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Neutrophil/lymphocyte ratio is increased in the acute phase of schizophrenia and regardless the use and types of antipsychotic drugs

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Abstract

Background It has been found that patients with schizophrenia are often accompanied by concomitant changes in inflammation levels during acute exacerbations, and some studies have suggested that the inflammatory indices neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR) may be biomarkers of acute exacerbations in schizophrenia; however, few studies have simultaneously explored the differences in these inflammatory indices in the drug-free patients with schizophrenia in acute phase (DSA), medicated patients with schizophrenia in acute phase (MSA), medicated patients with schizophrenia in remission period (MSR), as well as the effects of different antipsychotic medications on inflammatory indices.

Method A total of 651 subjects including 184 healthy controls (HC), 167 DSA, 119 MSA, and 181 MSR were included in this study. Demographic and disease information was collected from each individual and venous blood was collected to detect immune cells and calculate the inflammatory indices NLR, PLR, and MLR, and statistical methods such as analysis of variance (ANOVA) and multiple comparisons were utilized to explore the alteration of these inflammatory indices under the influence of different antipsychotics and in HC, DSA, MSA, and MSR.

Results NLR was significantly higher in DSA and MSA than in HC after adjusting the confounders of sex, age, smoking, years of education, marital status, BMI, diabetes, and hypertension. PLR and MLR were not significantly different in patients with schizophrenia and in HC, and were not significantly different in patients with schizophrenia in any group. In MSA and MSR, NLR was positively correlated with disease duration and negatively correlated with the use of mood stabilizers.

Conclusions NLR was significantly increased in acute phase of schizophrenia, regardless of use of antipsychotic drugs, but not significantly increased in stable phase, which might be a promising biomarker for acute phase of schizophrenia.

Keywords Schizophrenia, Neutrophil/lymphocyte ratio, Immune cell, Antipsychotic medication, Mood stabilizers

Introduction

Schizophrenia is a very serious mental illness with a lifetime prevalence of about 1% worldwide [1, 2]. Patients with schizophrenia are often accompanied by significant mental abnormalities, cognitive deficits, and decline in social function and daily life ability [3]. Schizophrenia is

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one of the top ten causes of long-term disability in the world and places a heavy financial burden on families and society. The causes of schizophrenia are very diverse, and genetic, environmental, and social factors may all contribute to its onset [4]. The pathogenesis of schizophrenia is complex and remains inconclusive [1, 5, 6]. There are many evidences to suggest that the immune and inflammatory response may play an important role in the pathogenesis of schizophrenia, as many studies have shown that patients with schizophrenia, especially those in the acute phase, have significant abnormalities in the levels of inflammatory markers, cytokines [7–9]. Epidemiologic studies have also confirmed the association between schizophrenia and infections and systemic inflammation [10–12].

Inflammatory index neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR) and platelet/lymphocyte ratio (PLR) are commonly used in adults in recent years because of their low cost and simple calculation method [13]. Relevant studies have confirmed that the NLR level is significantly increased in patients with schizophrenia [14]. In addition, NLR, MLR and PLR levels are also significantly increased in patients with schizophrenia during relapse compared with those during remission [15]. Other studies have found that, in addition to schizophrenia, NLR and MLR of many patients with non-affective psychosis are significantly higher than those of healthy people, and different drug treatment status, diagnosis and environment have little effect on the results [16, 17]. The study by Bhikram et al. also found that NLR was significantly elevated in adult patients with schizophrenia, major depression, and bipolar disorder [18]. These findings collectively suggest that the abnormal elevation of NLR and other inflammatory indexes may not be a unique feature of a certain mental disorder, but may be the pathological process of brain dysfunction in many mental disorders. Moreover, some studies have also suggested that these immune system markers are related to the outcome of schizophrenia. For example, elevated white blood cell count, NLR, and C-reactive protein (CRP) levels at initial diagnosis are associated with high mortality in patients [19].

Although several studies have investigated changes in inflammatory indices in schizophrenia, many of these studies have not adequately adjusted for confounding factors [17]. In addition, most studies often only focus on the comparison between patients in the acute phase and healthy controls, and few studies have conducted comprehensive comparisons among drug-free patients with schizophrenia in acute phase (DSA), medicated patients with schizophrenia in acute phase (MSA), medicated patients with schizophrenia in remission period (MSR) [20–22]. And many of the current studies did not consider the effect of antipsychotics on inflammatory indices. It is well known that antipsychotic medications have a significant effect on a variety of immune cells. Therefore, it is necessary to conduct a comprehensive analysis of the changes of inflammatory indexes in patients at all stages of schizophrenia under the influence of different types of antipsychotic medications.

The main novelties of this study were as follows: (1) patients with schizophrenia were divided into DSA, MSA and MSR groups according to different disease stages and medications, and the changes of inflammatory index in each group were explored; (2) the effects of different types of antipsychotic medications on inflammatory index were explored; (3) models adjusted for different numbers of covariates were constructed to examine the changes of inflammatory indices in each group.

Methods

Participants

This study was approved by the Medical Ethics Committee of Affiliated Xiaoshan Hospital, Hangzhou Normal University (Zhejiang Xiaoshan Hospital) (Approval NO. 2024–004). All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This study was a retrospective cross-sectional study, and we did not perform additional treatments or examinations on any of the individuals, so signed informed consent was not required.

Individuals with schizophrenia in this study were recruited from inpatients in the Department of Psychiatry of Affiliated Xiaoshan Hospital, Hangzhou Normal University between 2020 and 2023. Subjects of HC group were recruited from the nearby community population who came to this hospital for health examination. Inclusion criteria for individuals with schizophrenia in this study included: (1) age ranged from 15 to 70 years old; (2) Chinese Han population; (3) meeting the diagnostic criteria for schizophrenia in the Structured Clinical Interview for DSM-IV (SCID) [23]; (4) drug-free was defined as no previous medication or a washout period of more than 1 month after discontinuation; (5) medicated individuals with schizophrenia was defined as taking stable doses of antipsychotics for more than one month. Exclusion criteria include: (1) history of infection or antimicrobial medication within previous month; (2) diagnosed with autoimmune diseases or have taken immunomodulatory drugs in the month prior to inclusion; (3) pregnant or lactating women.

The inclusion criteria for HC group were (1) and (2) of the inclusion criteria for subjects with schizophrenia, and

the exclusion criteria were the same as those for subjects with schizophrenia.

Collection of sociodemographic and treatment information

At the time of admission, the height and weight of individuals with schizophrenia were obtained by physical examination and body mass index (BMI) was calculated. The education level, smoking history, marital status, history of hypertension, history of diabetes, and duration of schizophrenia of subjects were obtained by asking patients or their family members and consulting clinical records.

Antipsychotic medication use in individuals with schizophrenia was collected and converted to chlorpromazine equivalent doses by the defined daily dose (DDD) method [24]. In addition, whether patients were taking mood stabilizers was also recorded.

The above information of individuals in HC group was collected from physical examination during the health checkup, as well as from questioning and inquiry of the past medical records.

Analysis of effect of antipsychotic medications on inflammatory indices

In MSA and MSR groups, individuals were further grouped according to the types of antipsychotic medications (clozapine vs without clozapine, typical vs atypical) to analyze the possible effects of the different antipsychotic drugs on the inflammatory index.

Collection of immune system indicators

Individuals were asked to fast after 8:00 p.m. the night before blood collection and to complete venous blood collection from 7:00 a.m.-9:00 a.m. Immune system indicators including counts of white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, red blood cells, hemoglobin, and platelets were collected for each subject. In addition, the inflammatory indices NLR (neutrophil count/lymphocyte count), PLR (platelet count/lymphocyte count), and MLR (monocyte count/lymphocyte count) were calculated. Blood samples were sent to the laboratory immediately after collection and tested within 4 h. These indicators were tested by using the BC-5180 CRP Automated Blood Cell Analyzer (Brand: Myriad, Country of origin: China), and all operations were performed in accordance with the manufacturer's instructions.

Statistical analysis

The process of this study is shown in Fig. 1. The one-way analysis of variance (ANOVA) was used to explore continuous variables that were significantly different between each group, bootstrapping sampling was performed and bias corrected accelerated 95% confidence interval (CI) was calculated. First, each variable was tested for homogeneity of variance, and variables that satisfied variance homogeneity were checked for significance by ANOVA results, variables that did not satisfy variance homogeneity were checked for significance by Welch Test and Brown-Forsythe Test, and they were considered significant only if both Welch Test and Brown-Forsythe Test were satisfied with P value < 0.05. Variables that satisfied and did not satisfy variance homogeneity were subjected to multiple comparisons between groups by Tukey Test and Games-Howell Test, respectively. The Chi-square Test was used to test the significance of categorical variables. Missing values in this study were filled using multiple imputation. In addition, three separate models were constructed by binary logistic regression analysis, including model 1 (without adjustment for covariates), model 2 (adjusted covariates: gender, age), and model 3 (adjusted covariates: gender, age, smoking, years of education, marital status, BMI, diabetes and hypertension), to explore the difference of NLR in each group. Finally, the factors which significantly associated with NLR in each group were separately explored by using Pearson correlation for normally distributed continuous or categorical variables and using Spearman correlation for non-normally distributed continuous variables. All statistical analyses in this study were completed through SPSS 25.0.

Results

General information of the individuals

A total of 651 individuals were included in the statistical analysis of this study, including 167 DSA patients, 119 MSA patients, 181 MSR patients, and 184 HCs. There were 12 cases with missing BMI values, accounting for 1.8%, and the remaining information was complete. As shown in Table 1, there were significant differences between the 4 groups in age, gender, smoking, years of education, marital status, BMI, history of hypertension, and diabetes (all $P < 0.05$).

Immune cell differences between individuals in each group

As shown in Table 2, the results of multiple comparisons showed that the white blood cell counts of HC ($t = -3.12$, $d = -0.33$, $P = 0.02$, 95%CI: -0.97 ~ -0.07) and MSR ($t = -3.21$, $d = -0.34$, $P = 0.01$, 95%CI: -1.00 ~ -0.08) were significantly lower than those of DSA, the neutrophils count of HC was significantly lower than those of DSA ($t = -5.16$, $d = -0.55$, $P < 0.001$, 95%CI: -1.06 ~ -0.32) and MSA ($t = -3.46$, $d = -0.41$, $P < 0.01$, 95%CI: -0.88 ~ -0.13), the neutrophils count of MSR ($t = -3.32$, $d = -0.36$, $P < 0.01$, 95%CI: -0.81 ~ -0.08) was significantly lower than that of DSA, the lymphocytes count

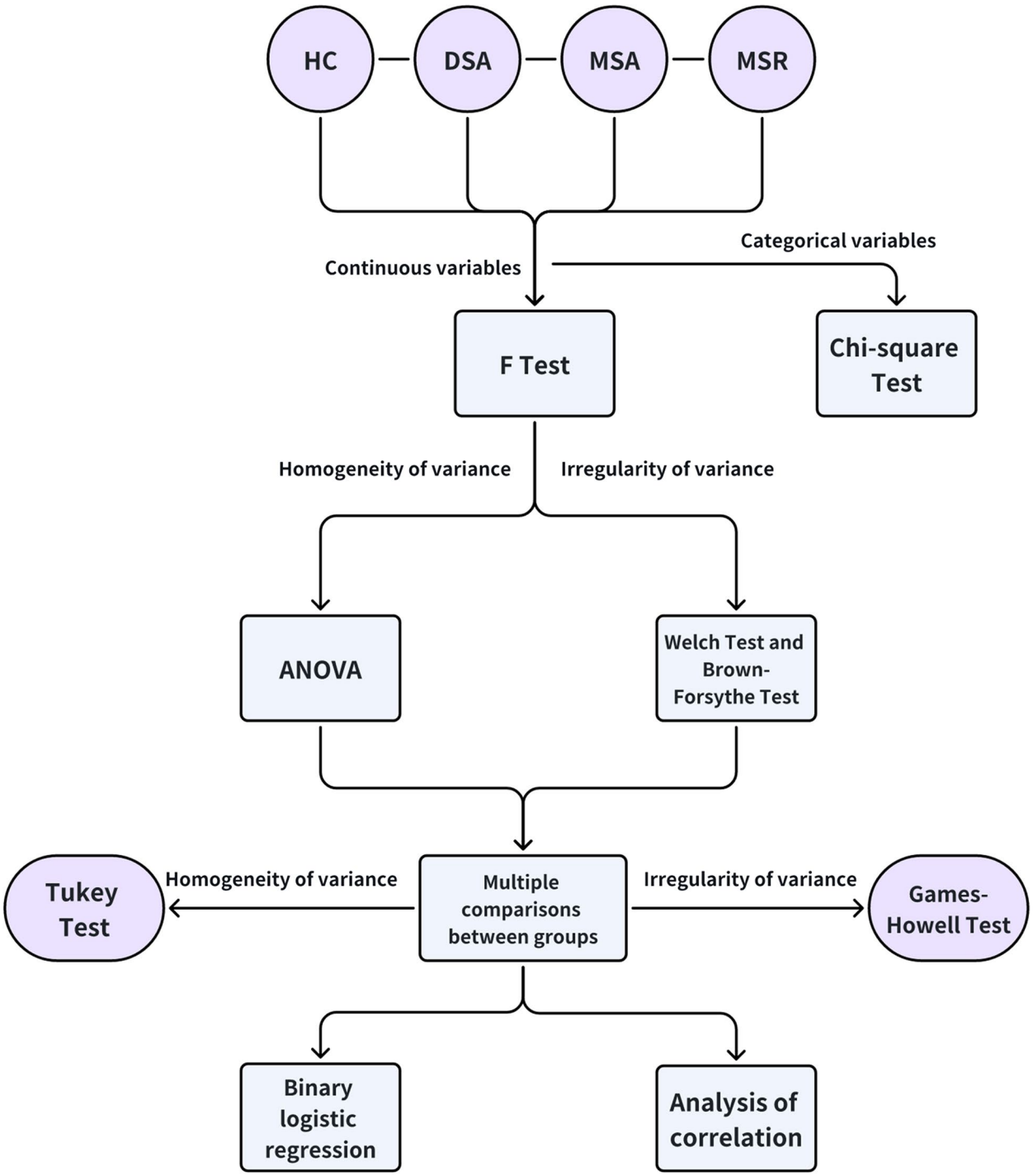

Fig. 1 Flow chart of this study. HC: healthy controls; DSA: drug-free patients with schizophrenia in acute phase, MSA: medicated patients with schizophrenia in acute phase, MSR: medicated patients with schizophrenia in remission period; ANOVA: analysis of variance

of HC ($t=3.87$, $d=0.41$, $P<0.001$, 95%CI: $0.10 \sim 0.49$) was significantly higher than that of MSR, the eosinophils count of MSR ($t=3.19$, $d=0.34$, $P=0.01$, 95%CI: $0.01 \sim 0.07$) was significantly higher than that of DSA, the basophils count of HC was significantly higher than those of DSA ($t=8.59$, $d=0.92$, $P<0.001$, 95%CI: $0.01 \sim 0.01$), MSA ($t=8.87$, $d=1.04$, $P<0.001$, 95%CI: $0.01 \sim 0.02$), and MSR ($t=8.37$, $d=0.88$, $P<0.001$,

Table 1 Sociodemographic and clinical characteristics of the participants

Variables	Total	Group				Corrected *P*-value
		Healthy controls	Drug-free schizophrenia patients with acute phase	Medicated schizophrenia patients with acute phase	Medicated schizophrenia patients with remission period	
N	651	184	167	119	181	
Age (years)	41.93 ± 12.42	34.78 ± 9.29	38.81 ± 11.65	42.53 ± 11.89	51.66 ± 9.74	< 0.001
Gender						< 0.001
Male, *n* (%)	270 (41.5%)	47 (25.5%)	61 (36.5%)	57 (47.9%)	105 (58.0%)	
Female, *n* (%)	381 (58.5%)	137 (74.5%)	106 (63.5%)	62 (52.1%)	76 (42.0%)	
Smoking						< 0.001
Yes, *n* (%)	99 (15.2%)	6 (3.3%)	24 (14.4%)	28 (23.5%)	41 (22.7%)	
No, *n* (%)	552 (84.8%)	178 (96.7%)	143 (85.6%)	91 (76.5%)	140 (77.3%)	
Years of education	12.27 ± 6.00	15.91 ± 1.36	10.32 ± 3.81	9.56 ± 3.72	12.15 ± 9.17	< 0.001
Marital status						< 0.001
Unmarried, *n* (%)	248 (38.1%)	30 (16.3%)	80 (47.9%)	48 (40.3%)	90 (49.7%)	
Married, *n* (%)	304 (46.7%)	151 (82.1%)	65 (38.9%)	52 (43.7%)	36 (19.9%)	
Divorced, *n* (%)	81 (12.4%)	3 (1.6%)	19 (11.4%)	15 (12.6%)	44 (24.3%)	
Widowed, *n* (%)	18 (2.8%)	0	3 (1.8%)	4 (3.4%)	11 (6.1%)	
BMI (kg/m^2)	23.87 ± 4.56	22.51 ± 4.16	23.17 ± 4.59	24.95 ± 4.70	25.15 ± 4.36	< 0.001
Diabetes						< 0.001
Yes, *n* (%)	62 (9.5%)	1 (0.5%)	6 (3.6%)	26 (21.8%)	29 (16.0%)	
No, *n* (%)	589 (90.5%)	183 (99.5%)	161 (96.4%)	93 (78.2%)	152 (84.0%)	
Hypertension						< 0.001
Yes, *n* (%)	92 (14.1%)	4 (2.2%)	13 (7.8%)	19 (16.0%)	56 (30.9%)	
No, *n* (%)	559 (85.9%)	180 (97.8%)	154 (92.2%)	100 (84.0%)	125 (69.1%)	
White blood cell count (*10^9/L)	6.01 ± 1.57	5.81 ± 1.45	6.33 ± 1.80	6.20 ± 1.48	5.79 ± 1.48	< 0.01
Neutrophils count (*10^9/L)	3.62 ± 1.28	3.28 ± 1.10	3.97 ± 1.50	3.79 ± 1.31	3.53 ± 1.09	< 0.001
Lymphocytes count (*10^9/L)	1.90 ± 0.74	2.06 ± 0.60	1.91 ± 0.99	1.87 ± 0.64	1.76 ± 0.62	< 0.01
Monocytes count (*10^9/L)	0.43 ± 1.95	0.32 ± 0.10	0.68 ± 3.84	0.39 ± 0.13	0.35 ± 0.13	> 0.05
Eosinophils count (*10^9/L)	0.12 ± 0.11	0.12 ± 0.11	0.10 ± 0.08	0.10 ± 0.09	0.14 ± 0.14	< 0.01
Basophils count (*10^9/L)	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	< 0.001
Red blood cells count (*10^12/L)	5.34 ± 21.27	4.62 ± 0.40	4.53 ± 0.53	9.15 ± 49.73	4.32 ± 0.56	> 0.05
Hemoglobin (g/L)	135.89 ± 17.02	137.74 ± 14.28	134.83 ± 19.58	137.62 ± 19.63	133.83 ± 14.88	> 0.05
Platelets count (*10^9/L)	231.88 ± 59.88	251.46 ± 56.18	232.13 ± 55.08	225.26 ± 55.83	216.10 ± 65.00	< 0.001
Neutrophil/lymphocyte ratio	2.11 ± 1.07	1.69 ± 0.65	2.33 ± 1.15	2.29 ± 1.24	2.24 ± 1.10	< 0.001
Platelet/lymphocyte ratio	133.43 ± 52.74	129.65 ± 40.92	134.24 ± 45.87	133.95 ± 65.27	136.17 ± 59.88	> 0.05
Monocyte/lymphocyte ratio	0.23 ± 0.67	0.16 ± 0.06	0.32 ± 1.32	0.24 ± 0.13	0.22 ± 0.08	> 0.05
Number of types of antipsychotic medications	1.54 ± 0.53			1.52 ± 0.57	1.55 ± 0.51	> 0.05
Dose of antipsychotic medications (mg)	432.74 ± 253.28			362.42 ± 269.94	478.98 ± 231.02	< 0.001

Data presented as n or mean ± standard deviation. The dose of antipsychotic medication was converted to equivalent chlorpromazine dose

Table 2 Immune cell differences between subjects in each group

Variables	Group		t	d	Corrected *P*-value	95%CI
White blood cell count	HC	DSA	-3.12	-0.33	0.02	(-0.97,-0.07)
	MSR	DSA	-3.21	-0.34	0.01	(-1.00,-0.08)
Neutrophils count	HC	DSA	-5.16	-0.55	< 0.001	(-1.06,-0.32)
		MSA	-3.46	-0.41	< 0.01	(-0.88,-0.13)
	MSR	DSA	-3.32	-0.36	< 0.01	(-0.81,-0.08)
Lymphocytes count	HC	MSR	3.87	0.41	< 0.001	(0.10,0.49)
Eosinophils count	MSR	DSA	3.19	0.34	0.01	(0.01,0.07)
Basophils count	HC	DSA	8.59	0.92	< 0.001	(0.01,0.01)
		MSA	8.87	1.04	< 0.001	(0.01,0.02)
		MSR	8.37	0.88	< 0.001	(0.01,0.01)
Platelets count	HC	DSA	3.09	0.33	0.01	(3.24,35.42)
		MSA	3.81	0.45	< 0.001	(8.50,43.91)
		MSR	5.78	0.61	< 0.001	(19.60,51.12)
Neutrophil/lymphocyte ratio	HC	DSA	-5.78	-0.62	< 0.001	(-0.90,-0.38)
		MSA	-4.94	-0.58	< 0.001	(-0.92,-0.28)
		MSR	-5.10	-0.53	< 0.001	(-0.80,-0.31)

HC Healthy controls, *DSA* Drug-free patients with schizophrenia in acute phase, *MSA* Medicated patients with schizophrenia in acute phase, *MSR* Medicated patients with schizophrenia in remission period, *t* statistic values for multiple comparisons, *d* effect value for multiple comparisons, with larger absolute values of d representing larger gaps, *CI* Confidence interval

Confounding factors were not controlled

95%CI: 0.01 ~ 0.01), the platelets count of HC was significantly higher than those of DSA ($t = 3.09$, $d = 0.33$, $P = 0.01$, 95%CI: 3.24 ~ 25.42), MSA ($t = 3.81$, $d = 0.45$, $P < 0.001$, 95%CI: 8.50 ~ 43.91), and MSR ($t = 5.78$, $d = 0.61$, $P < 0.001$, 95%CI: 19.60 ~ 51.12), and the neutrophil/lymphocyte ratio of HC was significantly lower than those of DSA ($t = -5.78$, $d = -0.62$, $P < 0.001$, 95%CI: -0.90 ~ -0.38), MSA ($t = -4.94$, $d = -0.58$, $P < 0.001$, 95%CI: -0.92 ~ -0.28), and MSR ($t = -5.10$, $d = -0.53$, $P < 0.001$, 95%CI: -0.80 ~ -0.31).

Immune cell differences between individuals after adjusting confounding factors

As shown in Table 3, after adjusting for gender, age, smoking, education age, marital status, BMI, diabetes, and hypertension as covariates, the results of binary

Table 3 Immune cell differences between subjects in each group after controlling for sociodemographic variables

Variables	Group		B	OR	Corrected *P*-value	95%CI
White blood cell count	HC	DSA	0.23	1.26	0.10	(0.96,1.65)
	MSR	DSA	-0.32	0.73	< 0.001	(0.61,0.88)
Neutrophils count	HC	DSA	0.49	1.62	0.01	(1.13,2.34)
		MSA	0.38	1.46	0.11	(0.91,2.35)
	MSR	DSA	-0.47	0.63	< 0.001	(0.49,0.79)
Lymphocytes count	HC	MSR	-0.44	0.65	0.21	(0.33,1.28)
Eosinophils count	MSR	DSA	2.83	16.95	0.07	(0.76,376.33)
Basophils count	HC	DSA	-74.48	< 0.01	< 0.01	(0,0)
		MSA	-175.03	< 0.001	< 0.001	(0,0)
		MSR	-115.79	< 0.001	< 0.001	(0,0)
Platelets count	HC	DSA	-0.01	0.99	0.12	(0.99,1.00)
		MSA	-0.01	0.99	0.02	(0.98,1.00)
		MSR	-0.01	0.99	0.02	(0.98,1.00)

HC Healthy controls, *DSA* Drug-free patients with schizophrenia in acute phase, *MSA* Medicated patients with schizophrenia in acute phase, *MSR* Medicated patients with schizophrenia in remission period, *B* regression coefficient, which represents the amount of change in the dependent variable corresponding to a unit change in the independent variable, *OR* Odds ratio, *CI* Confidence interval

Gender, age, smoking, education age, marital status, BMI, diabetes, and hypertension were adjusted to covariates

logistic regression analysis showed that, compared with MSR, DSA had a significantly higher level of white blood cell counts (B=-0.32, OR=0.73, P<0.001). DSA had a significantly higher level of neutrophils count than HC (B=0.49, OR=1.62, P=0.01), and DSA had a significantly higher level of neutrophil count than MSR (B=-0.47, OR=0.63, P<0.001). Compared with HC, DSA (B=-74.48, OR<0.01, P<0.01), MSA (B=-175.03, OR<0.001, P<0.001), MSR (B=-115.79, OR<0.001, P<0.001) had significantly lower levels of basophils counts. Compared with HC, MSA (B=-0.01, OR=0.99, P=0.02), and MSR (B=-0.01, OR=0.99, P=0.02) had significantly lower levels of platelets counts.

Differences in NLR between HC and patients with schizophrenia

As shown in Table 4, NLR was significantly higher in DSA and MSA than in HC in all models (all P<0.01). NLR of MSR was significantly higher than that of HC in unadjusted model (model 1) and model adjusted for sex and age (model 2) (both P<0.01), but not in model adjusted for sex, age, smoking, years of education, marital status, BMI, diabetes, and hypertension (model 3) (P>0.05).

Analysis of related factors of NLR

As shown in Fig. 2, the results of correlation analysis showed that NLR and hypertension were significantly

Table 4 Differences in neutrophil/lymphocyte ratio between healthy controls and patients with schizophrenia

Group	Model 1		Model 2		Model 3	
	OR (95%CI)	Corrected *P*-value	OR (95%CI)	Corrected *P*-value	OR (95%CI)	Corrected *P*-value
1	2.24 (1.70,2.96)	<0.001	2.15 (1.62,2.85)	<0.001	2.83 (1.53,5.22)	<0.001
2	2.14 (1.57,2.91)	<0.001	1.85 (1.35,2.53)	<0.001	2.59 (1.33,5.07)	<0.01
3	2.24 (1.66,3.03)	<0.001	1.73 (1.16,2.58)	<0.01	1.76 (0.95,3.29)	0.07

OR Odds ratio, *CI* Confidence interval

Group 1: Drug-free patients with schizophrenia in acute phase VS. healthy controls, group 2: Medicated patients with schizophrenia in acute phase VS. healthy controls, group 3: Medicated patients with schizophrenia in remission period VS. healthy controls; model1: unadjusted model, model 2: model adjusted for gender and age, model 3: model adjusted for sex, age, smoking, years of education, marital status, BMI, diabetes, and hypertension

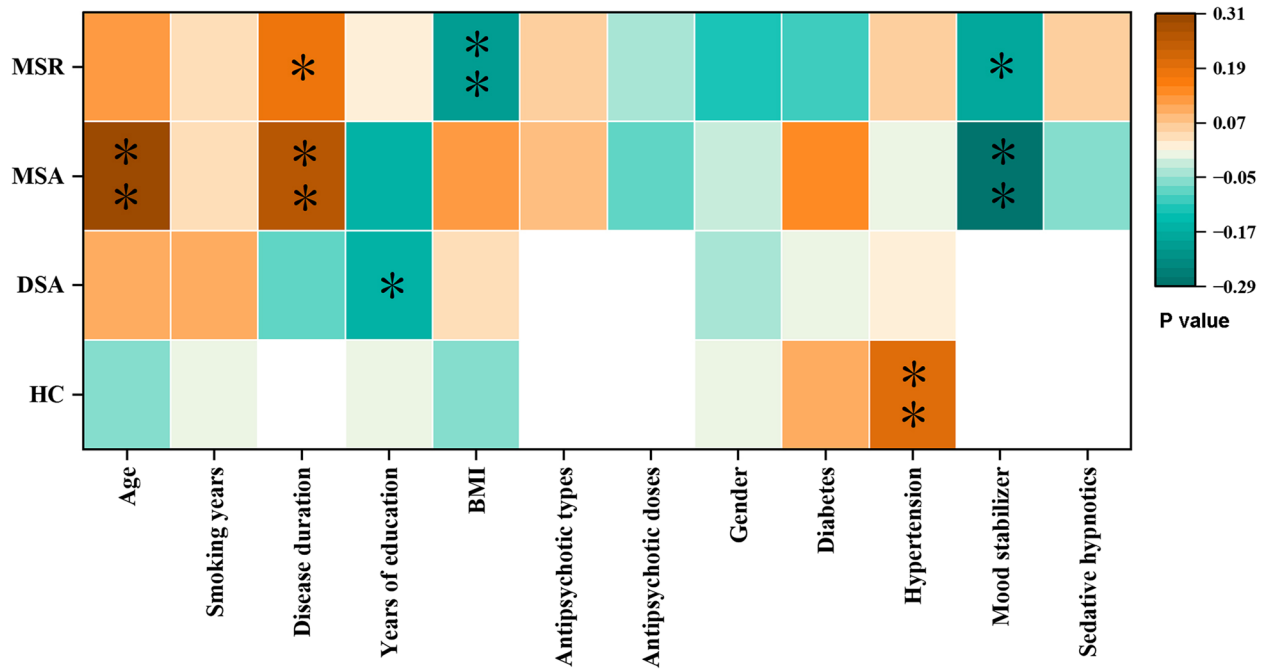

Fig. 2 Factors associated with NLR in HC, DSA, MSA and MSR group. Spearman correlation was used to calculate the correlation of age, smoking years, disease duration, years of education, BMI, antipsychotic types, and antipsychotic doses with NLR. Pearson correlation was used to calculate the correlation of gender, diabetes, hypertension, mood stabilizer and sedative hypnotics with NLR. NLR: neutrophil/lymphocyte ratio; HC: healthy controls; DSA: drug-free patients with schizophrenia in acute phase, MSA: medicated patients with schizophrenia in acute phase, MSR: medicated patients with schizophrenia in remission period. * Significant at P<0.05; ** Significant at P<0.01

positively correlated in HC ($r=0.21$, $P<0.01$). NLR and years of education were significantly negatively correlated in DSA ($\rho=-0.17$, $P=0.03$). In MSA, NLR was significantly positively correlated with age ($\rho=0.31$, $P<0.001$) and duration of illness ($\rho=0.27$, $P<0.01$), and was significantly negatively correlated with use of mood stabilizers ($r=-0.29$, $P<0.01$). In MSR, NLR was significantly positively correlated with disease duration ($\rho=0.19$, $P=0.01$) and significantly negatively correlated with BMI ($\rho=-0.20$, $P<0.01$), and use of mood stabilizers ($r=-0.17$, $P=0.02$).

Effects of different antipsychotics on immune cells

Among 119 MSA patients, 58 were treated with clozapine and 61 were not. Among them, 1 was treated with typical antipsychotics, 102 with atypical antipsychotics, and 16 with both typical and atypical antipsychotics. Among 181 MSR patients, 83 were treated with clozapine and 98 were not. Among them, 4 were treated with typical antipsychotics, 154 were treated with atypical antipsychotics, and 23 were treated with both typical and atypical antipsychotics. Given that clozapine may have a greater impact on immune cells such as white blood cells and neutrophils [25, 26], we investigated the effect of clozapine on immune cells in MSA and MSR group, respectively. As shown in Table S1, there was no significant difference in all immune cells between patients taking clozapine and those not taking clozapine in MSA and MSR groups (all adjusted $P>0.05$). Besides, there was no significant difference in all immune cells in patients taking typical antipsychotics or atypical antipsychotics in the MSA and MSR groups (all adjusted $P>0.05$) (Table S2).

Discussion

The main findings of this study were: (1) neutrophil counts were significantly higher in DSA than in HC and MSR, basophil counts were significantly lower in DSA, MSA, and MSR than in HC, and platelet counts were significantly lower in MSA and MSR than in HC; (2) compared with healthy populations and stable schizophrenia, high NLR was an independent risk factor for acute exacerbation of schizophrenia; (3) in individuals taking antipsychotic medications, there were no significant differences between different types of medications on the level of immune cells and inflammatory indices (NLR, MLR, PLR).

Although numerous previous studies have explored altered levels of immune cells in patients with schizophrenia, most have not considered the effects of medications on immune cells and the alterations of immune cells in patients at different stages of the disease. For example, some previous studies have found significantly higher NLR in patients with schizophrenia compared with healthy population. However, it should be noted that in these studies, subjects with schizophrenia were either simply first-episode, drug-naïve patients in the acute phase or patients with long-term hospitalization (we tend to think that these patients should be mostly classified as MSR), or patients with acute exacerbations (without distinguishing whether or not they were taking medication) [21, 27–29]. We believe that it is necessary to explore inflammatory markers in patients with schizophrenia at various disease stages simultaneously in the same study, in order to eliminate the concern that the results of different disease periods may differ due to the heterogeneity of samples in different studies. In the present study, there were no significant differences in immune cells between patients using clozapine and those not using clozapine, or between those using typical antipsychotics and those using atypical antipsychotics, which seemed to indicate that the different types of antipsychotics did not have much of an effect on the outcome of patients' immune cell levels. The inflammatory indicator of primary interest in this study was NLR, which was significantly increased in patients with schizophrenia in the acute phase regardless of whether they were taking antipsychotic medications after adjustment for confounding factors, while NLR levels were elevated but not significantly in patients in remission. We believe that this result is of great interest because it represents a difference in NLR levels between acute phase and remission phase of schizophrenia, which raises the possibility of using it as a biomarker for acute phase.

The results of the present study are both similar and different from those of previous studies. For example, the results of Rangel et al. showed that NLR, PLR, and MLR values were significantly higher in patients with schizophrenia in relapse period than in HC, and MLR and PLR were also significantly higher in patients in remission period. NLR, MLR, and PLR values of the same patient were significantly higher in relapse period than in remission period [21]. However, in the present study, we only found differences in NLR among the groups, while MLR and PLR did not differ significantly among the groups. The role of neutrophils in schizophrenia may be related to their release of neutrophil extracellular traps (NETs), exacerbated NETs can trigger chronic inflammation [30, 31]. Some studies have found that the level of NETs in the blood of patients with early schizophrenia is significantly increased, and it is not affected by confounding factors such as gender and BMI [32]. These findings to some extent explain the mechanism of elevated neutrophils in schizophrenia, and NETs released by activated neutrophils may play an important role in the chronic inflammatory state of schizophrenia by promoting the release of some

inflammatory cytokines such as IL6. In addition, some diseases known to be associated with NETs, such as diabetes, psoriasis, and cardiometabolic disorders, are also often common comorbidities of schizophrenia, which also proves the correlation between NETs and schizophrenia to a certain extent [33, 34].

This study also found that in MSA and MSR, NLR values were significantly positively associated with disease duration and significantly negatively associated with mood stabilizer use. This was the first time that an association between NLR and disease duration has been found in medicated schizophrenia patients. Patients with longer duration of disease have relatively higher NLR, and the longer the duration of disease often represents the longer the treatment time of antipsychotic medications. The increasing NLR in patients with schizophrenia is due to the long-term use of antipsychotic medications or the long-term chronic inflammatory process of schizophrenia, which is not yet clear. Studies have shown that white blood cell counts in patients with schizophrenia decrease after short-term treatment with antipsychotic drugs, but increase after long-term treatment [35]. Whether this complex nonlinear association is also present between NLR and antipsychotic medications warrants further investigation. On the other hand, in order to control psychiatric symptoms, patients with schizophrenia often need to take mood stabilizers (such as lithium, sodium valproate, lamotrigine). Although many studies, including this one, have focused on the effect of antipsychotic drugs on inflammatory indexes, few studies have focused on mood stabilizers. Future studies should also explore the effects of different classes of mood stabilizers on NLR.

One of the limitations of our study was that although all the patients were assessed with the Positive and Negative Syndrome Scale (PANSS), the assessment was performed independently by different physicians, which raised questions about the reliability and robustness of the assessment, and we had to abandon the use of these scale results. In addition, another limitation of this study was that we did not detect the inflammatory factors such as cytokines in individuals, so we could not explore the changes of these inflammatory factors in subjects and the effect of antipsychotic drugs on them. Third, DSA included both patients who had never taken antipsychotic medications and those who had previously taken antipsychotic medications and discontinued them for more than 1 month, and these two subgroups may also have different inflammatory indexes. Fourth, as stated in the Results 3.1 section, there were a small number of missing values in this study, and although we have used multiple imputation to fill in the missing values, the results of the study are inevitably biased.

In conclusion, this study investigated the changes of inflammatory indices in patients with schizophrenia at different disease stages and taking different antipsychotic drugs, and demonstrated the potential of NLR as a biomarker for acute exacerbation of schizophrenia. However, as the effects of antipsychotics and mood stabilizers on NLR may change over time, more research is needed in this area to explore the characteristics of biomarkers such as peripheral blood inflammation index in schizophrenia.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
Yali Zheng: original draft writing. Xianqin Zhou: statistical analysis and visualization. Kai Chen: data collection. Zhengchuang Fu: data collection. Peng Zhang: data collection. Quanfeng Zhu: project design and manuscript revision. All authors have reviewed the manuscript and approved the resubmission of the manuscript.

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Data availability
Raw data from this study can be provided with the consent of corresponding author when reasonably legal.

Declarations

Ethics approval and consent to participate
Considering that the study would not expose the privacy of any subjects and that some subjects were difficult to contact, we applied for a waiver of informed consent to the Institutional Review Board. The Medical Ethics Committee of Zhejiang Xiaoshan Hospital waived the need for consent to participate and approved this study on January 25, 2024 (Approval NO. 2024–004).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. Lancet. 2022;399(10323):473–86.
2. Lähteenvuo M, Tiihonen J. Antipsychotic polypharmacy for the management of schizophrenia: evidence and recommendations. Drugs. 2021;81(11):1273–84.
3. Thai H, Audet ÉC, Koestner R, Lepage M, O'Driscoll GA. The role of motivation in clinical presentation, treatment engagement and response in schizophrenia-spectrum disorders: A systematic review. Clin Psychol Rev. 2024;113:102471.
4. Mueser KT, McGurk SR. Schizophrenia. Lancet. 2004;363(9426):2063–72.
5. Pearlson GD. Etiologic, phenomenologic, and endophenotypic overlap of schizophrenia and bipolar disorder. Annu Rev Clin Psychol. 2015;11:251–81.
6. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-an overview. JAMA Psychiat. 2020;77(2):201–10.
7. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry. 2008;63(8):801–8.
8. Li Z, Li X, Jin M, Liu Y, He Y, Jia N, Cui X, Liu Y, Hu G, Yu Q. Identification of potential biomarkers and their correlation with immune infiltration cells in schizophrenia using combinative bioinformatics strategy. Psychiatry Res. 2022;314:114658.
9. Perry BI, Upthegrove R, Kappelmann N, Jones PB, Burgess S, Khandaker GM. Associations of immunological proteins/traits with schizophrenia, major depression and bipolar disorder: A bi-directional two-sample mendelian randomization study. Brain Behav Immun. 2021;97:176–85.
10. Lee EE, Hong S, Martin AS, Eyler LT, Jeste DV. Inflammation in schizophrenia: cytokine levels and their relationships to demographic and clinical variables. Am J Geriatr Psychiatry. 2017;25(1):50–61.
11. Said S, Pazoki R, Karhunen V, Võsa U, Ligthart S, Bodinier B, Koskeridis F, Welsh P, Alizadeh BZ, Chasman DI, et al. Genetic analysis of over half a million people characterises C-reactive protein loci. Nat Commun. 2022;13(1):2198.
12. Tamayo JM, Osman HC, Schwartzer JJ, Ashwood P. The influence of asthma on neuroinflammation and neurodevelopment: From epidemiology to basic models. Brain Behav Immun. 2024;116:218–28.
13. Zahorec R. Ratio of neutrophil to lymphocyte counts–rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102(1):321–3.
14. Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, Kayka N, Tosun M. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatr Danub. 2014;26(3):220–5.
15. Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res. 2019;271:131–5.
16. 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. World J Biol Psychiatry. 2020;21(5):326–38.
17. Clausen M, Christensen RHB, da Re M, Benros ME. Immune cell alterations in psychotic disorders: a comprehensive systematic review and meta-analysis. Biol Psychiatry. 2024;96(5):331–41.
18. Bhikram T, Sandor P. Neutrophil-lymphocyte ratios as inflammatory biomarkers in psychiatric patients. Brain Behav Immun. 2022;105:237–46.
19. Llorca-Bofí V, Petersen LV, Mortensen PB, Benros ME. White blood cell counts, ratios, and C-reactive protein among individuals with schizophrenia spectrum disorder and associations with long-term outcomes: a population-based study. Brain Behav Immun. 2024;122:18–26.
20. Zhu X, Zhou J, Zhu Y, Yan F, Han X, Tan Y, Li R. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in schizophrenia. Australas Psychiatry. 2022;30(1):95–9.
21. Cabello-Rangel H, Basurto-Morales M, Botello-Aceves E, Pazarán-Galicia O. Mean platelet volume, platelet count, and neutrophil/lymphocyte ratio in drug-naïve patients with schizophrenia: a cross-sectional study. Front Psychiatry. 2023;14:1150235.
22. Liang J, Guan X, Sun Q, Hao Y, Xiu M. Neutrophil/lymphocyte ratio and cognitive performances in first-episode patients with schizophrenia and healthy controls. Prog Neuropsychopharmacol Biol Psychiatry. 2024;135:111092.
23. Wakefield JC. Diagnostic issues and controversies in DSM-5: return of the false positives problem. Annu Rev Clin Psychol. 2016;12:105–32.
24. Benítez J, Puerto AM, Díaz JA. Differences in antidiabetic drug utilisation between three different health systems in the same national region. Eur J Clin Pharmacol. 1992;42(2):151–4.
25. Hinze-Selch D, Becker EW, Stein GM, Berg PA, Mullington J, Holsboer F, Pollmächer T. Effects of clozapine on in vitro immune parameters: a longitudinal study in clozapine-treated schizophrenic patients. Neuropsychopharmacology. 1998;19(2):114–22.
26. Pirmohamed M, Park K. Mechanism of clozapine-induced agranulocytosis : current status of research and implications for drug development. CNS Drugs. 1997;7(2):139–58.
27. 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.
28. Bilgin Koçak M, Öztürk Atkaya N, Oruç MA. Evaluation of inflammatory markers obtained from complete blood count in different stages of schizophrenia. Curr Med Res Opin. 2024;40(8):1413–9.
29. Zhu X, Li R, Zhu Y, Zhou J, Huang J, Zhou Y, Tong J, Zhang P, Luo X, Chen S, et al. Changes in inflammatory biomarkers in patients with schizophrenia: a 3-year retrospective study. Neuropsychiatr Dis Treat. 2023;19:1597–604.
30. Wigerblad G, Kaplan MJ. Neutrophil extracellular traps in systemic autoimmune and autoinflammatory diseases. Nat Rev Immunol. 2023;23(5):274–88.
31. Huang SU, O'Sullivan KM. The Expanding role of extracellular traps in inflammation and autoimmunity: The New Players in Casting Dark Webs. Int J Mol Sci. 2022;23(7):3793.
32. Corsi-Zuelli F, Schneider AH, Santos-Silva T, Loureiro CM, Shuhama R, Menezes PR, Guimarães FS, Gomes FV, Cunha FQ, Louzada-Junior P, et al. Increased blood neutrophil extracellular traps (NETs) associated with early life stress: translational findings in recent-onset schizophrenia and rodent model. Transl Psychiatry. 2022;12(1):526.
33. Mutua V, Gershwin LJ. A Review of Neutrophil Extracellular Traps (NETs) in Disease: Potential Anti-NETs Therapeutics. Clin Rev Allergy Immunol. 2021;61(2):194–211.
34. Klopf J, Brostjan C, Eilenberg W, Neumayer C. Neutrophil extracellular traps and their implications in cardiovascular and inflammatory disease. Int J Mol Sci. 2021;22(2):559.
35. Zhang Y, Tao S, Coid J, Wei W, Wang Q, Yue W, Yan H, Tan L, Chen Q, Yang G, et al. The role of total white blood cell count in antipsychotic treatment for patients with schizophrenia. Curr Neuropharmacol. 2024;22(1):159–67.

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