]. Various genetic susceptibility factors like Neuregulin 1 (Nrg1), Disrupted-in-Schizophrenia-1 (DISK1), etc [5]. Emerging evidence highlights the role of inflammation in the pathophysiology of schizophrenia [6,7] as corroborated by the alteration of acute phase protein levels [8]. Cytokines are the small cell signalling proteins released by a vast array of cells like granulocytes, lymphocytes, monocytes, etc [9]. Cytokines may indirectly play a role in the pathophysiology of schizophrenia by inducing excessive activation of astrocytes and microglia, altering haematopoiesis and immune cell differentiation [10,11]. Furthermore, adjunctive treatment with non steroidal anti-inflammatory medications results in clinical improvements in patients with psychosis [12]. The Neutrophil-to-Lymphocyte Ratio (NLR), Lymphocyte-to-Monocyte Ratio (LMR) and Platelet-to-Lymphocyte Ratio (PLR) are easy laboratory markers to identify systemic inflammation.

Normal levels of NLR ranges between 0.78 and 3.53 [13]. Normal LMR ranges from 10.69±2.91 to 11.60±3.29 [14]. Increased LMR in psychosis patients has been reported by many studies [14-16]. Normal PLR ranges between 36.63 and 149.13 for males and 43.36 and 172.68 for females. LMR and PLR are age and gender dependent in the normal adult population [17,18]. An increase in NLR, LMR and PLR has been correlated with positive symptoms and overall heightening of psychosis [19,20]. NLR has also been found to be elevated in patients with Metabolic Syndrome (MetS), hypertension and smoking, which are significantly found in schizophrenia [21-25]. Conversely, it is elevated in patients with schizophrenia regardless of MetS or smoking [15,17]. However, data regarding changes in LMR and PLR in MetS are lacking.

Likewise, previous studies have reported an association of inflammation and metabolic syndrome in schizophrenia [26-29]. The incidence of inflammation and metabolic syndrome in schizophrenia is explained by tryptophan-kynurenine pathway which leads to microglia activation and astrocyte apoptosis, imbalance between inflammatory cytokines and adiponectin resulting in obesity and inactivation of phosphatidylinositol-3-hydroxykinase [27,30,31].

Many studies have also commented on the change in NLR upon exposure to antipsychotics with mixed results [7,17,32,33], which can be explained by a decrease in neutrophil count directly due to antipsychotic exposure or indirectly due to a decrease in inflammation [6,7,17,32-34]. However, the relationship between MetS and raised inflammatory markers is not established, neither, a causal relationship between change in these biomarkers and schizophrenia, nor is its clinical relevance. Additionally, very few studies have assessed all the three parameters in a case-control design [16,17,20,35].

To the best of the knowledge, this was a novel study focusing on the relationship between various inflammatory markers and indices of MetS in schizophrenia patients and comparing them with the controls. This was also the first clinical study assessing the effect of antipsychotics on various indices of inflammation and MetS in patients of schizophrenia. This study also assessed the longitudinal changes in various parameters over time, which was also a unique approach.

The aim of the study was to find out the relationship between inflammatory markers and metabolic syndrome in patients of schizophrenia and normal population. The primary objective was to assess NLR, LMR and PLR at baseline, two months and four months in patients of schizophrenia taking antipsychotics and healthy controls. The secondary objective was to evaluate metabolic parameters (blood pressure, fasting blood glucose, fasting triglyceride, high density lipoprotein and waist circumference) in patients of schizophrenia taking antipsychotics and healthy controls at baseline, two months and four months and, to find the correlation, if any, of inflammatory markers with MetS. Lastly, to compare age, gender, Brief Psychiatric Rating Scale (BPRS) score, metabolic and inflammatory parameters between two groups (schizophrenia patients taking antipsychotics vs healthy controls). The null hypothesis stated that there was no relation between inflammatory markers and metabolic syndrome in patients of schizophrenia taking antipsychotics.

MATERIALS AND METHODS

A longitudinal case-control study was conducted in the Department of Psychiatry, Sanjay Gandhi Memorial Hospital, Rewa, Madhya Pradesh, India, between February 2019 and January 2020. Study consisted of 84 schizophrenia patients and 100 controls. Ethical approval from the Institutional Ethical Committee was taken (letter no 9468/SS/PG/MC/2019). Cases meeting inclusion and exclusion criteria were recruited from inpatient and outpatient services of the department by purposive sampling in the first three months of the study and finally 84 schizophrenia patients and 100 controls met the study criteria. This was a duration bound study, during the study period study participants were recruited as per inclusion/exclusion criteria. Final sample was selected in the initial four months of the study.

Inclusion criteria: For cases, patients diagnosed of schizophrenia according to Diagnostic Criteria for Research of International Classification of Diseases 10th edition (ICD-10 DCR) [36], patients giving written informed consent (either themselves or legal guardians), aged between 15-60 years, patients who were drug naïve or drug-free for atleast six months were included in the study. For controls, healthy population were matched for age and gender; and selected using simple random sampling consecutive to the cases and, participants aged between 15-60 years of either sex and giving written informed consent were included in the study. Consent for participants aged below 18 years was taken from legal guardians.

Exclusion criteria: Participants who did not give informed consent, who had the requirement of emergency treatment and for whom white blood cell count (WBC) was <4000 or >11000/mm^3 were excluded from the study.

Study Procedure

Participants having metabolic syndrome at the onset of the study were not excluded; seven cases and 31 controls had metabolic syndrome at the onset. After a thorough clinical examination and obtaining informed consent, participants were admitted to the ward, if required. Baseline investigations of all study variables was done, inpatient or outpatient. The next assessment was done at two months and then at four months.

The neutrophil-to-lymphocyte ratio (NLR), Lymphocyte-to-monocyte ratio (LMR), and Platelet-to-lymphocyte ratio (PLR): NLR (normal 0.78-3.53) [13], LMR (normal 3.46 to 26.67) [16,17], and PLR (normal 36.63-149.13 for males, and between 43.36-172.68 for females) [16,18] were obtained by dividing absolute neutrophil count by absolute lymphocyte count; absolute lymphocyte count by absolute monocyte count; platelet count by absolute lymphocyte count; from Complete Blood Count (CBC) data. If the patient was admitted, data from baseline investigations was taken to minimise any effect of healthcare treatment. A similar process was repeated at two months and four months.

Metabolic syndrome: As per the National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) [36], the presence of any three out of the following five criteria was diagnosed as a metabolic syndrome: Systolic Blood Pressure (SBP) >130 mmHg, Diastolic Blood Pressure (DBP) >85 mmHg, fasting Triglyceride (TG) levels >150 mg/dL, Waist Circumference (WC) >40 inches for men or 35 inches for women, fasting High-density Lipoprotein (HDL) levels <40 mg/dL for men or 50 mg/dL for women [37] and Fasting Blood Sugar (FBS) >100 mg/dL.

Brief Psychiatric Rating Scale (BPRS): An 18-item scale was used to assess clinical features in patients with schizophrenia throughout the study [38]. It was a clinician-appraised scale with a good inter-rater reliability. Scoring is done from 1 (not present) to 7 (extremely severe), thus score range from 18-126. Score of 0 was given when item was not assessed. A total score of 31-40 implies mild psychiatric symptoms, 41-52 for moderately ill and ≥53 for severe symptoms.

Patients of schizophrenia were prescribed either first-generation antipsychotic (haloperidol) or second-generation antipsychotic (olanzapine) for three months depending upon the availability in the centre, patient's choice and clinical symptoms; whereas controls were given placebo (multivitamins).

STATISTICAL ANALYSIS

Statistical analysis was performed on IBM Statistical Package for the Social Sciences (SPSS) version 22.0. The normal distributions of variables were examined visually by histogram. Descriptive statistics of variables were presented in mean±standard deviation. Student t-test (two-tailed) and one-way ANOVA were used to compare means in variables with normal distribution. Changes in variables between groups (with and without MetS) at baseline, two months, and at four months were assessed with repeated measure Analysis of Variance (ANOVA). Correlation between variables was assessed using Spearman's rho correlation. Furthermore, linear regression analysis was applied to analyse predictors of MetS at each visit (baseline, two months, and four months). A p-value <0.05 was considered statistically significant.

RESULTS

The general characteristics of the study population are shown in [Table/Fig-1]. Both cases and controls are matched in age and gender. BPRS score of cases showed improvement over four months.

[Table/Fig-2a,b] compared MetS parameters and various variable ratios between cases and controls with and without the presence of MetS at various time points. [Table/Fig-2c] described the difference in means of MetS and inflammatory indices between cases and controls. In [Table/Fig-2a], there was significant difference between patients with and without metabolic syndrome for LMR, NLR and

Characteristics		Cases (n=84) (Mean±SD)	Controls (n=100) (Mean±SD)
Age (years)		31.4±11.9	35.4±14.1
Gender	Males, n (%)	54 (64.3)	62 (62)
	Females, n (%)	30 (35.7)	38 (38)
BPRS score (Baseline)		66.66±6.31	-
BPRS score (at 2 months)		48.3±10.36	-
BPRS score (at 4 months)		34.33±11.1	-

[Table/Fig-1]: General characteristics of the study population.

PLR at baseline and two months, whereas all the factors were significantly different at four months. On the contrary, NLR and PLR were significantly different for all time points in controls [Table/Fig-2b]. LMR was significantly different for cases vs controls at all time points [Table/Fig-2c].

blood indices between First-generation Antipsychotics (FGA) and Second-generation Antipsychotics (SGA) was described in [Table/Fig-6]. A repeated measures ANOVA with a Greenhouse-Geisser correction was used to determine difference in variables between time points. Repeated measure ANOVA determined that for cases, mean NLR [F (1.869,1)=6.016, p-value=0.003}, mean PLR {F-value (1.995,1)=3.091, p-value=0.048} and mean LMR {F-value (1.599, 1)=26.60, p-value <0.001} differed significantly between time points.

There was a significant correlation between inflammatory markers and MetS at all time points [Table/Fig-7]. At baseline, there was a strong positive relationship between MetS and PLR, NLR for cases as well as for controls, which remained in follow-up. However, there was a weak association with LMR in the control population.

Variables	At baseline					At 2 months					At 4 months				
	MetS absent (n=77)	MetS present (n=7)	F value	p-value	Eta-squared	MetS absent (n=64)	MetS present (n=20)	F value	p-value	Eta-squared	MetS absent (n=52)	MetS present (n=32)	F value	p-value	Eta-squared
LMR	5.89	12.5	33.27	**<0.01**	0.289#	6.23	16.12	174.38	**<0.01**	0.680#	6.88	21.56	216.72#	**<0.01**	0.725
NLR	2.28	3.86	28.96	**<0.01**	0.261#	2.39	4.45	63.62	**<0.01**	0.437#	2.33	3.38	25.47#	<0.01	0.237
PLR	83.66	162.84	35.03	**<0.01**	0.299#	80.50	171.00	76.18	**<0.01**	0.482#	83.20	124.27	17.01#	<0.01	0.172

[Table/Fig-2a]: Metabolic syndrome and blood indices in cases (n=84) over four months.
Repeated measure ANOVA; Highlighted p-value is statistically significant (p<0.05); NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio

Variables	At baseline					At 2 months					At 4 months				
	MetS absent (n=69)	MetS present (n=31)	F value	p-value	Eta-squared	MetS absent (n=69)	MetS present (n=31)	F value	p-value	Eta-squared	MetS absent (n=69)	MetS present (n=31)	F value	p-value	Eta-squared
LMR	4.48	4.50	0.00	0.949	0.000	4.53	4.89	0.79	0.377	0.008	4.92	15.94	4.94	**0.028**	0.048
NLR	2.37	6.27	32.86	**<0.01**	0.251	2.68	4.64	23.87	**<0.01**	0.196	2.75	6.59	23.90	**<0.01**	0.196
PLR	83.97	147.03	31.98	**<0.01**	0.246	84.37	149.54	32.76	**<0.01**	0.251	86.75	163.90	33.47	**<0.01**	0.255

[Table/Fig-2b]: Metabolic syndrome and blood indices in controls (n=100) over four months.
Repeated measure ANOVA; NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio

Variables	At baseline		At 2 months		At 4 months	
	t-value	p-value	t-value	p-value	t-value	p-value
LMR	6.11	**<0.01**	15.42	**<0.01**	4.49	**<0.01**
NLR	2.44	**0.029**	0.39	0.69	2.99	**0.005**
PLR	0.94	0.688	1.35	0.35	2.13	0.065

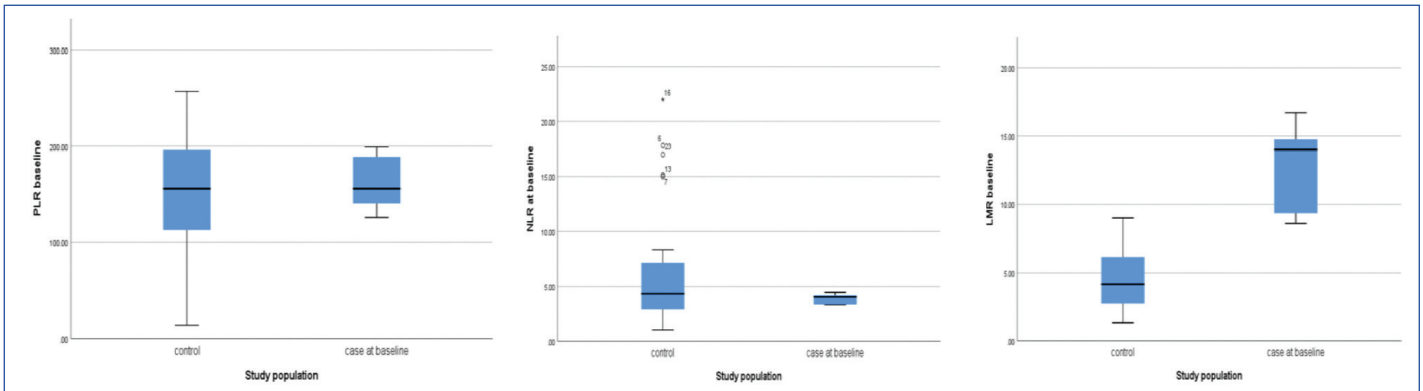
[Table/Fig-2c]: Comparison of means between cases and control in participants with metabolic syndrome.
Student t-test; NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio

[Table/Fig-3,4,5] are boxplots that compared NLR, LMR and PLR at baseline, two months and four months. The range of most indices in control group was more than cases. However, both groups have comparable median values at baseline and two months, but different at four months. A comparison of MetS and

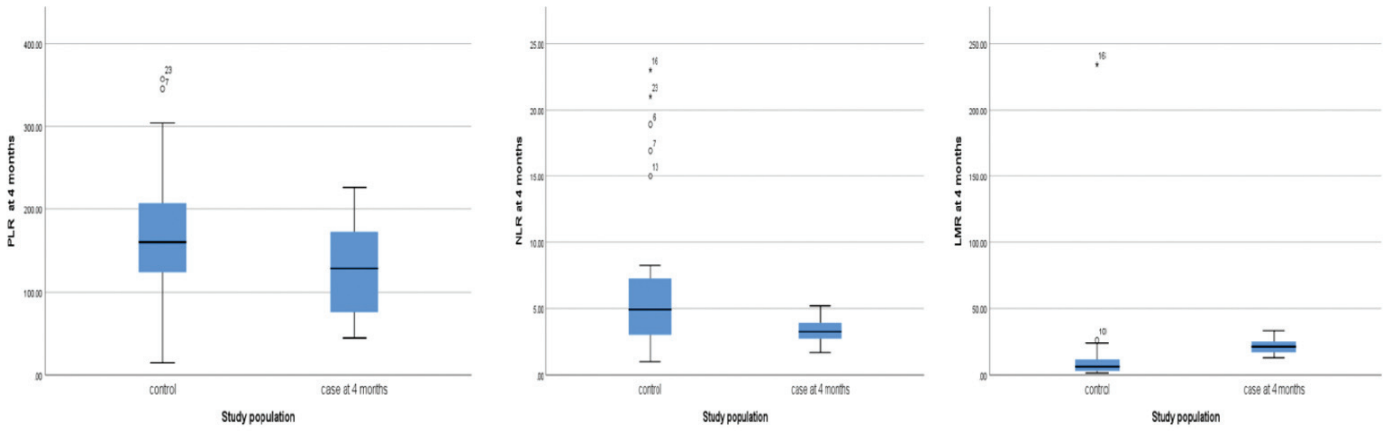
[Table/Fig-8] described predictors for NLR, LMR, and PLR at baseline, two months, and four months for cases as well as for controls. LMR was a predictor for NLR at all time points for cases as well as for controls, however, for cases, LMR was predicted by DBP, SBP, and RBS, and by NLR, PLR, and SBP for controls. PLR, in turn, was predicted by NLR for cases and by NLR as well as LMR for controls.

DISCUSSION

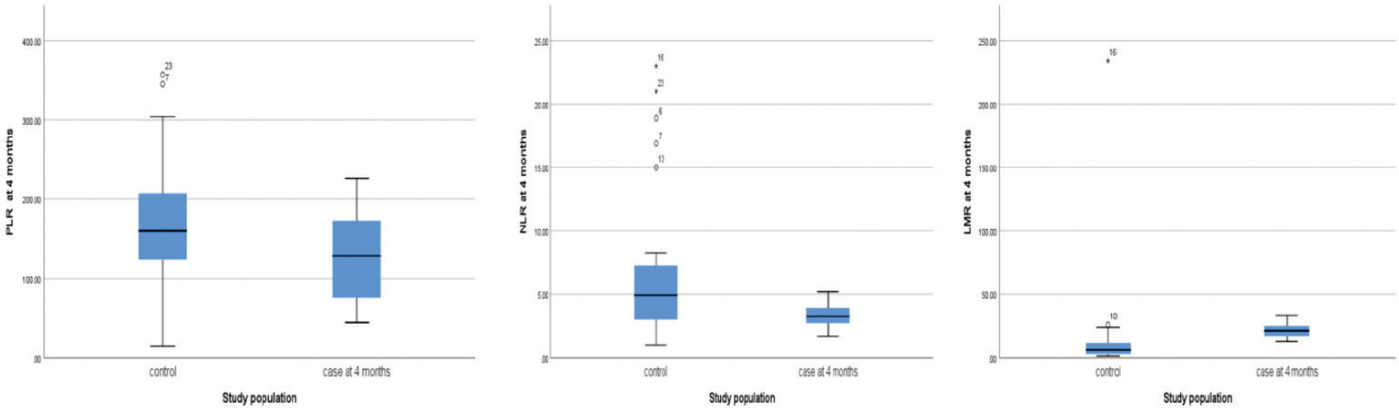
Cardiovascular causes turn out to be important cause of death among schizophrenia patients. These patients have higher propensity to develop metabolic syndrome. Use of antipsychotic may potentiate early development of metabolic syndrome in these patients. It is also found that inflammatory markers are raised in patients of schizophrenia. Inflammatory markers are helpful in early



[Table/Fig-3]: Blood indices in cases vs controls at baseline.



[Table/Fig-4]: Blood indices in cases vs controls at 2 months.



[Table/Fig-5]: Blood indices in cases vs controls at 4 months.

Variables	At baseline					At 2 months					At 4 months				
	FGA (n=42)	SGA (n=42)	F value	p-value	Eta-squared	FGA (n=42	SGA (n=42)	F value	p-value	Eta-squared	FGA (n=42)	SGA (n=42)	F value	p-value	Eta-squared
LMR	6.47	6.42	0.0	0.9	0.00	7.78	9.38	2.0	0.15	0.02	10.113	14.84	7.1	**<0.01**	0.08*
NLR	2.16	2.66	7.8	**<0.01**	0.08#	2.42	3.34	11.25	**<0.01**	0.12*	2.3126	3.1615	15.99	**<0.01**	0.16#
PLR	76.3514	104.168	11.2	**<0.01**	0.121*	84.12	119.986	9.54	**<0.01**	0.104*	80.2072	117.495	14.48	**<0.01**	0.150#

[Table/Fig-6]: Blood indices in cases (n=84) divided into antipsychotics subgroup (over four months).
Repeated measure ANOVA; NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; *Moderate effect size; #Large effect size

Spearman's rho		Cases			Controls		
		PLR	NLR	LMR	PLR	NLR	LMR
MetS at baseline	Correlation coefficient	0.433**	0.441**	0.412**	0.466**	0.481**	-0.023
MetS at 2 months	Correlation coefficient	0.632**	0.609**	0.693**	0.465**	0.422**	0.082
MetS at 4 months	Correlation coefficient	0.389**	0.518**	0.817**	0.468**	0.393**	0.184

[Table/Fig-7]: Correlation between Metabolic syndrome and inflammatory markers.
**Correlation is significant at the 0.01 level (2-tailed). NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; METs: Metabolic syndrome

Variables	Cases				Control			
	Predictors in model	Adjusted R^2	F-value	p-value of model	Predictors in model	Adjusted R^2	F-value	p-value of model
NLR_0	PLR_0, RBS_0	0.473	36.27	**<0.01**	PLR_0, WC_0	0.371	30.159	**<0.01**
NLR_2	PLR_2, RBS_2	0.604	64.27	**<0.01**	PLR_2	0.498	99.38	**<0.01**
NLR_4	PLR_4, RBS_4	0.244	14.425	**<0.01**	PLR_4, LMR_4	0.705	119.421	**<0.01**
LMR_0	DBP_0	0.254	29.22	**<0.01**	PLR_0	0.034	29.394	**<0.01**
LMR_2	DBP_2, SBP_2 RBS_2	0.560	36.168	**<0.01**	PLR_2, SBP_2	0.088	5.748	**<0.01**
LMR_4	DBP_4, HDL_4 RBS_4	0.801	112.13	**<0.01**	NLR_4, PLR_4, DBP_4	0.583	47.137	**<0.01**
PLR_0	NLR_0, TG_0	0.466	37.24	**<0.01**	SBP_0, NLR_0	0.034	29.394	**<0.01**
PLR_2	NLR_2, SBP_2	0.64	74.77	**<0.01**	NLR_2, LMR_2, SBP_2	0.583	47.132	**<0.01**
PLR_4	NLR_4, TG_4	0.215	12.37	**<0.01**	NLR_4, LMR_4, DBP_4	0.68	71.001	**<0.01**

[Table/Fig-8]: Linear regression analysis for predictors in cases vs control.
Subscript in blood indices: 0=at baseline; 2=at two months; 4=at four months; NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; HDL: High density lipoprotein; TG: Triglyceride; RBS: Random blood sugar; WC: Waist circumference

identification of metabolic syndrome, hence increase in inflammatory markers may help in early identification of metabolic syndrome and its treatment. This case-control study was conducted to assess whether there was any relationship of PLR, NLR, and MLR with metabolic syndrome in schizophrenic patients on antipsychotics. The study's primary findings included the following: (i) Cases with MetS had significantly larger values for PLR, NLR and LMR at all time points with moderate to large effect sizes and (ii) There was a significant relationship between MetS and inflammatory indices for cases as well as for controls.

Metabolic syndrome has been established as a serious public health concern over the last decade with increasing morbidity associated with it [39-42]. Relationship between MetS and low-grade inflammation has been established [21,22,43,44]. Various authors have hypothesised a vicious cycle of systemic inflammation, hypoxia, oxidative stress and coagulation [45]. Genetic susceptibility along with uncontrolled activities of the proinflammatory cytokine and microglial activation with impaired neurotransmitter function in the central nervous system are all thought to play a role in the pathophysiology of schizophrenia and subsequent degeneration [15,46]. NLR was found elevated in schizophrenic patients when compared with control populations in previous studies also [7,47,48]. Mazza MG et al., also observed a significant elevation of NLR, PLR, and LMR in non effective psychotic patients which was similar to the present study [20]. Similar to previous studies on the effect of antipsychotics and NLR ratio, the NLR values from baseline and first blood count showed significant differences with NLR on two months and four months follow-up [49]. Akboga MK et al., also reported PLR as an indicator of metabolic syndrome [41]. Similar to Lasić D et al., Na KS et al., Leonard BE et al., etc. this study also reported association of PLR, NLR and LMR in patients of schizophrenia with metabolic syndrome [26-28]. Contrary to this study, Miller BJ et al. and Kelly CW et al., reported white blood cell counts to be the predictor of MetS [8,29].

Limitation(s)

This was a single-centre study with a limited patient profile included in the study. Cases and controls were matched for age and gender, however, other demographic factors like socio-economic status, diet, locality, family history might have acted as confounders. Also, almost 30% of controls had MetS at enrolment, which may have altered the outcome for the control population. This study simultaneously assessed the effect of antipsychotics and MetS on inflammatory indices, which may have been a confounding factor in itself. Furthermore, direction of difference cannot be calculated as two-tailed Student's t-test was used.

CONCLUSION(S)

The study cements the alteration of NLR, LMR and PLR in patients of schizophrenia, and also establishes relationship between MetS and inflammatory markers which suggests some common pathways between inflammation, metabolic syndrome and schizophrenia, hence rejecting the null hypothesis. However, NLR, LMR and PLR were increased in significant number of controls with metabolic syndrome, which further emphasises their relation with metabolic syndrome. As is evidenced in this study, metabolic syndrome or few of its parameters are co-morbid with schizophrenia especially in patients on antipsychotics. Further studies need to be planned in patients with schizophrenia with appropriate matching with controls. Additionally, more longitudinal studies need to be planned with participants free of MetS at baseline. More comprehensive studies can be planned to assess inflammatory markers in different populations of schizophrenic patients. Further elaboration on the effect of antipsychotics on inflammatory markers can be planned.

REFERENCES

[1] Lakhan SE, Vieira KF. Schizophrenia pathophysiology: Are we any closer to a complete model? Annals of General Psychiatry. 2009;8(1):12.
[2] Deng C, Dean B. Mapping the pathophysiology of schizophrenia: Interactions between multiple cellular pathways. Frontiers in Cellular Neuroscience. 2013;7. Available from: https://www.frontiersin.org/articles/10.3389/fncel.2013.00238.
[3] Gibbons AS, Scarr E, Boer S, Money T, Jeon WJ, Felder C, et al. Widespread decreases in cortical muscarinic receptors in a subset of people with schizophrenia. International Journal of Neuropsychopharmacology. 2013;16(1):37-46.
[4] Benes FM. Neural circuitry models of schizophrenia: is it dopamine, GABA, glutamate, or something else? Biol Psychiatry. 2009;65(12):1003-05.
[5] Karam CS, Ballon JS, Bivens NM, Freyberg Z, Girgis RR, Lizardi-Ortiz JE, et al. Signaling pathways in schizophrenia: Emerging targets and therapeutic strategies. Trends in Pharmacological Sciences. 2010;31(8):381-90.
[6] Sandberg AA, Steen VM, Torsvik A. Is elevated neutrophil count and neutrophil-to-lymphocyte ratio a cause or consequence of schizophrenia?-A scoping review. Frontiers in Psychiatry. 2021;12:728990.
[7] Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, et al. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatr Danub. 2014;26(3):220-25.
[8] Miller BJ, Culpepper N, Rapaport MH. C-reactive protein levels in schizophrenia: A review and meta-analysis. Clin Schizophr Relat Psychoses. 2014;7(4):223-30.
[9] Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: Receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2016;138(4):984-10.
[10] Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. Journal of Neuroinflammation. 2013;10(1):816.
[11] Karageorgiou V, Milas GP, Michopoulos I. Neutrophil-to-lymphocyte ratio in schizophrenia: A systematic review and meta-analysis. Schizophr Res. 2019;206:04-12.
[12] Nitta M, Kishimoto T, Müller N, Weiser M, Davidson M, Kane JM, et al. Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: A meta-analytic investigation of randomized controlled trials. Schizophr Bull. 2013;39(6):1230-41.
[13] Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M, et al. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017;10(1):12.
[14] Moosazadeh M, Maleki I, Alizadeh-Navaei R, Kheradmand M, Hedayatizadeh-Omran A, Shamshirian A, et al. Normal values of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio among Iranian population: Results of Tabari cohort. Caspian J Intern Med. 2019;10(3):320-25.
[15] Yüksel RN, Ertek IE, Dikmen AU, Göka E. High neutrophil-lymphocyte ratio in schizophrenia independent of infectious and metabolic parameters. Nordic Journal of Psychiatry. 2018;72(5):336-40.
[16] Özdin S, Sarisoy G, Böke Ö. A comparison of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients- a retrospective file review. Nord J Psychiatry. 2017;71(7):509-12.
[17] Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Research. 2019;271:131-35.
[18] Wu L, Zou S, Wang C, Tan X, Yu M. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio in Chinese Han population from Chaoshan region in South China. BMC Cardiovascular Disorders. 2019;19(1):125.
[19] Zorrilla EP, Cannon TD, Kessler J, Gur RE. Leukocyte differentials predict short-term clinical outcome following antipsychotic treatment in schizophrenia. Biol Psychiatry. 1998;43(12):887-96.
[20] Mazza MG, Lucchi S, Rossetti A, Clerici M. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: A meta-analysis and systematic review. The World Journal of Biological Psychiatry. 2020;21(5):326-38.
[21] Mirhafez SR, Pasdar A, Avan A, Esmaily H, Moezzi A, Mohebati M, et al. Cytokine and growth factor profiling in patients with the metabolic syndrome. Br J Nutr. 2015;113(12):1911-19.
[22] Liu X, Zhang Q, Wu H, Du H, Liu L, Shi H, et al. Blood neutrophil to lymphocyte ratio as a predictor of hypertension. Am J Hypertens. 2015; 28(11):1339-46.
[23] Grieshober L, Graw S, Barnett MJ, Thornquist MD, Goodman GE, Chen C, et al. Methylation-derived neutrophil-to-lymphocyte ratio and lung cancer risk in Heavy smokers. Cancer Prev Res (Phila). 2018;11(11):727-34.
[24] Dieset I, Andreassen OA, Haukvik UK. Somatic comorbidity in Schizophrenia: Some possible biological mechanisms across the life span. Schizophr Bull. 2016;42(6):1316-19.
[25] Soleimani R, Shokrgozar S, Shekarriz-Fumani M, Jalali SM. Comparison of the metabolic syndrome risk factors in antipsychotic naïve and chronic schizophrenia patients. Arch Psych Psych. 2021;23(3):44-54.
[26] Na KS, Kim WH, Jung HY, Ryu SG, Min KJ, Park KC, et al. Relationship between inflammation and metabolic syndrome following treatment with paliperidone for schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(2):295-300.
[27] Leonard BE, Schwarz M, Myint AM. The metabolic syndrome in schizophrenia: Is inflammation a contributing cause? J Psychopharmacol. 2012;26(5 Suppl):33-41.
[28] Lasi D, Bevanda M, Bošnjak N, Uglešić B, Glavina T, Franić T. Metabolic syndrome and inflammation markers in patients with schizophrenia and recurrent depressive disorder. Psychiatr Danub. 2014;26(3):214-19.
[29] Kelly CW, McEvoy JP, Miller BJ. Total and differential white blood cell counts, inflammatory markers, adipokines, and incident metabolic syndrome in phase 1 of the clinical antipsychotic trials of intervention effectiveness study. Schizophrenia Research. 2019;209:193-97.

[30] Jin H, Meyer JM, Mudaliar S, Jeste DV. Impact of atypical antipsychotic therapy on leptin, ghrelin, and adiponectin. Schizophr Res. 2008;100(1-3):70-85.
[31] Demuro G, Obici S. Central nervous system and control of endogenous glucose production. Curr Diab Rep. 2006;6(3):188-93.
[32] Zhou X, Wang X, Li R, Yan J, Xiao Y, Li W, et al. Neutrophil-to-lymphocyte ratio is independently associated with severe psychopathology in schizophrenia and is changed by antipsychotic administration: A large-scale cross-sectional retrospective study. Front Psychiatry. 2020;11:581061. Available from: https://www.frontiersin.org/article/10.3389/fpsyt.2020.581061.
[33] De Hert M, Schreurs V, Vancampfort D, Van Winkel R. Metabolic syndrome in people with schizophrenia: A review. World Psychiatry. 2009;8(1):15-22.
[34] Stefanović V, Mihajlović G, Nenadović M, Dejanović SD, Borovcanin M, Trajković G, et al. The effect of antipsychotic drugs on nonspecific inflammation markers in the first episode of schizophrenia. Vojnosanit Pregl. 2015;72(12):1085-92.
[35] Zhu X, Zhou J, Zhu Y, Yan F, Han X, Tan Y, et al. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in schizophrenia. Australas Psychiatry. 2022;30(1):95-99.
[36] WHO. International classification of diseases-10 Diagnostic criteria for research of menatl and behavioural illness. [cited 2021 Oct 29]. Available from: https://www.who.int/classifications/icd/en/GRNBOOK.pdf.
[37] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97.
[38] Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep. 1962;10(3):799-12.
[39] Leclezio L, Jansen A, Whittemore VH, de Vries PJ. Pilot validation of the tuberous sclerosis-associated neuropsychiatric disorders (TAND) checklist. Pediatr Neurol. 2015;52(1):16-24.
[40] Arbel Y, Havakuk O, Halkin A, Revivo M, Berliner S, Herz I, et al. Relation of metabolic syndrome with long-term mortality in acute and stable coronary disease. American Journal of Cardiology. 2015;115(3):283-87.
[41] Akboga MK, Canpolat U, Yuksel M, Yayla C, Yilmaz S, Turak O, et al. Platelet to lymphocyte ratio as a novel indicator of inflammation is correlated with the severity of metabolic syndrome: A single center large-scale study. Platelets. 2016;27(2):178-83.
[42] Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-45.
[43] Vahit D, Akboga MK, Samet Y, Hüseyin E. Assessment of monocyte to high density lipoprotein cholesterol ratio and lymphocyte-to-monocyte ratio in patients with metabolic syndrome. Biomark Med. 2017;11(7):535-40.
[44] Cai D, Liu T. Inflammatory cause of metabolic syndrome via brain stress and NF-κB. Aging (Albany NY). 2012;4(2):98-115.
[45] Klöting N, Blüher M. Adipocyte dysfunction, inflammation and metabolic syndrome. Rev Endocr Metab Disord. 2014;15(4):277-87.
[46] Monji A, Kato T, Kanba S. Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. Psychiatry Clin Neurosci. 2009;63(3):257-65.
[47] Brinn A, Stone J. Neutrophil-lymphocyte ratio across psychiatric diagnoses: A cross-sectional study using electronic health records. BMJ Open. 2020;10(7):e036859.
[48] Çatak Z. Comparison of neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in patients with schizophrenia, bipolar and major depressive disorder. Int J Med Biochem. 2018 [cited 2022 Mar 12]. Available from: https://www.journalagent.com/ijmb/pdfs/IJMB-17363-RESEARCH_ARTICLE-CATAK.pdf.
[49] Dawidowski B, Grelecki G, Biłgorajski A, Podwalski P, Misiak B, Samochowiec J, et al. Effect of antipsychotic treatment on neutrophil-to-lymphocyte ratio during hospitalization for acute psychosis in the course of schizophrenia-A cross-sectional retrospective study. Journal of Clinical Medicine. 2022;11(1):232.

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