Research Square

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Peripheral Inflammatory Profiles in Acute Schizophrenia Relapse: Associations with 6- Month Antipsychotic Treatment Coverage

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Abstract

Objectives

Peripheral inflammatory markers are frequently elevated in schizophrenia, but the extent to which inflammatory indices at acute relapse are associated with preceding antipsychotic treatment coverage remains unclear. We examined whether 6-month treatment coverage patterns—long-acting injectable (LAI) monotherapy, regular oral monotherapy, or no antipsychotic treatment—were associated with peripheral inflammatory indices measured at hospitalization for acute relapse.

Methods

We retrospectively evaluated 127 adults hospitalized for acute psychosis. Laboratory values obtained within 24 hours of admission and PANSS scores were extracted. Inflammatory indices (NLR, PLR, MLR, MHR, and CRP/albumin ratio) were calculated. Patients were categorized by treatment pattern in the preceding six months.

Results

The no-treatment group had higher PANSS scores than treated groups. In adjusted models, LAI treatment was associated with lower NLR (β = 0.75; p = 0.004), whereas regular oral treatment did not differ from no treatment. Similar patterns were observed for PLR (β = 0.78; p = 0.003) and MLR (β = 0.74; p = 0.004). When the reference was set to regular oral treatment, LAI remained associated with lower NLR (β = 0.804; p = 0.008). In treated-only overlap analyses additionally adjusting for molecule category and dose, LAI remained associated with lower NLR compared with oral treatment (p = 0.037).

Discussion

Schizophrenia involves a chronic inflammatory component shaped by treatment patterns. Findings suggest regular antipsychotic exposure, particularly via LAI, is associated with a lower peripheral inflammatory burden during relapse.

Conclusion

Preceding LAI treatment coverage was consistently associated with lower peripheral inflammatory ratios at acute relapse compared with no treatment and regular oral treatment, even after adjustment for symptom severity and metabolic covariates.

1. Introduction

Schizophrenia is one of the major psychiatric disorders that affects approximately 1% of the world population, has genetic and neurobiological factors, influences early brain development, and causes long-term disability [1, 2]. Although it is a multifactorial disease in which genetic, neurodevelopmental, and environmental effects play a role in its etiology, in recent years studies have started to focus on the role of immune and inflammatory processes in its pathophysiology [3–5]. While traditionally defined by dopaminergic and glutamatergic neurotransmission abnormalities, the conceptualization of schizophrenia has evolved significantly over the last two decades. Accumulating evidence now positions it as a systemic inflammatory disorder accompanied by both central and peripheral immune dysregulation [6, 7]. This systemic burden is clinically reflected in the high prevalence of metabolic syndrome, cardiovascular mortality, and autoimmune comorbidities observed in these patients [7, 8].

Peripheral inflammation in schizophrenia is marked by abnormal levels of cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) [9–11]. However, the cost and logistical challenges of routine cytokine measurement have shifted clinical interest toward more accessible biomarkers [12–15]. Indices derived from complete blood counts—specifically the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR)—have

emerged as reliable, cost-effective indicators of systemic inflammation and physiological stress. In schizophrenia, these ratios are frequently elevated compared to healthy controls and fluctuate with disease stages, suggesting a dynamic relationship between immune activation and symptom exacerbation [16, 17].

Antipsychotic medications, the cornerstone of schizophrenia treatment, are known to have immunomodulatory effects beyond dopaminergic blockade. Evidence suggests that antipsychotics can suppress pro-inflammatory cytokines and enhance anti-inflammatory responses, potentially contributing to clinical improvement [18]. However, the literature is not uniform; while some agents (particularly atypicals like clozapine and olanzapine) are associated with metabolic side effects that may trigger long-term inflammation, others appear to have neutral or protective effects [19–21]. This variability raises critical questions about whether the observed inflammatory status is a trait of the disorder or a state modified by specific treatment regimens.

While the anti-inflammatory properties of antipsychotics are well-documented [22–24], the impact of delivery systems—specifically long-acting injectable (LAI) versus oral formulations—remains understudied [25, 26]. Pharmacokinetically, LAIs minimize the peak-trough plasma fluctuations often seen with oral medication, potentially offering a more stable immunomodulatory environment [27]. Furthermore, addressing the "pseudo-resistance" caused by covert non-adherence is crucial. We hypothesize that the sustained release and guaranteed adherence provided by LAIs may confer a distinct advantage in attenuating peripheral inflammation, independent of symptomatic severity [28, 29].

Therefore, we aimed to examine whether peripheral inflammatory indices measured within 24 hours of hospitalization for acute relapse are associated with antipsychotic treatment coverage patterns in the preceding 6 months (regular LAI monotherapy, regular oral monotherapy, or no antipsychotic treatment). Given medication heterogeneity across groups, we prespecified sensitivity analyses restricting to overlap molecules and adjusting for dose among treated patients. We hypothesized that more continuous treatment coverage would be associated with lower inflammatory indices; however, due to the retrospective cross-sectional design, we did not aim to infer causality. Specifically, we sought to determine whether treatment continuity and formulation type influence inflammatory burden even when patients present with acute relapse.

2. Method

2.1. Data Collection Tools and Participants

This retrospective study was conducted at the Istanbul Erenköy Mental Health and Neurological Diseases Training and Research Hospital. Electronic medical records and archival files of all psychiatric inpatient admissions between January 2020 and January 2025 were reviewed. A total of 653 individuals aged 18–65 years who had received a DSM-5 diagnosis of schizophrenia were initially identified. Of these, 46 patients were excluded for not meeting the predefined inclusion criteria, which required documentation of antipsychotic use for at least six months prior to hospitalization and the availability of laboratory results obtained within the first 24 hours of admission. The remaining 607 patients were subsequently evaluated according to the study's exclusion criteria. A total of 480 patients were excluded due to the use of medications known to influence inflammatory status such as steroids, nonsteroidal anti-inflammatory drugs or antibiotics (n = 88), incomplete or missing clinical records (n = 76), the presence of an acute infection at the time of admission (n = 73), concurrent use of antidepressants, anxiolytics or mood stabilizers (n = 64), chronic inflammatory, autoimmune, neurological or metabolic conditions (n = 63), alcohol or substance use (n = 62), and obesity defined as a body mass index greater than 30 kg/m² (n = 54). After applying these criteria, a total of 127 patients were found to be eligible for the study and constituted the study sample.Data inclusion followed the process outlined in the flow diagram, with each step of case selection transparently documented (Fig. 1).

2.2. Assessment Instruments

Sociodemographic and clinical data such as age, sex, educational level, employment status, smoking, family psychiatric history, disorder duration, number of hospitalizations, and history of suicide attempts were obtained from medical files. Clinical

severity was assessed using the Positive and Negative Syndrome Scale (PANSS), which is routinely administered at admission. PANSS scores, including positive, negative, and general psychopathology subscales, were recorded.

Patients were classified based on antipsychotic treatment coverage during the 180 days preceding admission, verified using prescription records, community mental health center follow-up data, and the national electronic health system. Three mutually exclusive monotherapy groups were defined: (i) regular oral monotherapy, with no treatment gap longer than 14 days; (ii) regular LAI monotherapy (aripiprazole/paliperidone/risperidone LAI), with all scheduled injections administered within the expected dosing interval allowing a pre-specified grace window; and (iii) no antipsychotic treatment, defined as the absence of any antipsychotic prescription or administration record during the 6-month period. Patients with antipsychotic polypharmacy or mixed oral–LAI regimens during the look-back window were excluded.

Positive and Negative Syndrome Scale (PANSS)

PANSS was developed by Kay et al. (1987) to assess positive and negative symptoms and general psychopathology in schizophrenia [30]. It was adapted for the Turkish sample by Kostakoğlu et al. [31]. When the internal consistency was examined, Cronbach alpha coefficients were similar to those in the original study (0.75, 0.77 and 0.71).

Blood samples were drawn routinely the morning after admission (06:00–08:00 AM) following an overnight fast, minimizing the acute effect of emergency sedation administered upon arrival. Laboratory analyses included complete blood count (white blood cells, neutrophils, lymphocytes, platelets, and monocytes), C-reactive protein (CRP), albumin, and high-density lipoprotein cholesterol (HDL) levels. Using these parameters, several inflammatory ratios were calculated: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), monocyte-to-HDL ratio (MHR), and CRP-to-albumin ratio (CRP/Alb). These indices were selected because they are well-known markers of systemic inflammation and have been widely studied in schizophrenia and other psychiatric and somatic disorders.

2.3. Analysis of Data

All statistical analyses were performed using IBM SPSS Statistics version 27.0 [32]. Descriptive statistics were reported as means and standard deviations for continuous variables, and as frequencies and percentages for categorical variables. The normality of distributions was evaluated with the Kolmogorov–Smirnov test, and homogeneity of variances was assessed with Levene's test. Depending on distributional assumptions, group comparisons were performed using independent samples t-test or Mann–Whitney U test for two-group comparisons, and one-way ANOVA with Tukey's post-hoc test or Kruskal–Wallis test for comparisons involving two or more groups. Relationships between categorical variables were examined using chi-square test or Fisher's exact test, while correlations were analyzed using Pearson or Spearman methods according to data distribution. Log-transformed inflammatory indices were modeled using multivariable linear regression with HC3 heteroskedasticity-consistent standard errors. The main models included treatment coverage group and adjusted for age, sex, smoking status, disorder duration, Framingham risk score, LDL, triglycerides, HDL, and PANSS total. The no-treatment group was the reference category in primary analyses. Sensitivity analyses (i) excluded clozapine and olanzapine from the oral group, and (ii) restricted analyses to treated-only overlap molecules (aripiprazole/risperidone/paliperidone), additionally adjusting for molecule category and chlorpromazine-equivalent dose. Statistical significance was set at a two-tailed p-value < 0.05.

The final sample size was determined according to the number of eligible patients available during the study period. A post-hoc power analysis performed using G*Power version 3.1.9.7 showed that a sample of 127 participants provided adequate power (80%) to detect medium effect sizes at a significance level of $\alpha = 0.05$, thereby confirming the adequacy of the study sample.

Ethics Committee Approval

Approval was received from the Health Sciences University Erenkoy Mental and Nervous Diseases Scientific Research Ethics Committee with decision number 65 dated 10/07/2025. The study procedure conformed to the latest version of the Declaration of Helsinki.

3. Results

A total of 127 patients were included in the study and were divided into depot antipsychotic, oral antipsychotic, and irregular AP use groups. No statistically significant differences were found between the groups in terms of mean age, gender, marital status, education level, occupational status, suicide history, family history of psychiatric disorder, or smoking ($p > 0.05$). The mean chlorpromazine equivalent dose was 515.00 ± 78.05 mg/day in patients receiving depot antipsychotics and 544.91 ± 112.83 mg/day in those receiving oral antipsychotics, with no statistically significant difference between groups. (Table 1).

Table 1
Sociodemographic Characteristics of Patients Across Antipsychotic Treatment Groups

Variable	Depot AP (n = 29)	Oral AP (n = 59)	Irregular AP (n = 39)	Total (n = 127)	p
Age (year), mean ± SD	39.21 ± 5.09	39.41 ± 6.65	41.44 ± 6.44	39.98 ± 6.29	0.223
Sex, n (%)					0.630
Female	14 (48.3%)	30 (50.8%)	16 (41.0%)	60 (47.2%)	
Male	15 (51.7%)	29 (49.2%)	23 (59.0%)	67 (52.8%)	
Marital Status, n (%)					0.352
Single	19 (65.5%)	43 (72.9%)	23 (59.0%)	85 (66.9%)	
Married	10 (34.5%)	16 (27.1%)	16 (41.0%)	42 (33.1%)	
Education Level, n (%)					0.297
Literate	6 (20.7%)	5 (8.5%)	2 (5.1%)	13 (10.2%)	
Primary school	14 (48.3%)	35 (59.3%)	19 (48.7%)	68 (53.5%)	
High school	5 (17.2%)	13 (22.0%)	10 (25.6%)	28 (22.0%)	
University	4 (13.8%)	6 (10.2%)	8 (20.5%)	18 (14.2%)	
Employment Status, n (%)					0.830
Unemployed	22 (75.9%)	47 (79.7%)	31 (79.5%)	100 (78.7%)	
Irregular	0 (0%)	8 (13.6%)	4 (10.3%)	12 (9.4%)	
Regular employment	3 (10.3%)	2 (3.4%)	4 (10.3%)	9 (7.1%)	
Housewife	3 (10.3%)	2 (3.4%)	0 (0%)	5 (3.9%)	
Retired	1 (3.4%)	0 (0%)	0 (0%)	1 (0.8%)	
History of Suicide Attempt, n (%)					0.367
No	29 (100%)	55 (93.2%)	37 (94.9%)	121 (95.3%)	
Have	0 (0%)	4 (6.8%)	2 (5.1%)	6 (4.7%)	
Family History of Psychiatric Disorder, n (%)					0.999
No	20 (69.0%)	41 (69.5%)	27 (69.2%)	88 (69.3%)	
Have	9 (31.0%)	18 (30.5%)	12 (30.8%)	39 (30.7%)	
Smoking Status, n (%)					0.846
Non-smoker	18 (62.1%)	36 (61.0%)	26 (66.7%)	80 (63.0%)	
Smoker	11 (37.9%)	23 (39.0%)	13 (33.3%)	47 (37.0%)	
Chlorpromazine Equivalent Dose (mg/daily) , mean ± SD	515,00 ± 78,05	544,91 ± 112,83	NA	NA	0.203

Data are presented as mean ± standard deviation for continuous variables or number (%) for categorical variables.

Comparison for Chlorpromazine equivalent dose was performed only between Depot and Oral groups using independent samples t-test

Variable	Depot AP (n = 29)	Oral AP (n = 59)	Irregular AP (n = 39)	Total (n = 127)	p

Statistical significance determined by one-way ANOVA and Pearson Chi-square tests.

* p < 0.05 **p < 0.001

Regarding antipsychotic use during the last six months 30.7 percent of the participants reported no antipsychotic use. Among those receiving oral pharmacotherapy, risperidone was used by 10.2 percent, paliperidone by 6.3 percent, aripiprazole by 8.7 percent, olanzapine by 11.0 percent, and clozapine by 10.2 percent. Long acting injectable (LAI) antipsychotics were used by 7.9 percent of the patients for risperidone LAI, 7.1 percent for paliperidone LAI, and 7.9 percent for aripiprazole LAI (Table 2).

Table 2
Distribution of antipsychotic medications used in the last 6 months among participants

Antipsychotic Use in the Last 6 Months	N	%
None	39	30.7%
Risperidone	13	10.2%
Paliperidone	8	6.3%
Aripiprazole	11	8.7%
Olanzapine	14	11.0%
Clozapine	13	10.2%
Risperidone long-acting injectable	10	7.9%
Paliperidone long-acting injectable	9	7.1%
Aripiprazole long-acting injectable	10	7.9%

Clinical characteristics showed no significant group differences in disorder duration or number of psychiatric hospitalizations (p = 0.295). Positive symptom scores of the PANSS differed significantly among the groups, with means of 32.4 ± 6.3 in the depot group, 32.9 ± 6.4 in the oral group, and 36.8 ± 7.2 in the irregular-use group (p = 0.008). Post-hoc analyses demonstrated that the depot group had significantly lower PANSS-P scores than the irregular-use group (p = 0.026), and similarly the oral group scored lower than the irregular-use group (p = 0.017). There was no significant difference between depot and oral groups (Depot ≈ Oral < Irregular). Negative symptom scores did not differ significantly between treatment groups (27.5 ± 6.5 vs. 29.1 ± 6.4 vs. 29.7 ± 6.1; p = 0.352). PANSS general psychopathology scores were significantly higher in the irregular-use group (64.5 ± 12.3) compared with the depot (54.3 ± 16.1) and oral groups (53.9 ± 13.7) (p < 0.001). Post-hoc analyses confirmed that both depot and oral users had significantly lower PANSS-G scores than irregular users (p = 0.010 and p < 0.001, respectively), with no difference between depot and oral groups (Depot ≈ Oral < Irregular). Total PANSS scores followed a similar pattern: the irregular-use group (131.1 ± 18.2) scored significantly higher than both depot (114.3 ± 19.2) and oral users (115.9 ± 18.3) (p < 0.001). Post-hoc analyses confirmed significantly lower PANSS-T scores in depot and oral groups compared with irregular users (both p < 0.001), with no difference between depot and oral groups (Depot ≈ Oral < Irregular) (Table 3).

Table 3
Clinical Characteristics and PANSS Scores by Antipsychotic Treatment Pattern

Variable	Depot AP (n = 29)	Oral AP (n = 59)	Irregular AP (n = 39)	p (overall)	p1	p2	p3
Duration of Disorder (years)	6.72 ± 3.21	7.05 ± 2.42	7.07 ± 2.53	0.834	–	–	–
PANSS-P	32.45 ± 6.36	32.93 ± 6.44	36.82 ± 7.27	0.008*	1.000	0.026*	0.017*
PANSS-N	27.48 ± 6.57	29.07 ± 6.44	29.72 ± 6.16	0.352	–	–	–
PANSS-G	54.38 ± 16.15	53.88 ± 13.77	64.59 ± 12.36	< 0.001**	1.000	0.010*	< 0.001**
PANSS-T	114.31 ± 19.24	115.88 ± 18.36	131.13 ± 18.26	< 0.001**	1.000	< 0.001**	< 0.001**
Number of hospitalizations	3.20 ± 1.52	3.86 ± 2.21	3.76 ± 1.56	0.295	–	–	–

PANSS refers to the Positive and Negative Syndrome Scale, including the subscales PANSS-P (Positive Symptoms), PANSS-N (Negative Symptoms), PANSS-G (General Psychopathology), and PANSS-T (Total Score).

Values were presented as mean and standard deviation and One-way ANOVA used.

Pairwise comparisons were made with Bonferroni-corrected post hoc test ($p < 0.017$ was considered significant).

P1: Comparison of Depot group and Oral AP Use group

P2: Comparison of Depot and Irregular AP Use group

P3: Comparison of Oral AP Use group and Irregular AP Use group

* $p < 0.05$ **$p < 0.001$

Examination of hematological parameters showed a significant difference in WBC levels between the groups ($p = 0.023$). Post hoc analyses indicated that the depot group had lower WBC levels than the irregular-use group ($p = 0.024$), while no significant differences were observed between the depot and oral groups or between the oral and irregular groups (Depot < Irregular; Oral ≈ Depot and Oral ≈ Irregular). Neutrophil counts also differed significantly among groups ($p < 0.001$), with the irregular-use group exhibiting higher levels compared with both the depot ($p < 0.001$) and oral groups ($p = 0.009$). No difference was observed between depot and oral users (Depot ≈ Oral < Irregular). Lymphocyte counts were also significantly different across groups ($p = 0.003$). The depot group showed higher lymphocyte levels than the irregular-use group ($p = 0.002$), whereas no significant differences emerged between depot–oral or oral–irregular groups (Irregular < Oral ≈ Depot). Monocyte and platelet counts did not differ significantly across groups (all $p > 0.05$). In addition, lipid profile measures (LDL, HDL, triglycerides, total cholesterol), CRP and albumin did not show significant group differences (all $p > 0.05$) (Table 4).

Analysis of inflammatory ratios demonstrated clear and clinically meaningful differences among the groups. NLR, PLR, and MLR levels were significantly higher in the irregular-use group compared with both the depot and oral groups. For NLR, the irregular-use group showed elevated values relative to the depot group ($p < 0.001$) and the oral group ($p = 0.014$). PLR levels were also higher in the irregular-use group than in the depot group ($p < 0.001$) and the oral group ($p = 0.014$). Similarly, MLR was significantly increased in the irregular-use group compared with the depot group ($p < 0.001$) and the oral group ($p = 0.003$). No significant differences were observed between depot and oral users for any of these ratios (all $p > 0.05$) (Table 4).

Table 4
Comparison of hematological, metabolic, and inflammatory markers across antipsychotic treatment groups.

Variable	Depot AP (n = 29)	Oral AP (n = 59)	Irregular AP (n = 39)	p (overall)	p1	p2	p3
WBC (×10³/µL)	8.49 ± 1.97	8.96 ± 1.57	9.74 ± 2.27	0.023*	0.828	0.024*	0.143
Neutrophils (×10³/µL)	5.15 ± 1.08	5.75 ± 1.35	6.71 ± 2.01	< 0.001**	0.250	< 0.001**	0.009*
Monocytes (×10³/µL)	0.79 ± 0.29	0.78 ± 0.22	0.89 ± 0.29	0.093	–	–	–
Lymphocytes (×10³/µL)	2.69 ± 0.82	2.37 ± 0.58	2.14 ± 0.60	0.003*	0.095	0.002*	0.261
Platelets (×10³/µL)	246.52 ± 43.95	253.61 ± 49.92	272.36 ± 65.43	0.112	–	–	–
CRP (mg/L)	0.23 ± 0.25	0.20 ± 0.23	0.26 ± 0.21	0.505	–	–	–
LDL (mg/dL)	114.97 ± 29.82	109.48 ± 28.95	102.56 ± 29.47	0.219	–	–	–
Triglycerides (mg/dL)	119.03 ± 47.78	121.25 ± 51.25	102.56 ± 38.88	0.140	–	–	–
HDL (mg/dL)	44.93 ± 10.07	44.19 ± 9.66	44.41 ± 8.17	0.940	–	–	–
Total Cholesterol (mg/dL)	179.38 ± 28.30	174.78 ± 32.14	168.15 ± 33.94	0.342	–	–	–
Albumin (g/dL)	4.18 ± 0.28	4.20 ± 0.35	4.13 ± 0.34	0.589	–	–	–
NLR	2.07 ± 0.66	2.72 ± 1.09	3.38 ± 1.41	< 0.001**	0.038*	< 0.001**	0.014*
PLR	99.31 ± 32.14	112.89 ± 35.56	135.47 ± 44.68	< 0.001**	0.350	< 0.001**	0.014*
MLR	0.31 ± 0.12	0.35 ± 0.10	0.44 ± 0.16	< 0.001**	0.434	< 0.001**	0.003*
MHR	0.019 ± 0.008	0.019 ± 0.008	0.021 ± 0.009	0.315	–	–	–
Crp/Alb	0.055 ± 0.059	0.049 ± 0.057	0.063 ± 0.052	0.493	–	–	–

WBC: white blood cell, CRP: C-reactive protein, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MLR: monocyte/lymphocyte ratio, MHR: monocyte/HDL ratio, Crp/Alb: CRP/albumin ratio.

Values were presented as mean and standard deviation and One-way ANOVA used.

Pairwise comparisons were made with Bonferroni-corrected post hoc test ($p < 0.017$ was considered significant).

P1: Comparison of Depot group and Oral AP Use group

P2: Comparison of Depot and Irregular AP Use group

P3: Comparison of Oral AP Use group and Irregular AP Use group

* $p < 0.05$ **$p < 0.001$

Clinical severity indices were meaningfully correlated. PANSS-P subscale showed weak correlations with PANSS-G and a moderate correlation with PANSS-T (r = 0.305; r = 0.626). PANSS-N demonstrated a moderate correlation with PANSS-T (r =

0.427) and a very weak correlation with disorder duration (r = 0.218). PANSS-G was strongly correlated with PANSS-T (r = 0.869) and very weakly correlated with disorder duration (r = 0.189) (Table 5).

Inflammatory biomarkers showed a distinct clustering pattern. NLR demonstrated moderate correlations with PLR and MLR (r = 0.686; r = 0.569), a weak correlation with PANSS-T (r = 0.317), and very weak correlations with PANSS-P and PANSS-N (r = 0.203; r = 0.234). PLR correlated moderately with NLR and MLR (r = 0.686; r = 0.452), very weakly with PANSS-P and PANSS-T (r = 0.192; r = 0.223), and showed a weak negative correlation with MHR (r = − 0.280). MLR showed moderate correlations with NLR, PLR, and MHR (r = 0.569; r = 0.452; r = 0.457), and a very weak correlation with PANSS-T (r = 0.178). MHR was weakly and negatively correlated with PLR (r = − 0.280) and moderately correlated with MLR (r = 0.457). Crp/Alb was weakly correlated only with MHR (r = 0.245) (Table 5).

Table 5
Correlations Between Clinical Measures and Inflammatory Biomarkers

Variable		PANSS-P	PANSS-N	PANSS-G	PANSS-T	Disorder Duration	NLR	PLR	MLR	MHR	Crp/Alb
PANSS-P	r	1									
	p										
PANSS-N	r	0.160	1								
	p	0.073									
PANSS-G	r	**0.305****	0.065	1							
	p	0.000	0.469								
PANSS-T	r	**0.626****	**0.427****	**0.869****	1						
	p	0.000	0.000	0.000							
Disorder Duration	r	0.081	**0.218***	**0.189***	**0.239****	1					
	p	0.365	0.014	0.034	0.007						
NLR	r	**0.203***	**0.234****	**0.230****	**0.317****	0.164	1				
	p	0.022	0.008	0.009	0.000	0.066					
PLR	r	**0.192***	0.094	0.170	**0.223***	0.072	**0.686****	1			
	p	0.030	0.291	0.056	0.012	0.421	0.000				
MLR	r	0.104	0.129	0.135	**0.178***	-0.019	**0.569****	**0.452****	1		
	p	0.244	0.148	0.132	0.046	0.833	0.000	0.000			
MHR	r	-0.010	0.018	0.102	0.078	-0.041	-0.116	**-0.280****	**0.457****	1	
	p	0.911	0.844	0.252	0.383	0.646	0.196	0.001	0.000		
Crp/Alb	r	0.064	-0.092	-0.048	-0.043	-0.134	0.090	0.115	0.121	**0.245****	1
	p	0.477	0.301	0.593	0.631	0.133	0.316	0.199	0.174	0.006	

PANSS: Positive and Negative Syndrome Scale, including the subscales, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MLR: monocyte/lymphocyte ratio, MHR: monocyte/HDL ratio, Crp/Alb: CRP/albumin ratio.

-Pearson correlation analysis was applied. Significant correlations indicated in bold.

* p < 0.05 **p < 0.001

ANCOVA analyses partly supported the notion that inflammatory differences are not solely attributable to clinical severity. After adjusting for PANSS total score as a covariate, NLR remained significantly different among treatment groups (F = 7.40, p = 0.001), and PANSS-T also had a significant effect on NLR levels (F = 6.13, p = 0.015). Adjusted mean values (EMM) were 2.15 (1.74–2.56) for the depot group, 2.77 (2.48–3.05) for the oral group, and 3.24 (2.87–3.60) for the irregular-use group. Post-hoc analyses indicated significantly lower NLR levels in the depot group compared with the oral (p = 0.042) and irregular groups (p = 0.001). Oral and irregular groups did not differ significantly (p = 0.162). For PLR and MLR, the effect of PANSS-T was not significant (p > 0.05), suggesting that the observed inflammatory differences among treatment groups were largely independent of clinical severity (Table 6).

Table 6
ANCOVA Results for Inflammatory Markers Adjusted for PANSS Total Score

	Group Effect (F, p, η²)	PANSS Effect (F, p)	EMM – Depot	EMM – Oral	EMM – Irregular AP	Post-hoc Comparisons (Bonferroni)
NLR	**F(2.123) = 7.40, p = 0.001**, η²=0.107**	**F(1.123) = 6.13, p = 0.015***	**2.15 (1.74–2.56)**	**2.77 (2.48–3.05)**	**3.24 (2.87–3.60)**	**Depot < Oral (p = 0.042); Depot < Irregular (p = 0.001); Oral ≈ Irregular (p = 0.162)**
PLR	F(2.123) = 5.54, p = 0.005*, η²=0.083	F(1.123) = 1.75, p = 0.188	100.7(86.7–114.8)	113.9 (104.1–123.8)	132.8 (120.2–145.4)	Depot < Irregular (p = 0.004); Oral ≈ Depot; Oral ≈ Irregular
MLR	F(2.123) = 7.61, p = 0.001**, η²=0.110	F(1.123) = 0.35, p = 0.558	0.31 (0.26–0.36)	0.35 (0.32–0.39)	0.43 (0.39–0.48)	Depot < Irregular (p = 0.001); Oral < Irregular (p = 0.012); Depot ≈ Oral

PANSS: Positive and Negative Syndrome Scale Total Score, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MLR: monocyte/lymphocyte ratio.

* p < 0.05 **p < 0.001

In HC3 heteroskedasticity-consistent multivariable regression models adjusted for age, sex, smoking status, disorder duration, metabolic covariates (Framingham score and lipids), and PANSS total, long-acting injectable coverage over the prior six months was associated with significantly lower inflammatory ratios at acute schizophrenia relapse compared with no treatment. Specifically, LAI coverage was linked to lower NLR (expβ = 0.747 (− 25.3%), 95% CI: 0.612–0.913, p = 0.004). Similar associations were observed for PLR (expβ = 0.779 (− 22.1%), 95% CI: 0.660–0.920, p = 0.003), MLR (expβ = 0.735 (− 26.5%), 95% CI: 0.596–0.908, p = 0.004).

In contrast, regular oral coverage did not differ significantly from no treatment for NLR (expβ = 0.929, (− 7.1%), 95% CI: 0.780–1.107, p = 0.408). Oral coverage showed only borderline differences for platelet-to-lymphocyte ratio (expβ = 0.873, p = 0.056) and MLR (expβ = 0.845, p = 0.061). MHR did not significantly differ across groups (oral vs no treatment: p = 0.170; LAI vs no treatment: p = 0.181) (Table 7).

Table 7
Adjusted associations between 6-month antipsychotic treatment coverage patterns and peripheral inflammatory indices at acute schizophrenia relapse

NLR	Contrast	expβ (95% CI)	%Δ (95% CI)	p
	ORAL vs NONE	**0.929 (0.780–1.107)**	**−7.1 (− 22.0 to 10.7)**	**0.408**
NLR	LAI vs NONE	0.747 (0.612–0.913)	−25.3 (− 38.8 to − 8.7)	0.005*
PLR	ORAL vs NONE	0.873 (0.759–1.004)	−12.7 (− 24.1 to 0.4)	0.056
PLR	LAI vs NONE	0.779 (0.660–0.920)	−22.1 (− 34.0 to − 8.0)	0.003*
MLR	ORAL vs NONE	0.845 (0.709–1.008)	−15.5 (− 29.1 to 0.8)	0.061
MLR	LAI vs NONE	0.735 (0.596–0.908)	−26.5 (− 40.4 to − 9.2)	0.005*
MHR	ORAL vs NONE	0.896 (0.766–1.049)	−10.4 (− 23.4 to 4.9)	0.170
MHR	LAI vs NONE	0.877 (0.724–1.064)	−12.3 (− 27.6 to 6.4)	0.181

Note: Outcomes were log-transformed. expβ is the exponentiated regression coefficient, interpreted as the ratio of geometric means relative to the reference group (NONE). %Δ = (expβ − 1) × 100. Models were estimated using multivariable linear regression with HC3 heteroskedasticity-consistent (robust) standard errors.

Covariates: age, sex, smoking status, disorder duration, Framingham risk score, LDL, triglycerides, HDL, and PANSS total.

Abbreviations: LAI, long-acting injectable; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; MHR, monocyte-to-HDL ratio; CI, confidence interval.

Sensitivity analyses supported the robustness of these findings. Results were materially unchanged after excluding clozapine and olanzapine from the oral group. In analyses restricted to treated patients with overlapping molecules limited to aripiprazole, risperidone, and paliperidone, and with additional adjustment for molecule category and chlorpromazine-equivalent dose, LAI formulation remained associated with a lower neutrophil-to-lymphocyte ratio compared with regular oral treatment (p = 0.037).

4. Discussion

This study examined whether different antipsychotic treatment patterns, including regular long-acting injectable (LAI) use, regular oral antipsychotic use, and irregular or absent treatment in the six months preceding hospitalization, were associated with peripheral inflammatory markers during an acute psychotic relapse. The principal finding was that patients who maintained regular antipsychotic treatment, particularly with LAI formulations, exhibited substantially lower levels of inflammatory indices (NLR, PLR, MLR) compared with those with irregular or no treatment. Importantly, the LAI group demonstrated the lowest NLR values even after adjusting for PANSS total scores, indicating that part of this difference cannot be explained solely by variations in clinical symptom severity. Together, these results suggest that treatment continuity and formulation type may contribute meaningfully to the inflammatory profile observed during relapse in schizophrenia.

Our results align with growing evidence that antipsychotic treatment exerts a modulatory effect on the immune system in schizophrenia. Previous meta-analyses have demonstrated marked decreases in pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) following the initiation of antipsychotics in first-episode psychosis [33]. Similarly, reductions in inflammatory markers have been observed in relapsed patients after stabilizing treatment, suggesting that antipsychotics may suppress the acute inflammatory burden associated with psychosis [34, 35]. In addition, serum interleukin (IL)-17 values were detected to change after stable depot antipsychotic treatment, indicating suppression of high inflammation [36]. However, most available studies have examined either medicated versus unmedicated patients or have treated antipsychotic exposure as a binary variable, without differentiating between specific treatment patterns [37, 38]. Our findings extend this literature by demonstrating that not only the presence of treatment but also its regularity and formulation are relevant to inflammatory status. This level of differentiation is largely absent in prior research, making the present study one of the few to evaluate inflammation across clinically meaningful adherence-related subgroups in a naturalistic inpatient context.

The observed inflammatory advantage associated with LAI treatment may be explained by several mechanisms. First, LAIs minimize fluctuations in plasma drug levels, providing more stable dopaminergic and immunomodulatory effects [28, 29]. Irregular oral use or prolonged treatment gaps are likely to induce repeated cycles of partial dopaminergic blockade and withdrawal, each potentially contributing to immune activation. Second, non-adherence is often linked to psychosocial stress, lifestyle instability, and sleep disruption. Each of these factors independently contributes to heightened systemic inflammation and may compound psychiatric deterioration [39, 40]. Third, LAI use may reduce relapse frequency and severity across months, limiting cumulative neuroinflammatory burden. Although the present study captures inflammation at a single relapse point, long-term adherence patterns may still exert meaningful upstream effects that shape inflammatory trajectories.

A key finding of our study is the convergence of inflammatory profiles between the depot and the strictly adherent oral monotherapy groups. While the LAI group exhibited the numerically lowest NLR values, the statistical difference between adherent oral users and LAI users was not substantial for most markers. This suggests that the immunomodulatory benefit is likely intrinsic to the antipsychotic molecule itself rather than the delivery vehicle. However it is crucial to interpret this in a clinical context considering that our oral group consisted of patients with confirmed adherence. In real-world practice, where adherence to oral medication is often incomplete or difficult to verify, the more reliable drug delivery provided by long-acting injectable antipsychotics may represent a pharmacokinetic safeguard [27]. Thus, the lack of widespread statistical difference between the two adherent groups actually reinforces the biological efficacy of the treatment; LAIs simply ensure this biological effect is sustained against the behavioral volatility of the disorder [26].

We must also acknowledge the potential for reciprocal causality in the relationship between treatment discontinuation and elevated inflammation. While our primary hypothesis posits that withdrawing antipsychotic suppression leads to an inflammatory rebound [21], the reverse pathway is also plausible. It has been proposed that pro-inflammatory cytokines may induce sickness behavior, manifesting as cognitive dulling or motivational deficits that contribute to non-adherence [40]. Therefore, patients with higher intrinsic inflammatory baselines might be more prone to stopping medication. Regardless of the direction of the association—whether inflammation contributes to non-adherence or non-adherence reflects an underlying inflammatory burden—the clinical relevance remains broadly similar. Maintaining continuous antipsychotic coverage, including with long-acting injectable formulations, may support more stable treatment exposure and lower relapse risk in real-world practice. Nevertheless, the extent to which treatment continuity itself affects inflammatory pathways, as well as the direction of such an effect, requires confirmation in longitudinal studies with repeated biomarker measurements [41]. Our study was not designed to differentiate drug-specific effects, as medication classes varied within groups. Nevertheless the consistent gradient observed across the LAI oral and irregular treatment groups suggests that treatment pattern may be a stronger determinant of inflammatory status than the specific antipsychotic used. This finding may suggest that drug persistence and stability of neurobiological signaling may be critical regulators of immunological tone in schizophrenia.

Furthermore, the persistence of inflammatory differences, specifically NLR, between treatment groups even after adjusting for clinical severity is a noteworthy result. While previous studies have linked NLR directly to psychopathology severity [37, 42], our ANCOVA models indicate that group differences in inflammatory indices persisted after adjustment for PANSS, suggesting that observed differences were not fully accounted for by symptom severity, without implying a direct anti-inflammatory effect of continuity. This supports the concept that schizophrenia involves a chronic inflammatory component that requires sustained management, much like the somatic maintenance treatment in autoimmune conditions. An unexpected moderate negative correlation between MHR and PLR was observed in the entire sample. This finding might reflect differing roles of lipid metabolism and platelet-driven inflammation in the immune dysregulation observed in schizophrenia. While MHR reflects atherogenic and metabolic inflammation, PLR is more indicative of acute inflammatory response [43]. Their inverse relationship may represent compensatory or divergent immunological mechanisms, warranting further exploration. While CRP/albumin ratio is a sensitive and validated systemic inflammatory index in many psychiatric and medical conditions, it did not significantly differ across groups in our cohort. This might be due to the overall exclusion of patients with overt metabolic or infectious comorbidities, which typically elevate c-reactive protein. Nonetheless, the inclusion of Crp/Alb enriches the biomarker profile and may offer diagnostic value in broader or untreated populations.

Limitations

This study contributes to the literature by simultaneously comparing depot, oral, and irregular-use groups using a composite panel of inflammatory indices (NLR, PLR, MLR, MHR) rather than single markers. However, several limitations must be considered. The retrospective and cross-sectional design prevents definitive causal conclusions. Although we adjusted for clinical severity, unmeasured lifestyle factors such as diet, smoking intensity, and physical activity could act as confounders. Additionally, adherence in the oral group was inferred from prescription records, which may not fully reflect actual intake compared to the objective nature of depot administration. Finally, inflammatory markers were assessed at a single time point; longitudinal monitoring would better elucidate the temporal relationship between treatment formulation and immune regulation.

5. Conclusion

In conclusion this study provides evidence that antipsychotic treatment continuity is associated with a significantly lower peripheral inflammatory burden during relapse in schizophrenia. Our findings demonstrate that while regular oral and depot treatment coverage was associated with lower peripheral inflammatory indices compared with no antipsychotic use. LAI formulations may offer a pragmatic advantage by supporting more continuous exposure in routine care, but the present design cannot confirm a protective or direct anti-inflammatory effect, nor determine mechanisms. These results highlight the critical role of adherence-focused treatment strategies and suggest that accessible inflammatory markers such as NLR and PLR could serve as informative adjuncts in evaluating clinical stability. Future prospective studies incorporating longitudinal monitoring are needed to further clarify the causal mechanisms and to determine whether optimizing treatment patterns can contribute to improved long-term systemic health outcomes.

Declarations

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

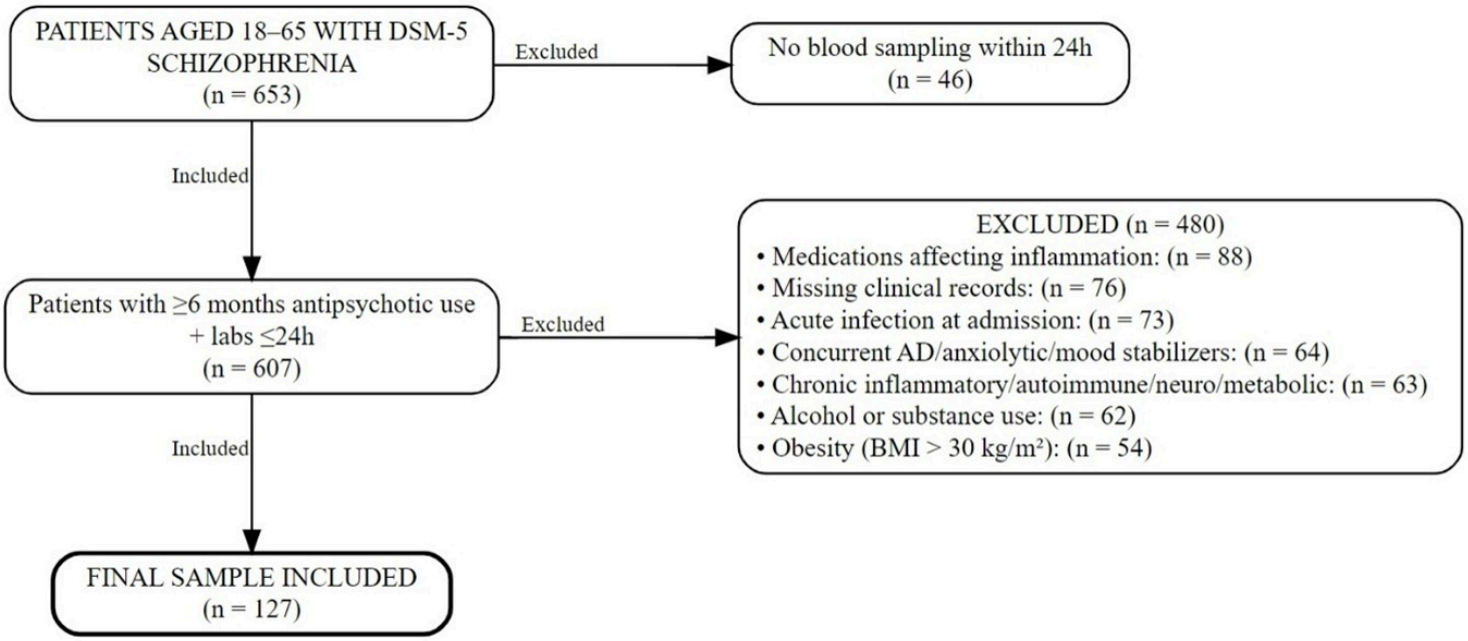


Figure 1

Flow diagram of patient screening, eligibility assessment, and final sample selection