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# Complete blood count-derived inflammatory markers and symptom phenotypes in schizophrenia spectrum disorders: A hierarchical clustering analysis

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ABSTRACT

*Background:* Schizophrenia spectrum disorders (SSDs) show substantial clinical heterogeneity, potentially reflecting distinct pathophysiological mechanisms. Peripheral immune-inflammatory alterations have been implicated in SSDs, yet their links with specific clinical phenotypes remain largely unexplored. This study thus aimed to examine associations between complete blood count-derived inflammatory markers and symptom patterns in inpatients with SSDs.

*Methods:* This cross-sectional study included inpatients with SSDs. Hierarchical clustering was applied to Positive and Negative Syndrome Scale (PANSS) five-factor scores to identify symptom-based phenotypes. Six markers – neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) – were compared across clusters using analysis of variance and multivariable linear regressions.

*Results:* Among 454 inpatients with SSDs aged 18–65, three clusters emerged: Positive/excited-dominant ($n$ = 185, 40.8%), Negative/disorganised/depressive-dominant ($n$ = 133, 29.3%), and Balanced ($n$ = 136, 30.0%). All inflammatory markers significantly differed across clusters: NLR ($F = 3.29$, $p = 0.038$), MLR ($F = 11.13$, $p < 0.001$), PLR ($F = 3.71$, $p = 0.025$), SII ($F = 3.34$, $p = 0.036$), SIRI ($F = 7.42$, $p < 0.001$), and AISI ($F = 6.49$, $p = 0.002$). The Negative/disorganised/depressive-dominant cluster exhibited the most pronounced inflammatory profile, with covariate-adjusted increases compared to the Balanced cluster of +30% for MLR ($p = 0.001$), +20% for PLR ($p = 0.040$), +32% for SII ($p = 0.043$), +43% for SIRI ($p = 0.011$), and +52% for AISI ($p = 0.015$). The Positive/excited-dominant cluster showed selective, covariate-adjusted elevations in MLR (+19%, $p = 0.020$) and SIRI (+29%, $p = 0.028$) versus the Balanced cluster.

*Conclusions:* Distinct SSD phenotypes are associated with heterogeneous inflammatory profiles, with monocyte-driven inflammation particularly characterizing negative/disorganised/depressive presentations, probably supporting phenotype-stratified approaches in precision psychiatry.

## 1. Introduction

Schizophrenia spectrum disorders (SSDs) are severe mental conditions mainly characterized by positive and negative symptoms (Carrà et al., 2022). However, SSDs show substantial relative clinical heterogeneity and interindividual variation in symptom profiles (Wolfers et al., 2018). This is especially true during acute phases (Demjaha et al., 2009), when people suffering from SSDs display varying combinations of independent symptom structures rather than uniform clinical presentations (Fekih-Romdhane et al., 2023). This heterogeneity may reflect distinct underlying pathophysiological mechanisms across subjects still meeting the same categorical diagnostic criteria (Fekih-Romdhane et al., 2023; Wolfers et al., 2018).

Among the multiple neurobiological, psychological, and environmental factors putatively implicated in SSDs (Misiak et al., 2021; Pillinger et al., 2019), alterations in immune-inflammatory processes may represent key pathophysiological mechanisms that underlie this complex clinical presentation (Kachouchi et al., 2024; Khandaker et al., 2015; Kirkpatrick and Miller, 2013; Müller, 2018). Meta-analytic evidence has shown peripheral immune-inflammatory marker alterations

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in subjects with SSDs (Goldsmith et al., 2016; Misiak et al., 2021), with elevated pro-inflammatory cytokines, chemokines, and antibodies observed throughout illness course (Halstead et al., 2023; Miller et al., 2011; Na et al., 2014). However, many of these biomarkers require specialized laboratory assays, constraining their scalability and routine implementation in clinical settings. In this context, complete blood count (CBC)-derived indices have gained attention as accessible, easily reproducible, and cost-effective alternatives for assessing relevant immune-inflammatory processes (Brinn and Stone, 2020; Sandberg et al., 2021). These include the neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-lymphocyte ratio (MLR), and the platelet-to-lymphocyte ratio (PLR), as well as emerging composite indices such as the systemic immune-inflammation index (SII), the systemic inflammation response index (SIRI), and the aggregate index of systemic inflammation (AISI). Each of these is characterized by different immune cell proportions, potentially reflecting different pathophysiological processes (Ninla-aesong et al., 2024).

Along with their potential role as diagnostic and prognostic biomarkers across several medical conditions (e.g., Ou et al., 2025; Refaat et al., 2025), such indices may mirror pathobiological processes relevant for brain dysfunction (Bhikram and Sandor, 2022; Bioque et al., 2022) and are increasingly studied as clinically informative biomarkers in severe mental disorders (Cavaleri et al., 2025, 2026; Duan et al., 2025), including SSDs (Karageorgiou et al., 2019; Moody and Miller, 2018). Previous investigations have shown that these markers differ among individuals with schizophrenia as compared with healthy controls (Clausen et al., 2024; Zhu et al., 2022), in that they increase during relapse (Özdin and Böke, 2019), and correlate with positive and negative symptom severity (Cavaleri et al., 2024; Wang et al., 2024). Nonetheless, it remains unclear if any of these markers associate with specific symptom profiles, as just one study has examined their association with Positive and Negative Syndrome Scale (PANSS) factors (Liu et al., 2024) and none has investigated whether they map onto specific symptom patterns and phenotypes.

Indeed, a phenotype-oriented approach that groups subjects based on multivariate symptom configurations – rather than isolated symptom dimensions – might provide a more clinically informative framework to test biomarker-symptom links. In this context, factor-based PANSS models can help operationalise this approach by deriving a set of clinically interpretable symptom dimensions (i.e., factor scores) suitable for symptom-based clustering. Among the PANSS five-factor models proposed in the literature, the construct by Wallwork and colleagues (Wallwork et al., 2012) represents a consensus-derived "core-item" solution; unlike broader 30-item models (e.g., Marder's), Wallwork's retains only 20 PANSS items selected for their most consistent item-to-factor allocation across prior five-factor models, showing the best fit indices compared to alternatives (Roithmeier et al., 2025).

With this work we thus aimed to examine the associations between CBC-derived markers and different symptom patterns in inpatients with SSDs. Specifically, we sought to compare NLR, MLR, PLR, SII, SIRI, and AISI across distinct symptom phenotypes identified through cluster analysis of PANSS five-factor scores according to Wallwork's model, also accounting for the possible influence of demographic, clinical, and treatment covariates.

## 2. Material and methods

This cross-sectional study was designed and reported following the "Strengthening the Reporting of Observational studies in Epidemiology (STROBE)" statement (von Elm et al., 2008). It was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) (World Medical Association, 2025) and approved by the local Ethics Committee ("Comitato Etico Territoriale Area 3", Milan) as a part of the broader Northern Milan Area Cohort (NOMIAC) project (registration number: 672–17112020) (Bartoli et al., 2025; Cavaleri et al., 2025). Written informed consent was collected for the processing of personal data as part of routine clinical care.

### 2.1. Setting and eligibility criteria

We included individuals consecutively admitted for inpatient treatment from May 2020 to September 2025 to psychiatric intensive care units of the broader Milan metropolitan area.

Subjects were included if they: i) were aged between 18 and 65 years at admission; ii) were diagnosed with a SSD as per DSM-5 criteria (American Psychiatric Association, 2013); iii) underwent routine blood sampling and psychometric evaluations on the first full day of hospitalization.

We excluded people: i) aged $< 18$ or $> 65$ years; ii) with intellectual disability, cognitive impairment, or dementia as the primary diagnosis; iii) without available CBC data; iv) with ongoing inflammatory, infectious (SARS-CoV-2 infection was systematically excluded in all patients via nasopharyngeal swab testing), or autoimmune diseases at the time of admission, as ascertained through clinical assessment, physical examination, and review of medical records; v) treated with clozapine, considering its known influence on granulocytes (Girardin et al., 2014).

For study participants with multiple admissions, we analysed data from the first complete record.

### 2.2. Data collection

We collected socio-demographic and clinical information, particularly correlates potentially influencing CBC-based inflammatory parameters, such as age, sex, diagnosis, current alcohol (AUD) and substance (SUD) use disorders, and antipsychotic treatment (drugs and dosages) at admission. The ratio between the prescribed daily dose (PDD) and the defined daily dose (DDD), according to the WHO ATC/DDD index, last updated on 27 December 2024 (https://atcddd.fhi.no/atc_ddd_index/, accessed 3 November 2025), was used to estimate the equivalent daily doses of antipsychotics (PDD/DDD ratio).

Data were obtained from clinical interviews, individual electronic records, and chart review. Trained assessors identified hospitalized subjects with SSDs using the Structured Clinical Interview for DSM-5 (SCID-5) (First et al., 2016). Psychotic symptoms were assessed using the PANSS (Kay et al., 1987).

Blood samples were routinely collected around 8.00 a.m., after an overnight fast, and immediately analysed employing flow cytometry techniques performed on fully automated haematology workstations to obtain CBCs, including differential neutrophil, leucocyte, monocyte, and platelet counts. Relevant inflammatory markers were estimated from the CBC as follows: i) NLR = neutrophils/lymphocytes; ii) MLR = monocytes/lymphocytes; iii) PLR = platelets/lymphocytes; iv) SII = (neutrophils×platelets)/lymphocytes; v) SIRI = (neutrophils×monocytes)/lymphocytes; vi) AISI = (neutrophils×monocytes×platelets)/lymphocytes.

Pseudonymized data were included in a standardized extraction template and double-checked to ensure accuracy.

### 2.3. Wallwork's five-factor model

Wallwork's five-factor model (Wallwork et al., 2012) is a widely validated dimensional structure of the PANSS that organizes 20 PANSS items into five distinct symptom dimensions: positive factor (P1, P3, P5, G9); negative factor (N1, N2, N3, N4, N6, G7); disorganised/concrete factor (P2, N5, G11); excited factor (P4, P7, G8, G14), and depressed factor (G2, G3, G6). This model demonstrated superior fit indices compared to the original three-subscale PANSS structure as well as to other five-factor models (Wallwork et al., 2012).

### 2.4. Cluster analysis

Hierarchical clustering using Ward's method was performed on

standardized PANSS scores according to Wallwork's approach (Wallwork et al., 2012). PANSS five-factor scores were standardized using z-score transformation (z = [x − mean] / SD) to ensure equal contribution to clustering of all factors, despite differing in number of items. The optimal number of clusters (k) between two and ten was determined using the Calinski/Harabasz pseudo-F index, with higher values indicating a better-defined cluster solution. Cluster stability was examined via bootstrap resampling (1000 resamples); in each resample, Ward's hierarchical clustering was repeated, and the optimal number of clusters was re-evaluated using the original stopping rule, selecting the value of k that maximized the Calinski-Harabasz pseudo-F statistic (Supplementary Table 1).

Resulting clusters were characterized and interpreted as data-driven constructs according to the mean z-scored PANSS five-factor profiles of each group. Each cluster was labelled according to the symptom dimensions showing the highest standardized mean scores relative to the other clusters, with differences further described using one-way ANOVA and Bonferroni-corrected pairwise comparisons.

### 2.5. Comparative analyses across clusters

Standard descriptive statistics were used to characterize the study sample and each identified cluster. For categorical variables, chi-square or exact tests were run to assess associations with cluster assignment. Continuous variables were assessed for normality using the Shapiro-Wilk test. For right-skewed distributions but no zero-inflation, log-transformation was conducted. Based on relevant assumptions, one-way analyses of variance (ANOVAs) with Bonferroni post-hoc correction were conducted. Additionally, for continuous variables with zero-inflated distributions (defined as >50% zero values), Kruskal-Wallis tests were performed to handle zero-inflated data by assigning tied ranks to zero values. In all cases, descriptive statistics were reported on the original scale for clinical interpretability.

To examine relationships between clusters and complete blood count-derived inflammatory indexes (NLR, MLR, PLR, SII, SIRI, AISI), separate ANOVAs were performed for each inflammatory marker across clusters followed by Bonferroni-corrected pairwise comparisons. Multivariable linear regression analyses with robust standard errors (to account for potential heteroskedasticity) were then conducted on log-transformed inflammatory markers to estimate Bonferroni-corrected covariate-adjusted group differences while controlling for potential confounders, i.e., age, sex, diagnostic category, comorbid AUD and SUD, and first- and second-generation antipsychotic PDD/DDD (Argote et al., 2023; Pillinger et al., 2020); first- and second-generation antipsychotic PDD/DDD ratios were included as separate covariates rather than as a single total antipsychotic load based on evidence that first- and second-generation antipsychotics exert differential inflammatory, immunomodulatory, and metabolic effects that may independently influence CBC-derived inflammatory indices, allowing for a more granular and biologically informed adjustment. Adjusted Cohen's d effect sizes with 95% confidence intervals (CIs) were computed from regression t-statistics for all pairwise cluster comparisons.

Statistical significance was set at $\alpha = 0.05$ (two-tailed). All analyses were performed using Stata 19 (StataCorp LLC. 2025, College Station, TX, USA).

## 3. Results

### 3.1. Participant inclusion and characteristics

Out of 805 observations collected between May 2020 and September 2025, only data from the first psychiatric admission for each subject with complete data was retained to ensure independence of observations. A total of 570 unique individuals were identified. Five individuals < 18 years and 48 > 65 years were excluded. Among the remaining 517 subjects, 27 lacked CBC data (missing completely at random assumption). Of the 490 individuals with available CBC data, 36 were excluded due to ongoing clozapine treatment. The final sample comprised 454 participants (288 males, 63.4%) with a mean age of 41.2 (SD = 13.0) years.

The flow chart of participant inclusion process is reported in Fig. 1.

Among SSDs, the most represented diagnoses were unspecified SSD ($n = 151$, 33.3%), schizophrenia ($n = 104$, 22.9%), and schizoaffective disorder ($n = 67$, 14.8%). Comorbid AUD was present in 8.4% ($n = 38$), while comorbid SUD in 20.9% of the sample ($n = 95$). Less than half of the sample ($n = 212$, 46.7%) was undergoing antipsychotic treatment at admission, and among them 76 (35.8%) were receiving antipsychotic polypharmacy. Sample characteristics are reported in Table 1.

### 3.2. Cluster description

Using Ward's hierarchical clustering method applied to standardized PANSS five-factor scores, the Calinski–Harabasz pseudo-F statistic suggested three clusters as optimal (pseudo-F = 99.08) (Supplementary Table 1a). The corresponding hierarchical cluster dendrogram is shown in Supplementary Fig. 1. Bootstrap resampling (1000 resamples) provided support for the three-cluster solution, with k = 3 yielding the highest Calinski–Harabasz pseudo-F in 567 out of 1000 resamples (56.7%) (Supplementary Table 1b).

The resulting clusters showed clear separation, as indicated by ANOVAs and Bonferroni-corrected pairwise comparisons of the five factors across these three clusters.

The first cluster ($n = 185$, 40.8%) displayed the highest positive and excited symptom levels, while simultaneously exhibiting the lowest negative, disorganised/concrete, and depressive symptom levels. Such a clinical profile, characterized by florid positive symptoms and pronounced excitement and agitation, was therefore labelled as the "Positive/excited-dominant cluster".

The second cluster ($n = 133$, 29.3%) showed highest negative, disorganised/concrete, and depression/anxiety symptoms, while positive and excited symptoms were moderate-low. This profile reflected prominent negative syndrome, marked conceptual disorganization, and substantial depressive symptomatology, thus defined as the "Negative/disorganised/depressive-dominant cluster".

The third cluster ($n = 136$, 30.0%) was characterized by a balanced distribution of symptom scores across all factors. Since it had a heterogeneous presentation with no prevalent single symptom domain within the group or relative to the other clusters, it was designated as the "Balanced cluster".

The comparisons of PANSS five-factor scores across clusters are shown in Table 2.

The three clusters showed comparability in terms of age and sex. No statistically significant differences in absolute counts of neutrophils ($p = 0.281$), lymphocytes ($p = 0.100$), and platelets ($p = 0.423$) across clusters emerged. However, a statistically significant cluster effect was observed for monocytes ($p = 0.002$), with the Balanced symptom cluster having significantly lower monocyte counts than both Positive/excited-dominant cluster ($p = 0.025$) and Negative/disorganised/depressive-dominant cluster ($p = 0.002$).

The characteristics of the study sample and of each cluster, with cross-comparison statistics, are reported in Table 3.

### 3.3. Inflammatory markers across clusters: unadjusted and covariate-adjusted comparative analyses

Across clusters, one-way ANOVA indicated statistically significant differences for all inflammatory markers: NLR ($F = 3.29$, $p = 0.038$), MLR ($F = 11.13$, $p < 0.001$), PLR ($F = 3.71$, $p = 0.025$), SII ($F = 3.34$, $p = 0.036$), SIRI ($F = 7.42$, $p < 0.001$), and AISI ($F = 6.49$, $p = 0.002$) (Table 3).

Pairwise comparisons showed no statistically significant differences between the Positive/excited-dominant and Negative/disorganised/

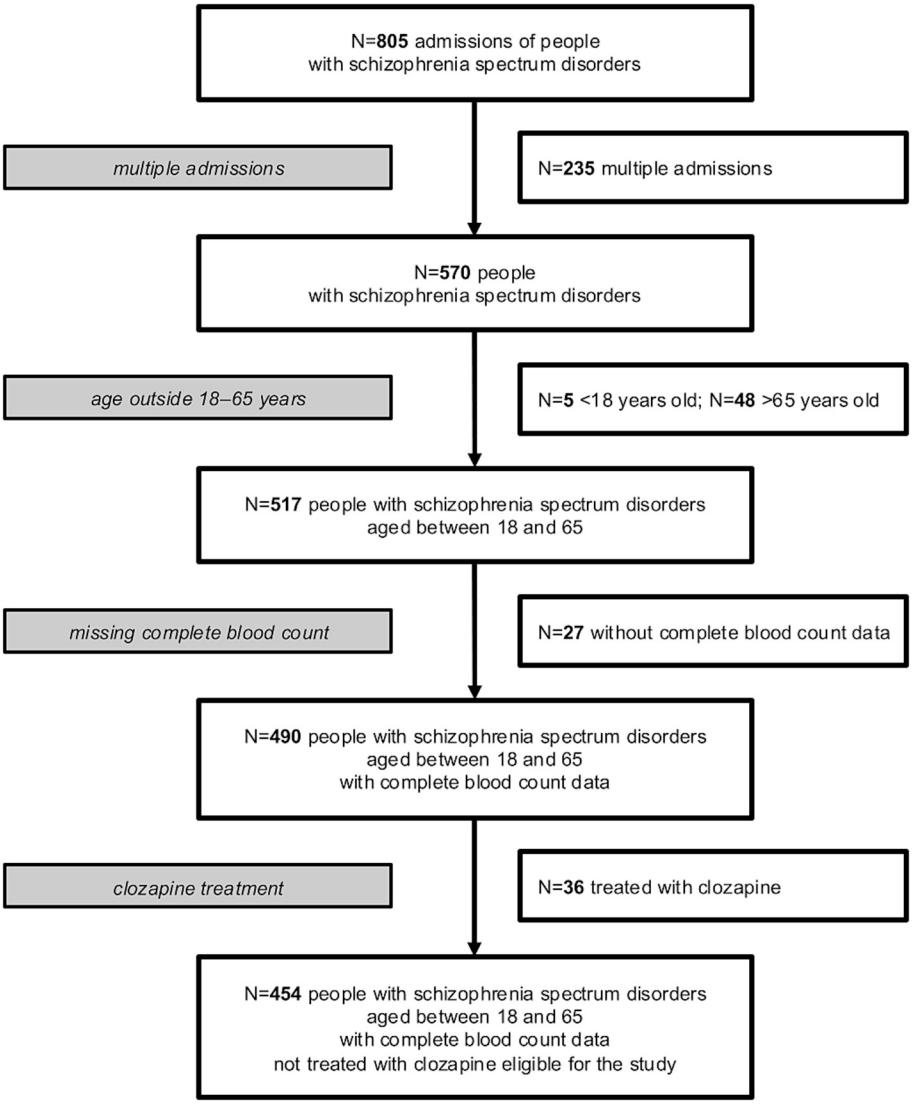


**Fig. 1.** Flow chart of participant inclusion process.

depressive-dominant clusters for any marker, in either unadjusted or covariate-adjusted analyses.

The Positive/excited-dominant cluster showed MLR (+19%, $p$ = 0.007) and SIRI (+28%, $p$ = 0.019) higher than the Balanced cluster in unadjusted analyses, while no statistically significant unadjusted differences were detected for NLR ($p$ = 0.243), PLR ($p$ > 0.999), SII ($p$ = 0.488), or AISI (p = 0.068). After covariate adjustment, MLR (+19%, p = 0.020) and SIRI (+29%, p = 0.028) were significantly higher in the Positive/excited-dominant cluster, whereas NLR ($p$ = 0.136), PLR ($p$ = 0.644), SII ($p$ = 0.223), and AISI ($p$ = 0.071) again did not differ significantly from the Balanced cluster.

The Negative/disorganised/depressive-dominant cluster had significantly higher indices than the Balanced cluster across all markers in unadjusted analyses: NLR (+20%, $p$ = 0.036), MLR (+34%, $p$ < 0.001), PLR (+15%, $p$ = 0.028), SII (+24%, $p$ = 0.030), SIRI (+44%, $p$ = 0.001), and AISI (+49%, p = 0.001). After adjusting for covariates, statistical significance was found for all comparisons between the Negative/disorganised/depressive-dominant and the Balanced clusters but the one on NLR ($p$ = 0.057), with only minimal changes in magnitude: MLR (+30%, $p$ = 0.001), PLR (+20%, p = 0.040), SII (+32%, p = 0.043), SIRI (+43%, p = 0.011), and AISI (+52%, p = 0.015).

Univariate and covariate-adjusted comparisons of inflammatory markers across clusters, along with Cohen's d effect sizes for all pairwise comparisons, are reported in Table 4, while full regression analyses details are reported in Supplementary Tables 2–7.

Forest plots of covariate-adjusted comparisons of inflammatory markers across clusters are presented in Fig. 2.

## 4. Discussion

### 4.1. Summary and interpretation of findings

This study employed hierarchical clustering to examine the association between CBC-derived inflammatory markers – namely NLR, MLR, PLR, SII, SIRI, and AISI – and specific symptom patterns in inpatients with SSDs. While evidence in this field is currently limited to a small number of investigations assessing associations between individual inflammatory markers and either global severity (Karageorgiou et al., 2019; Mojadadi et al., 2024) or broad symptom dimensions (Cavaleri et al., 2024; Šagud et al., 2023), our approach allowed us to explore whether distinct phenotypic presentations of SSDs are associated with different inflammatory biomarker profiles.

In our study, direct comparison of inflammatory markers demonstrated significant differences in all six inflammatory indices across the three identified clusters. Both the Positive/excited- and the Negative/disorganised/depressive-dominant clusters had significantly higher

**Table 1**
Sample characteristics.

| Characteristic | Total sample ($N = 454$) |
|---|---|
| *Demographics* | |
| Age (years), *mean ± SD* | 41.2 ± 13.0 |
| Male sex, *n (%)* | 288 (63.4%) |
| *Diagnosis* | |
| Brief psychotic disorder, *n (%)* | 43 (9.5%) |
| Delusional disorder, *n (%)* | 36 (7.9%) |
| Psychotic disorder due to another medical condition, *n (%)* | 4 (0.9%) |
| Other specified schizophrenia spectrum and other psychotic disorder, *n (%)* | 11 (2.4%) |
| Schizoaffective disorder, *n (%)* | 67 (14.8%) |
| Schizophrenia, *n (%)* | 104 (22.9%) |
| Schizophreniform disorder, *n (%)* | 4 (0.9%) |
| Substance/medication-induced psychotic disorder, *n (%)* | 34 (7.5%) |
| Unspecified schizophrenia spectrum and other psychotic disorder, *n (%)* | 151 (33.3%) |
| *Comorbid alcohol and substance use disorders* | |
| Comorbid Alcohol Use Disorder, *n (%)* | 38 (8.4%) |
| Comorbid Substance Use Disorder, *n (%)* | 95 (20.9%) |
| *PANSS factors* | |
| Positive factor, *mean ± SD* | 13.1 ± 5.1 |
| Negative factor, *mean ± SD* | 14.7 ± 7.7 |
| Disorganised/concrete factor, *mean ± SD* | 8.6 ± 3.5 |
| Excited factor, *mean ± SD* | 11.0 ± 5.5 |
| Depressed factor, *mean ± SD* | 6.8 ± 3.0 |
| *Antipsychotic treatment* | |
| Taking any AP, *n (%)* | 212 (46.7%) |
| Taking more than one AP, *n (%)* | 76 (16.7%) |
| AP PDD/DDD [a] | |
| *mean ± SD* | 0.63 ± 0.92 |
| *median (Q1–Q3)* | 0.0 (0.0–1.0) |
| Taking FGA, *n (%)* | 111 (24.5%) |
| FGA PDD/DDD [b] | |
| *mean ± SD* | 0.21 ± 0.56 |
| *median (Q1–Q3)* | 0.0 (0.0–0.0) |
| Taking SGA, *n (%)* | 146 (32.2%) |
| SGA PDD/DDD [c] | |
| *mean ± SD* | 0.42 ± 0.74 |
| *median (Q1–Q3)* | 0.0 (0.0–0.7) |
| *Blood cell counts* | |
| Neutrophils ($10^3$/μL) | |
| *mean ± SD* | 5.37 ± 2.60 |
| *median (Q1–Q3)* | 4.86 (3.53–6.54) |
| Lymphocytes ($10^3$/μL) | |
| *mean ± SD* | 2.25 ± 0.87 |
| *median (Q1–Q3)* | 2.12 (1.69–2.74) |
| Monocytes ($10^3$/μL) | |
| *mean ± SD* | 0.68 ± 0.25 |
| *median (Q1–Q3)* | 0.64 (0.51–0.83) |
| Platelets ($10^3$/μL) | |
| *mean ± SD* | 257.5 ± 76.1 |
| *median (Q1–Q3)* | 249 (210–289) |
| *Inflammatory markers* | |
| NLR | |
| *mean ± SD* | 2.82 ± 2.17 |
| *median (Q1–Q3)* | 2.18 (1.54–3.31) |
| MLR | |
| *mean ± SD* | 0.343 ± 0.188 |
| *median (Q1–Q3)* | 0.299 (0.227–0.402) |
| PLR | |
| *mean ± SD* | 130.8 ± 64.4 |
| *median (Q1–Q3)* | 117 (89–159) |
| SII | |
| *mean ± SD* | 739.7 ± 648.3 |
| *median (Q1–Q3)* | 549 (357–899) |
| SIRI | |
| *mean ± SD* | 2.08 ± 2.38 |
| *median (Q1–Q3)* | 1.41 (0.86–2.27) |
| AISI | |
| *mean ± SD* | 558.8 ± 717.8 |
| *median (Q1–Q3)* | 353 (199–650) |

Abbreviations: AISI, aggregate index of systemic inflammation; AP, antipsychotic; FGA, first-generation antipsychotic; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PANSS, Positive and Negative Syndrome Scale; PDD/DDD: ratio between the prescribed daily dose (PDD) and the defined daily dose (DDD); PLR, platelet-to-lymphocyte ratio; Q1, first quartile; Q3, third quartile; SGA, second-generation antipsychotic; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.
[a] n = 6 missing.
[b] n = 3 missing.
[c] *n* = 3 missing.

**Table 2**
One-way ANOVA and Bonferroni post-hoc comparisons of PANSS five-factor scores across clusters.

| PANSS factor | Overall ANOVA *F(2,451), p-value* | Bonferroni-corrected comparisons *Comparison: MD, p-value* |
|---|---|---|
| Positive (P1, P3, P5, G9) | F = 103.90, p < 0.001 | Pos/exc vs Neg/dis/dep: MD = 3.25, $p < 0.001$<br>Pos/exc vs Bal: MD = 6.86, $p < 0.001$<br>Neg/dis/dep vs Bal: MD = 3.61, p < 0.001 |
| Negative (N1, N2, N3, N4, N6, G7) | F = 247.62, p < 0.001 | Pos/exc vs Neg/dis/dep: MD = −12.84, $p < 0.001$<br>Pos/exc vs Bal: MD = −1.81, $p = 0.008$<br>Neg/dis/dep vs Bal: MD = 11.03, p < 0.001 |
| Disorganised/concrete (P2, N5, G11) | F = 66.28, $p <$ 0.001 | Pos/exc vs Neg/dis/dep: MD = −1.81, $p < 0.001$<br>Pos/exc vs Bal: MD = 2.51, p < 0.001<br>Neg/dis/dep vs Bal: MD = 4.32, p < 0.001 |
| Excited (P4, P7, G8, G14) | F = 116.13, p < 0.001 | Pos/exc vs Neg/dis/dep: MD = 3.84, p < 0.001<br>Pos/exc vs Bal: MD = 7.72, p < 0.001<br>Neg/dis/dep vs Bal: MD = 3.89, p < 0.001 |
| Depressed (G2, G3, G6) | F = 30.86, p < 0.001 | Pos/exc vs Neg/dis/dep: MD = −2.49, $p < 0.001$<br>Pos/exc vs Bal: MD = −0.83, $p = 0.026$<br>Neg/dis/dep vs Bal: MD = 1.65, p < 0.001 |

Mean differences (MDs) were calculated as "first cluster raw scores – second cluster raw scores"; negative values indicate that the first cluster has lower scores.
Abbreviations: Bal: Balanced cluster; Neg/dis/dep: Negative/disorganised/depressive-dominant cluster; Pos/exc: Positive/excited-dominant cluster.

inflammatory marker levels than the Balanced cluster. Specifically, the Negative/disorganised/depressive-dominant cluster exhibited the most pronounced inflammatory profile across all indices at the univariate level. These findings were confirmed by covariate-adjusted analyses for all markers but the NLR. From a neurobiological perspective, this seems to suggest that negative, disorganised, and depressive features appear to be underpinned by a marked and diffuse immune-inflammatory response, consistently with theories that inflammation may represent a pathophysiologic mechanism that underlies motivational and reward processing deficits in people with schizophrenia (Goldsmith and Rapaport, 2020). On the other hand, the Positive/excited-dominant

**Table 3**
Cluster characteristics with comparisons across clusters.

| Characteristic | Positive/excited-dominant cluster (*n* = 185, 40.8%) | Negative/disorganised/depressive-dominant cluster (n = 133, 29.3%) | Balanced cluster (n = 136, 30.0%) | Test statistic, p-value |
|---|---|---|---|---|
| *Demographics* | | | | |
| Age (years), *mean ± SD* | 40.1 ± 12.7 | 40.8 ± 13.7 | 43.0 ± 12.5 | F = 2.06, $p = 0.128$ |
| Male sex, *n (%)* | 126 (68.1%) | 84 (63.2%) | 78 (57.4%) | $\chi^2 = 3.92$, $p = 0.141$ |
| *Diagnosis* | | | | **$\chi^2 = 38.2$, p = 0.001** |
| Brief psychotic disorder, *n (%)* | 16 (8.6%) | 8 (6.0%) | 19 (14.0%) | |
| Delusional disorder, *n (%)* | 24 (13.0%) | 5 (3.8%) | 7 (5.1%) | |
| Psychotic disorder due to another medical condition, *n (%)* | 3 (1.6%) | 1 (0.8%) | 0 (0%) | |
| Other specified schizophrenia spectrum and other psychotic disorder, *n (%)* | 4 (2.2%) | 3 (2.3%) | 4 (2.9%) | |
| Schizoaffective disorder, *n (%)* | 30 (16.2%) | 14 (10.5%) | 23 (16.9%) | |
| Schizophrenia, *n (%)* | 38 (20.5%) | 38 (28.6%) | 28 (20.6%) | |
| Schizophreniform disorder, *n (%)* | 1 (0.5%) | 3 (2.3%) | 0 (0%) | |
| Substance/medication-induced psychotic disorder, *n (%)* | 20 (10.8%) | 9 (6.8%) | 5 (3.7%) | |
| Unspecified schizophrenia spectrum and other psychotic disorder, *n (%)* | 49 (26.5%) | 52 (39.1%) | 50 (36.8%) | |
| *Comorbid alcohol and substance use disorders* | | | | |
| Comorbid Alcohol Use Disorder, *n (%)* | 17 (9.2%) | 9 (6.8%) | 12 (8.8%) | $\chi^2 = 0.64$, $p = 0.725$ |
| Comorbid Substance Use Disorder, *n (%)* | 50 (27.0%) | 23 (17.3%) | 22 (16.2%) | **$\chi^2 = 7.08$, $p = 0.029$** |
| *PANSS factors* | | | | |
| Positive factor, *mean ± SD* | 16.1 ± 4.2 | 12.8 ± 5.1 | 9.2 ± 3.1 | **F = 103.90, p < 0.001** |
| Negative factor, *mean ± SD* | 10.4 ± 3.8 | 23.2 ± 7.4 | 12.2 ± 4.7 | **F = 247.62, p < 0.001** |
| Disorganised/concrete factor, *mean ± SD* | 8.8 ± 3.3 | 10.7 ± 3.4 | 6.3 ± 2.3 | **F = 66.28, p < 0.001** |
| Excited factor, *mean ± SD* | 14.4 ± 5.4 | 10.6 ± 4.8 | 6.7 ± 2.3 | **F = 116.13, p < 0.001** |
| Depressed factor, *mean ± SD* | 5.8 ± 1.9 | 8.3 ± 3.7 | 6.7 ± 2.8 | **F = 30.86, p < 0.001** |
| *Antipsychotic treatment* | | | | |
| Taking any AP, *n (%)* | 66 (35.7%) | 74 (55.6%) | 72 (52.9%) | **$\chi^2 = 15.4$, p < 0.001** |
| Taking more than one AP, *n (%)* | 18 (9.7%) | 28 (21.1%) | 30 (22.1%) | **$\chi^2 = 11.1$, $p = 0.004$** |
| AP PDD/DDD [a] | | | | |
| *mean ± SD* | 0.48 ± 0.88 | 0.75 ± 0.89 | 0.71 ± 0.98 | **H = 13.3, p = 0.001** |
| *median (Q1–Q3)* | 0.0 (0.0–0.7) | 0.3 (0.0–1.3) | 0.2 (0.0–1.2) | |
| Taking FGA, *n (%)* | 35 (18.9%) | 36 (27.1%) | 40 (29.4%) | $\chi^2 = 5.37$, $p = 0.068$ |
| FGA PDD/DDD [b] | | | | |
| *mean ± SD* | 0.19 ± 0.57 | 0.21 ± 0.53 | 0.24 ± 0.59 | H = 3.69, $p = 0.158$ |
| *median (Q1–Q3)* | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | |
| Taking SGA, *n (%)* | 45 (24.3%) | 51 (38.3%) | 50 (36.8%) | $\chi^2 = 8.86$, **$p = 0.012$** |
| SGA PDD/DDD [c] | | | | |
| *mean ± SD* | 0.29 ± 0.66 | 0.53 ± 0.79 | 0.48 ± 0.78 | **H = 10.4, $p = 0.006$** |
| *median (Q1–Q3)* | 0.0 (0.0–0.3) | 0.0 (0.0–1.0) | 0.0 (0.0–0.9) | |
| *Blood cell counts* | | | | |
| Neutrophils ($10^3$/μL) | | | | |
| *mean ± SD* | 5.34 ± 2.69 | 5.47 ± 2.80 | 5.28 ± 2.25 | F = 1.27, p = 0.281 |
| *median (Q1–Q3)* | 4.93 (3.54–6.43) | 4.95 (3.45–6.72) | 4.58 (3.58–6.42) | |
| Lymphocytes ($10^3$/μL) | | | | |
| *mean ± SD* | 2.27 ± 0.91 | 2.16 ± 0.78 | 2.32 ± 0.90 | F = 2.31, p = 0.100 |
| *median (Q1–Q3)* | 2.09 (1.68–2.72) | 1.97 (1.67–2.56) | 2.19 (1.72–2.84) | |
| Monocytes ($10^3$/μL) | | | | |
| *mean ± SD* | 0.69 ± 0.24 | 0.71 ± 0.24 | 0.63 ± 0.27 | **F = 6.34, p = 0.002** |
| *median (Q1–Q3)* | 0.65 (0.51–0.84) | 0.68 (0.54–0.86) | 0.57 (0.47–0.77) | |
| Platelets ($10^3$/μL) | | | | |
| *mean ± SD* | 255.7 ± 76.2 | 264.7 ± 78.0 | 253.2 ± 74.2 | F = 0.86, p = 0.423 |
| *median (Q1–Q3)* | 243 (205–283) | 254 (220–300) | 247 (213–288) | |
| *Inflammatory markers* | | | | |

(*continued on next page*)

**Table 3** (*continued*)

| Characteristic | Positive/excited-dominant cluster (*n* = 185, 40.8%) | Negative/disorganised/depressive-dominant cluster (n = 133, 29.3%) | Balanced cluster (n = 136, 30.0%) | Test statistic, p-value |
|---|---|---|---|---|
| NLR | | | | |
| *mean ± SD* | 2.95 ± 2.42 | 3.09 ± 2.35 | 2.39 ± 1.46 | **F = 3.29, p = 0.038** |
| *median (Q1–Q3)* | 2.12 (1.55–3.43) | 2.32 (1.61–3.79) | 2.05 (1.39–2.92) | |
| MLR | | | | |
| *mean ± SD* | 0.353 ± 0.217 | 0.382 ± 0.188 | 0.291 ± 0.127 | **F = 11.1, p < 0.001** |
| *median (Q1–Q3)* | 0.296 (0.215–0.415) | 0.324 (0.272–0.428) | 0.263 (0.205–0.356) | |
| PLR | | | | |
| *mean ± SD* | 127.2 ± 57.6 | 141.2 ± 64.0 | 125.5 ± 72.4 | **F = 3.71, p = 0.025** |
| *median (Q1–Q3)* | 112 (88–151) | 129 (98–164) | 115 (84–149) | |
| SII | | | | |
| *mean ± SD* | 754.8 ± 701.9 | 832.7 ± 716.8 | 628.2 ± 463.7 | **F = 3.34, p = 0.036** |
| *median (Q1–Q3)* | 529 (360–923) | 597 (374–935) | 508 (325–799) | |
| SIRI | | | | |
| *mean ± SD* | 2.28 ± 2.96 | 2.38 ± 2.36 | 1.51 ± 1.09 | **F = 7.42, p = 0.001** |
| *median (Q1–Q3)* | 1.41 (0.85–2.48) | 1.64 (1.05–2.83) | 1.26 (0.76–1.91) | |
| AISI | | | | |
| *mean ± SD* | 602.9 ± 896.4 | 650.8 ± 699.6 | 408.7 ± 348.3 | **F = 6.49, p = 0.002** |
| *median (Q1–Q3)* | 356 (185–672) | 395 (245–723) | 291 (153–501) | |

Test statistics: F, ANOVA; H, Kruskal-Wallis with ties correction; $\chi^2$, chi-square. ANOVAs were performed on log-transformed values. Because some cells in the diagnosis-by-cluster contingency table were sparse and exact tests were computationally unfeasible, the association was evaluated using the likelihood-ratio $\chi^2$ statistic. Descriptive statistics are on a raw scale. Significant differences are highlighted in bold.

Abbreviations: AISI, aggregate index of systemic inflammation; AP, antipsychotic; FGA, first-generation antipsychotic; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PANSS, Positive and Negative Syndrome Scale; PDD/DDD: ratio between the prescribed daily dose (PDD) and the defined daily dose (DDD); PLR, platelet-to-lymphocyte ratio; Q1, first quartile; Q3, third quartile; SGA, second-generation antipsychotic; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index.

[a] n = 6 missing.

[b] n = 3 missing.

[c] n = 3 missing.

cluster showed a more selective inflammatory signature, with higher MLR and SIRI than the Balanced cluster. This aligns with the hypothesis of partially distinct neurobiological substrates, whereby positive psychotic symptoms, excitement, and aggression are driven primarily by mesolimbic dopaminergic dysregulation (Heinz and Schlagenhauf, 2010; McCutcheon et al., 2019), while negative, disorganised, and depressive features are more closely linked to cytokine-mediated reward suppression (Goldsmith and Rapaport, 2020). Nonetheless, direct comparison between Positive/excited-dominant and Negative/disorganised/depressive-dominant clusters revealed no evidence of meaningful differences across inflammatory indices. Effect sizes for all six inflammatory markers in this comparison were negligible to small, with confidence intervals excluding zero only for PLR, though this finding did not survive Bonferroni correction and the effect remained within the negligible-to-small range. This suggests that differences between the two groups, if any, are likely to be of limited clinical relevance. Although the power to detect very small effects may be constrained, the consistently small effect sizes argue against the presence of substantial differences in inflammatory profiles between the two symptom-dominant phenotypes. Thus, despite the remarkable divergence in symptom profile, these two clinically distinct subgroups may share elevated peripheral inflammation, when compared to more balanced presentations.

Taken together, these findings indicate that peripheral inflammation differentiates patients with dominant symptom profiles (whether predominantly positive/excited or negative/disorganised/depressive) from those with a more balanced presentation, but do not provide evidence for a definite association with specific symptom configurations. In doing so, our study partly addresses a gap acknowledged in the literature (Karageorgiou et al., 2019), that is, the inability to evaluate the effect of specific symptomatology on CBC-derived inflammatory markers. By adopting a cluster-based approach applied to PANSS five-factor scores, our study provides the first phenotype-level evidence that monocyte-driven inflammatory indices – particularly MLR, SIRI, and AISI – are significantly higher in subjects with a clearly polarised presentation. This pattern was observed in both the Positive/excited- and the Negative/disorganised/depressive-dominant clusters, with the latter showing the most pronounced inflammatory profile. A noteworthy finding is that monocyte-related indices demonstrated the most robust associations with symptom clusters. Indeed, MLR and SIRI were the only two markers whose significant increase relative to the Balanced cluster was common to the Positive/excited-dominant and the Negative/disorganised/depressive-dominant clusters, and were those with the largest effect sizes. Hence, while indices more broadly reflecting systemic inflammation are more susceptible to confounding (Gasparyan et al., 2019; Song et al., 2021), MLR and SIRI, being substantially determined by monocyte counts, may capture the neuroinflammatory signal in SSDs with superior sensitivity. Recent studies have demonstrated that monocytes play a central role in psychosis-related immune dysregulation (Hu et al., 2025; Melbourne et al., 2021; Müller et al., 2015), releasing pro-inflammatory cytokines (Kany et al., 2019; Soares et al., 2023) and trafficking to the brain (Zhang et al., 2025), where they interact with resident microglia or differentiate into it, contributing to the amplification and maintenance of neuroinflammatory response (Ding et al., 2021). These mechanisms have been observed in schizophrenia (Sellgren et al., 2019). Hence, the stronger and more consistent associations observed for MLR and SIRI found by our study strengthen the hypothesis that monocyte-driven processes may represent a relevant peripheral correlate of specific symptom patterns in SSDs (Bloomfield et al., 2016; Goldsmith and Rapaport, 2020).

### 4.2. Potential clinical and treatment implications

The clustering-based identification of symptom-phenotype-specific inflammatory profiles suggests potential clinical applications. Growing evidence from psychoneuroimmunology studies suggests that pro-inflammatory mediators influence key metabolic pathways in SSDs, including glutamatergic neurotransmission and tryptophan metabolism via the kynurenine pathway (Bartoli et al., 2021a; Khandaker et al., 2015). However, direct measurement of inflammatory cytokines and

**Table 4**
Univariate and covariate-adjusted comparisons of inflammatory markers across clusters.

| Cluster comparison | Marker | Univariate comparison, Bonferroni-corrected (% difference, p-value) | Adjusted† comparison, Bonferroni-corrected (% difference), *p*-value | Adjusted Cohen's d (95% CI) |
|---|---|---|---|---|
| Pos/exc vs Neg/dis/dep | NLR | −7%, p > 0.999 | −7%, p > 0.999 | −0.10 (−0.32, 0.13) |
| | MLR | −11%, *p* = 0.153 | −10%, *p* = 0.428 | −0.17 (−0.39, 0.06) |
| | PLR | −10%, *p* = 0.115 | −10%, *p* = 0.147 | **−0.23 (−0.45, 0.002)** |
| | SII | −10%, *p* = 0.502 | −11%, *p* = 0.615 | −0.14 (−0.37, 0.08) |
| | SIRI | −11%, *p* = 0.593 | −10%, p > 0.999 | −0.11 (−0.33, 0.12) |
| | AISI | −15%, *p* = 0.356 | −14%, *p* = 0.629 | −0.14 (−0.37, 0.08) |
| Pos/exc vs Bal | NLR | +13%, p = 0.243 | +16%, p = 0.136 | 0.23 (0.01, 0.45) |
| | MLR | **+19%, p = 0.007** | **+19%, p = 0.020** | **0.31 (0.09, 0.53)** |
| | PLR | +4%, p > 0.999 | +8%, p = 0.644 | 0.14 (−0.08, 0.36) |
| | SII | +12%, p = 0.488 | +17%, p = 0.223 | 0.20 (−0.02, 0.42) |
| | SIRI | **+28%, *p* = 0.019** | **+29%, *p* = 0.028** | **0.30 (0.07, 0.52)** |
| | AISI | +27%, p = 0.068 | +30%, p = 0.071 | **0.26 (0.03, 0.48)** |
| Neg/dis/dep vs Bal | NLR | **+20%, p = 0.036** | +24%, p = 0.057 | **0.29 (0.05, 0.53)** |
| | MLR | **+34%, p < 0.001** | **+30%, p = 0.001** | **0.44 (0.20, 0.68)** |
| | PLR | **+15%, p = 0.028** | **+20%, p = 0.040** | **0.30 (0.06, 0.54)** |
| | SII | **+24%, p = 0.030** | **+32%, p = 0.043** | **0.30 (0.06, 0.54)** |
| | SIRI | **+44%, p = 0.001** | **+43%, p = 0.011** | **0.36 (0.12, 0.60)** |
| | AISI | **+49%, p = 0.001** | **+52%, p = 0.015** | **0.35 (0.11, 0.59)** |

Overall analyses of variance (ANOVAs) comparing inflammatory biomarker levels across diagnostic groups (F(2,451), p-value): NLR: F = 3.29, p = 0.038; MLR: F = 11.13, p < 0.001; PLR: F = 3.71, p = 0.025; SII: F = 3.34, p = 0.036; SIRI: F = 7.42, *p* < 0.001; AISI: F = 6.49, *p* = 0.002.
Percentage differences are approximated as $(e^{\beta} - 1) \times 100$, where β (Bonferroni-corrected regression coefficient) is the mean difference on log scale. Negative percentages indicate lower levels in the first group; positive percentages indicate higher levels in the first group. Cohen's d values represent the adjusted standardized mean difference derived from the regression t-statistic; 95% confidence intervals (CIs) are not adjusted for multiple comparisons. Significant differences are highlighted in bold.
Abbreviations: AISI: aggregate index of systemic inflammation; Bal: Balanced cluster; MLR: monocyte-to-lymphocyte ratio; Neg/dis/dep: Negative/disorganised/depressive-dominant cluster; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; Pos/exc: Positive/excited-dominant cluster; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index.
† Adjusted for age, sex, diagnosis, current alcohol and substance sue disorders, total severity, first-generation antipsychotic dosage, and second-generation antipsychotic dosage using linear regression with robust standard errors. All *p*-values are Bonferroni-corrected for three pairwise comparisons.

specific metabolic pathways typically requires specialized immunoassays that are often expensive and not readily available in clinical settings (Brinn and Stone, 2020). CBC-derived indices offer a practical alternative: they are simple, reproducible, low-cost measures, routinely used even in resource-limited settings, representing accessible proxies for systemic inflammatory unbalances.

In addition, profiling inflammation via accessible biomarkers such as CBC-derived indices may also help identifying patient subpopulations at heightened risk of systemic inflammatory complications, accelerated atherosclerosis, and insulin resistance (Pillinger et al., 2019; Zhang et al., 2022), stratifying high-risk subjects for targeted interventions aimed at reducing metabolic and cardiovascular morbidity and mortality.

Furthermore, given the potential therapeutic role of targeting inflammation in SSDs (Khandaker et al., 2015), CBC-derived markers may help predict treatment outcomes. For instance, recent evidence has shown that baseline NLR positively correlates with response to risperidone monotherapy in drug-naïve first-episode psychosis (Lu et al., 2024). Moreover, some lines of evidence supporting the efficacy of agents such as minocycline, acetylsalicylic acid, and cyclooxygenase-2 (COX-2) inhibitors (Laan et al., 2010; Müller, 2010; Truong et al., 2024), as well as omega-3 fatty acids and *N*-acetylcysteine (Amminger et al., 2010; Berk et al., 2008), in SSDs putatively suggest that drug repurposing of anti-inflammatory and anti-oxidant compounds remains a promising strategy in psychiatry (Bartoli et al., 2021b; Fava, 2018). Accordingly, patients presenting with elevated inflammatory profiles – such as those with a predominantly negative/disorganised/depressive presentation – might represent candidates for adjunctive anti-inflammatory or immunomodulatory interventions. This is consistent with the emerging hypothesis that negative symptoms are more closely linked to peripheral immune dysregulation than positive or excited ones (Enache et al., 2021; Ingabire et al., 2026), suggesting that inflammatory burden may drive – or at least accompany – the neurotoxic processes underlying negative and cognitive symptom domains in psychosis. Identifying patients belonging to an immune-enriched symptomatic subtype, such as the Negative/disorganised/depressive-dominant cluster described in this study, may therefore contribute to the stratification of candidates for such augmentation therapies.

### 4.3. Limitations

Some limitations of this study should be acknowledged. First, the cross-sectional nature of our data precluded causal inferences about whether inflammation drives specific symptom patterns. Second, data on important confounding variables (such as illness duration, medication exposure over time, body mass index, and smoking) were not thoroughly available in the present dataset and could therefore not be included as covariates: this represents a relevant limitation, as these factors are highly prevalent in individuals with SSDs and may independently contribute to inflammatory marker variability. Third, participants with no prescribed treatment or documented non-adherence were assigned a PDD/DDD ratio of 0. However, subtherapeutic antipsychotic exposure prior to admission cannot be excluded in subjects with a formal prescription, considering how common poor medication adherence is in this population, and may have attenuated drug effects on CBC-derived indices. Fourth, while we assumed that CBC data were missing completely at random, this cannot be formally verified. Nonetheless, formal comparisons between participants with missing CBC data ($n = 27$, 5.6%) and those included in the final sample showed no statistically significant differences in age, sex, diagnosis, comorbid substance use, total PANSS score, or any individual PANSS five-factor score, with the sole exception of the excited factor (means: 8.7 vs. 11.0, $p = 0.034$), where missing participants had lower rather than higher scores, therefore arguing against systematic exclusion of more severely ill patients. Fifth, the focus on inpatient settings limits generalizability to less severely ill populations. Sixth, although patients with clinically overt

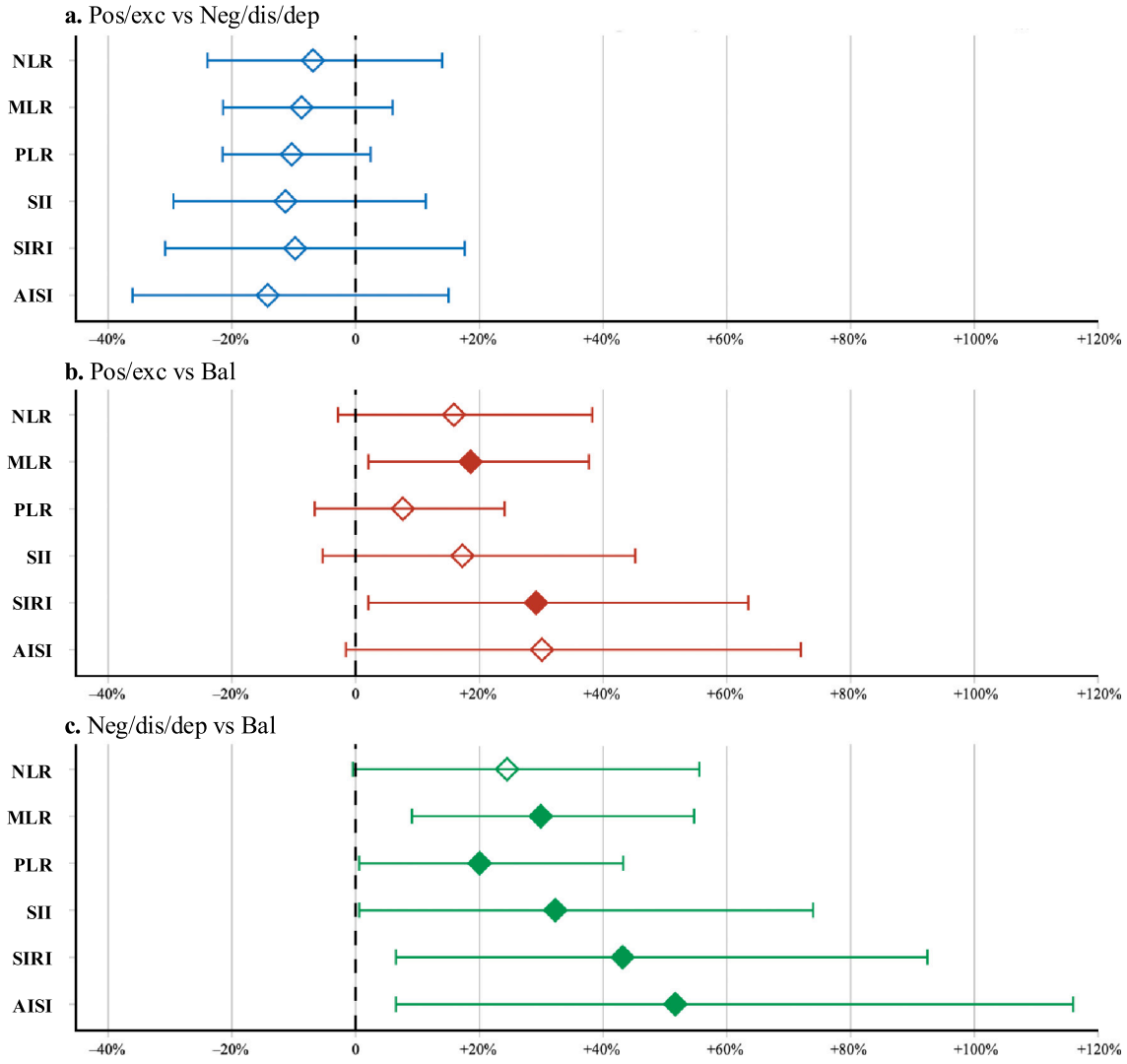


**Fig. 2.** Covariate-adjusted comparisons of inflammatory markers across clusters: forest plots.
Fig. 2a. Pos/exc vs Neg/dis/dep; Fig. 2b. Pos/exc vs Bal; Fig. 2c. Neg/dis/dep vs Bal.
Point estimates represent adjusted percentage differences with 95% confidence intervals (bars). Percentage differences are approximated as $(e^{\beta} - 1) \times 100$, where β (Bonferroni-corrected regression coefficient) is the mean difference on log scale. Negative percentages indicate lower levels in the first group; positive percentages indicate higher levels in the first group. Filled diamonds (◆) indicate statistically significant differences after Bonferroni correction ($p < 0.05$); open diamonds (◇) indicate non-significant comparisons ($p \geq 0.05$).
Abbreviations: AISI: aggregate index of systemic inflammation; Bal: Balanced cluster; MLR: monocyte-to-lymphocyte ratio; Neg/dis/dep: Negative/disorganised/depressive-dominant cluster; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; Pos/exc: Positive/excited-dominant cluster; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index.

inflammatory, infectious, or autoimmune conditions were excluded based on clinical assessment, physical examination, and review of medical records, we cannot fully rule out the potential contribution of subclinical or undiagnosed conditions (such as influenza or subsyndromal autoimmune disorders) to inflammatory marker variability. Finally, while CBC-derived indices offer practical clinical utility and low cost, they provide limited mechanistic specificity: integration with specialized immunoassays (cytokine profiling) and immune cell phenotyping would enable a more precise characterization of the cellular and molecular underpinnings of the observed patterns.

## 5. Conclusions

This study shows that distinct clinical presentations are associated with heterogeneous inflammatory profiles, supporting the value of phenotype-stratified approaches to dissect the biological heterogeneity of SSDs. In particular, the robust associations observed for MLR and SIRI indicate that monocyte-driven inflammatory activation may be especially relevant in presentations dominated by negative, disorganised, and depressive symptoms. Clustering-based methods thus offer a pragmatic framework for mapping symptom pattern-specific inflammatory signatures and advancing understanding of the role of inflammation in psychotic symptom heterogeneity. Nonetheless, longitudinal studies are needed to clarify mechanistic links between symptom phenotypes and inflammatory activation, evaluate predictive utility for relapse risk and symptom trajectories, and ultimately inform personalized treatment strategies in SSDs.

## CRediT authorship contribution statement

**Daniele Cavaleri:** Writing – original draft, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cristina Crocamo:** Writing – review & editing, Validation, Software, Methodology, Formal analysis,

Conceptualization. **Giorgio Cucchi:** Writing – review & editing, Investigation, Data curation. **Francesco Bartoli:** Writing – review & editing, Validation, Supervision, Project administration. **Giuseppe Carrà:** Writing – review & editing, Validation, Supervision, Project administration.

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used GPT-5.2 (OpenAI) to improve the clarity and readability of the text (grammar, phrasing, and style) and to assist in the creation of Fig. 2. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2026.06.015.

## References

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Association.

Amminger, G.P., Schäfer, M.R., Papageorgiou, K., Klier, C.M., Cotton, S.M., Harrigan, S. M., Mackinnon, A., McGorry, P.D., Berger, G.E., 2010. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch. Gen. Psychiatry. 67 (2), 146–154. https://doi.org/10.1001/archgenpsychiatry.2009.192.

Argote, M., Sescousse, G., Brunelin, J., Baudin, G., Schaub, M.P., Rabin, R., Schnell, T., Ringen, P.A., Andreassen, O.A., Addington, J.M., Brambilla, P., Delvecchio, G., Bechdolf, A., Wobrock, T., Schneider-Axmann, T., Herzig, D., Mohr, C., Vila-Badia, R., Rodie, J.U., Mallet, J., Ricci, V., Martinotti, G., Knížková, K., Rodriguez, M., Cookey, J., Tibbo, P., Scheffler, F., Asmal, L., Garcia-Rizo, C., Amoretti, S., Huber, C., Thibeau, H., Kline, E., Fakra, E., Jardri, R., Nourredine, M., Rolland, B., 2023. Association between cannabis use and symptom dimensions in schizophrenia spectrum disorders: an individual participant data meta-analysis on 3053 individuals. EClinicalMedicine 64, 102–109. https://doi.org/10.1016/j.eclinm.2023.102199.

Bartoli, F., Cioni, R.M., Callovini, T., Cavaleri, D., Crocamo, C., Carrà, G., 2021a. The kynurenine pathway in schizophrenia and other mental disorders: insight from meta-analyses on the peripheral blood levels of tryptophan and related metabolites. Schizophr. Res. 232, 61–62. https://doi.org/10.1016/j.schres.2021.04.008.

Bartoli, F., Cavaleri, D., Bachi, B., Moretti, F., Riboldi, I., Crocamo, C., Carrà, G., 2021b. Repurposed drugs as adjunctive treatments for mania and bipolar depression: a meta-review and critical appraisal of meta-analyses of randomized placebo-controlled trials. J. Psychiatr. Res. 143, 230–238. https://doi.org/10.1016/j.jpsychires.2021.09.018.

Bartoli, F., Cavaleri, D., Callovini, T., Palpella, D., Piacenti, S., Crocamo, C., Carrà, G., NOMIAC Investigators, 2025. Clinical and metabolic correlates of DSM-5 mixed features in subjects with bipolar depression and mania: a cross-sectional study. J. Psychosom. Res. 188, 111990. https://doi.org/10.1016/j.jpsychores.2024.111990.

Berk, M., Copolov, D., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., Anderson-Hunt, M., Judd, F., Katz, F., Katz, P., Ording-Jespersen, S., Little, J., Conus, P., Cuenod, M., Do, K.Q., Bush, A.I., 2008. N-acetyl cysteine as a glutathione precursor for schizophrenia–a double-blind, randomized, placebo-controlled trial. Biol. Psychiatry 64 (5), 361–368. https://doi.org/10.1016/j.biopsych.2008.03.004.

Bhikram, T., Sandor, P., 2022. Neutrophil-lymphocyte ratios as inflammatory biomarkers in psychiatric patients. Brain Behav. Immun. 105, 237–246. https://doi.org/10.1016/j.bbi.2022.07.006.

Bioque, M., Matias-Martins, A.C., Llorca-Bofí, V., Mezquida, G., Cuesta, M.J., Vieta, E., Amoretti, S., Lobo, A., González-Pinto, A., Moreno, C., Roldán, A., Martinez-Aran, A., Baeza, I., Bergé, D., García-Rizo, C., Herrero, S.M., Bernardo, M., 2022. Neutrophil-to-lymphocyte ratio in patients with a first episode of psychosis: a two-year longitudinal follow-up study. Schizophr. Bull. 48 (6), 1327–1335. https://doi.org/10.1093/schbul/sbac089.

Bloomfield, P.S., Selvaraj, S., Veronese, M., Rizzo, G., Bertoldo, A., Owen, D.R., Bloomfield, M.A., Bonoldi, I., Kalk, N., Turkheimer, F., McGuire, P., de Paola, V., Howes, O.D., 2016. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [(11)C]PBR28 PET brain imaging study. Am. J. Psychiatry. 173 (1), 44–52. https://doi.org/10.1176/appi.ajp.2015.14101358.

Brinn, A., Stone, J., 2020. Neutrophil-lymphocyte ratio across psychiatric diagnoses: a cross-sectional study using electronic health records. BMJ Open 10, e036859. https://doi.org/10.1136/bmjopen-2020-036859.

Carrà, G., Crocamo, C., Bartoli, F., Angermeyer, M., Brugha, T., Toumi, M., Bebbington, P., 2022. Influence of positive and negative symptoms on hedonic and eudaemonic well-being in people with schizophrenia: a longitudinal analysis from the EuroSc study. Schizophr. Res. 244, 21–28. https://doi.org/10.1016/j.schres.2022.04.009.

Cavaleri, D., De Pietra, A., Gazzola, M., Crocamo, C., Bartoli, F., Carrà, G., 2025. Complete blood count-based inflammation indexes and symptom severity in people with schizophrenia spectrum disorders: an analysis based on structural equation modelling. Psychoneuroendocrinology 168, 107134. https://doi.org/10.1016/j.psyneuen.2024.107134.

Cavaleri, D., Crocamo, C., Riboldi, I., Boniello, F., Clerici, B., Molendini, M., Carrà, G., Bartoli, F., 2025. Exploring the predictive role of the first mood episode on the predominant polarity in bipolar disorder: insights from a path analysis. Ann. Gen. Psychiatry 24 (1), 19. https://doi.org/10.1186/s12991-025-00556-y.

Cavaleri, D., Cucchi, G., Citton, M., Monti, M., Crocamo, C., Bartoli, F., Carrà, G., 2026. Complete blood count-based inflammatory ratios in people with bipolar disorder: a systematic review and meta-analysis of neutrophil-to-lymphocyte, monocyte-to-lymphocyte, and platelet-to-lymphocyte ratios. Eur. Psychiatry. 69 (1), e26. https://doi.org/10.1192/j.eurpsy.2026.10174.

Clausen, M., Christensen, R.H.B., da Re, M., Benros, M.E., 2024. Immune cell alterations in psychotic disorders: a comprehensive systematic review and meta-analysis. Biol. Psychiatry. 96 (5), 331–341. https://doi.org/10.1016/j.biopsych.2023.11.029.

Demjaha, A., Morgan, K., Morgan, C., Landau, S., Dean, K., Reichenberg, A., Sham, P., Fearon, P., Hutchinson, G., Jones, P.B., Murray, R.M., Dazzan, P., 2009. Combining dimensional and categorical representation of psychosis: the way forward for DSM-V and ICD-11? Psychol. Med. 39 (12), 1943–1955. https://doi.org/10.1017/S0033291709990651.

Ding, K.Q., Lai, Z.H., Zhang, Y., Yang, G.Y., He, J.R., Zeng, L.L., 2021. Monocyte-to-lymphocyte ratio is associated with depression 3 months after stroke. Neuropsychiatr. Dis. Treat. 17, 835–845. https://doi.org/10.2147/NDT.S299462.

Duan, J., Chen, J., Xiang, Z., 2025. The U-shape relationship between the aggregate index of systemic inflammation and depression in American adults: a cross-sectional study. J. Affect. Disord. 380, 270–278. https://doi.org/10.1016/j.jad.2025.03.139.

von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., STROBE Initiative, 2008. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J. Clin. Epidemiol. 61 (4), 344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008.

Enache, D., Nikkheslat, N., Fathalla, D., Morgan, B.P., Lewis, S., Drake, R., Deakin, B., Walters, J., Lawrie, S.M., Egerton, A., MacCabe, J.H., Mondelli, V., 2021. Peripheral immune markers and antipsychotic non-response in psychosis. Schizophr. Res. 230, 1–8. https://doi.org/10.1016/j.schres.2020.12.020.

Fava, M., 2018. The promise and challenges of drug repurposing in psychiatry. World Psychiatry 17 (1), 28–29. https://doi.org/10.1002/wps.20481.

Fekih-Romdhane, F., Hajje, R., Haddad, C., Hallit, S., Azar, J., 2023. Exploring negative symptoms heterogeneity in patients diagnosed with schizophrenia and schizoaffective disorder using cluster analysis. BMC Psychiatry 23, 595. https://doi.org/10.1186/s12888-023-05101-3.

First, M.B., Williams, J.B.W., Karg, R.S., Spitzer, R.L., 2016. User's guide for the SCID-5-CV structured clinical interview for DSM-5 disorders: Clinical version. American Psychiatric Publishing.

Gasparyan, A.Y., Ayvazyan, L., Mukanova, U., Yessirkepov, M., Kitas, G.D., 2019. The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann. Lab. Med. 39 (4), 345–357. https://doi.org/10.3343/alm.2019.39.4.345.

Girardin, F.R., Poncet, A., Blondon, M., Rollason, V., Vernaz, N., Chalandon, Y., Dayer, P., Combescure, C., 2014. Monitoring white blood cell count in adult patients with schizophrenia who are taking clozapine: a cost-effectiveness analysis. Lancet Psychiatry 1 (1), 55–62. https://doi.org/10.1016/S2215-0366(14)70245-7.

Goldsmith, D.R., Rapaport, M.H., 2020. Inflammation and negative symptoms of schizophrenia: implications for reward processing and motivational deficits. Front. Psychiatry 11, 46. https://doi.org/10.3389/fpsyt.2020.00046.

Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol. Psychiatry 21 (12), 1696–1709. https://doi.org/10.1038/mp.2016.3.

Halstead, S., Siskind, D., Amft, M., Wagner, E., Yakimov, V., Liu, Z.S.-J., Walder, K., Warren, N., 2023. Alteration patterns of peripheral concentrations of cytokines and associated inflammatory proteins in acute and chronic stages of schizophrenia: a systematic review and network meta-analysis. Lancet Psychiatry 10 (4), 260–271. https://doi.org/10.1016/S2215-0366(23)00025-1.

Heinz, A., Schlagenhauf, F., 2010. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. Schizophr. Bull. 36 (3), 472–485. https://doi.org/10.1093/schbul/sbq031.

Hu, C., Du, N., Li, J., Chen, L., Meng, X., Yao, L., Yu, T., Shi, L., Zhang, X., 2025. Correlation between monocyte count, monocyte-lymphocyte ratio, and other inflammatory cells with sleep and psychiatric symptoms in first-episode schizophrenia patients. Neuropsychiatr. Dis. Treat. 21, 373–381. https://doi.org/10.2147/NDT.S506074.

Ingabire, G., Scarabelot, L.F., Del-Ben, C.M., Corsi-Zuelli, F., 2026. Peripheral blood immune markers associated with negative symptoms in first episode psychosis: a systematic review. Front. Psychiatry. 17, 1782134. https://doi.org/10.3389/fpsyt.2026.1782134.

Kachouchi, A., Ahmed, L., Saadia, K., Imane, A., Fatiha, M., 2024. Quality of life and C-reactive protein in patients with schizophrenia: a cross-sectional study. Alpha Psychiatry 25 (2), 256–261. https://doi.org/10.5152/alphapsychiatry.2024.231437.

Kany, S., Vollrath, J.T., Relja, B., 2019. Cytokines in inflammatory disease. Int. J. Mol. Sci. 20 (23), 6008. https://doi.org/10.3390/ijms20236008.

Karageorgiou, V., Milas, G.P., Michopoulos, I., 2019. Neutrophil-to-lymphocyte ratio in schizophrenia: a systematic review and meta-analysis. Schizophr. Res. 206, 4–12. https://doi.org/10.1016/j.schres.2018.12.017.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Khandaker, G.M., Cousins, L., Deakin, J., Lennox, B.R., Yolken, R., Jones, P.B., 2015. Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. Lancet Psychiatry 2 (3), 258–270. https://doi.org/10.1016/S2215-0366(14)00122-9.

Kirkpatrick, B., Miller, B.J., 2013. Inflammation and schizophrenia. Schizophr. Bull. *39* (6), 1174–1179. https://doi.org/10.1093/schbul/sbt141.

Laan, W., Grobbee, D.E., Selten, J.P., Heijnen, C.J., Kahn, R.S., Burger, H., 2010. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J. Clin. Psychiatry 71 (5), 520–527. https://doi.org/10.4088/JCP.09m05117yel.

Liu, Z., Lv, D., Li, J., Li, F., Zhang, Y., Liu, Y., Gao, C., Qiu, Y., Ma, J., Zhang, R., 2024. The potential predictive value and relationship of blood-based inflammatory markers with the clinical symptoms of Han Chinese patients with first-episode adolescent-onset schizophrenia. Front. Psychiatry. 15, 1431350. https://doi.org/10.3389/fpsyt.2024.1431350.

Lu, X., Sun, Q., Wu, L., Liao, M., Yao, J., Xiu, M., 2024. The neutrophil-lymphocyte ratio in first-episode medication-naïve patients with schizophrenia: a 12-week longitudinal follow-up study. Prog. Neuropsychopharmacol. Biol. Psychiatry 131, 110959. https://doi.org/10.1016/j.pnpbp.2024.110959.

McCutcheon, R.A., Abi-Dargham, A., Howes, O.D., 2019. Schizophrenia, dopamine and the striatum: from biology to symptoms. Trends Neurosci. 42 (3), 205–220. https://doi.org/10.1016/j.tins.2018.12.004.

Melbourne, J.K., Rosen, C., Chase, K.A., Feiner, B., Sharma, R.P., 2021. Monocyte transcriptional profiling highlights a shift in immune signatures over the course of illness in schizophrenia. Front. Psychiatry 12, 649494. https://doi.org/10.3389/fpsyt.2021.649494.

Miller, B.J., Buckley, P., Seabolt, W., Mellor, A., Kirkpatrick, B., 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 70 (7), 663–671. https://doi.org/10.1016/j.biopsych.2011.04.013.

Misiak, B., Bartoli, F., Carrà, G., Stańczykiewicz, B., Gładka, A., Frydecka, D., Samochowiec, J., Jarosz, K., Hadryś, T., Miller, B.J., 2021. Immune-inflammatory markers and psychosis risk: a systematic review and meta-analysis. Psychoneuroendocrinology 127, 105200. https://doi.org/10.1016/j.psyneuen.2021.105200.

Mojadadi, M.S., Mahjour, M., Fahimi, H., Raoofi, A., Shobeiri, S.S., 2024. Relationship between blood-based inflammatory indices and clinical score of schizophrenia patients: a cross-sectional study. Behav. Brain Res. 460, 114807. https://doi.org/10.1016/j.bbr.2023.114807.

Moody, G., Miller, B.J., 2018. Total and differential white blood cell counts and hemodynamic parameters in first-episode psychosis. Psychiatry Res. 260, 307–312. https://doi.org/10.1016/j.psychres.2017.11.086.

Müller, N., 2010. COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. Curr. Opin. Investig. Drugs. 11 (1), 31–42.

Müller, N., 2018. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. Schizophr. Bull. 44 (5), 973–982. https://doi.org/10.1093/schbul/sby024.

Müller, N., Weidinger, E., Leitner, B., Schwarz, M.J., 2015. The role of inflammation in schizophrenia. Front. Neurosci. 9, 372. https://doi.org/10.3389/fnins.2015.00372.

Na, K.S., Jung, H.Y., Kim, Y.K., 2014. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 48, 277–286. https://doi.org/10.1016/j.pnpbp.2012.10.022.

Ninla-Aesong, P., Kietdumrongwong, P., Neupane, S.P., Puangsri, P., Jongkrijak, H., Chotipong, P., Kaewpijit, P., 2024. Relative value of novel systemic immune-inflammatory indices and classical hematological parameters in predicting depression, suicide attempts and treatment response. Sci. Rep. 14, 19018. https://doi.org/10.1038/s41598-024-70097-z.

Ou, S., Lu, H., Qu, R., Cui, X., Xiong, Z., Fan, F., Yu, X., Hasi, C., 2025. The clinical value of systemic immune inflammatory index in predicting the prognosis of patients with bloodstream infection. J. Inflamm. Res. 18, 10181–10192. https://doi.org/10.2147/JIR.S531272.

Özdin, S., Böke, Ö., 2019. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res. 271, 131–135. https://doi.org/10.1016/j.psychres.2018.11.043.

Pillinger, T., D'Ambrosio, E., McCutcheon, R., Howes, O.D., 2019. Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. Mol. Psychiatry 24, 776–794. https://doi.org/10.1038/s41380-018-0058-9.

Pillinger, T., McCutcheon, R.A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., Howes, O.D., 2020. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 7 (1), 64–77. https://doi.org/10.1016/S2215-0366(19)30416-X.

Refaat, L., Eissa, M.S., Elnaggar, G.N., Mehesen, M., Eissa, M.S., Kamal, A., Abdellateif, M.S., 2025. Systemic inflammatory indices comprising monocytes provide a clinical significance for thyroid cancer identification. Sci. Rep. 15, 39967. https://doi.org/10.1038/s41598-025-23765-7.

Roithmeier, M., Geck, S., Bühner, M., Wehr, S., Weigel, L., Priller, J., Davis, J.M., Leucht, S., 2025. COSMIN review of the PANSS Marder factor solution and other factor models in people with schizophrenia. Schizophrenia 11, 51. https://doi.org/10.1038/s41537-025-00600-6.

Šagud, M., Madžarac, Z., Nedić Erjavec, G., Šimunović Filipčić, I., Mikulić, F.L., Rogić, D., Bradaš, Z., Bajs Janović, M., Pivac, N., 2023. The associations of neutrophil-lymphocyte, platelet-lymphocyte, monocyte-lymphocyte ratios and immune-inflammation index with negative symptoms in patients with schizophrenia. Biomolecules 13 (2), 297. https://doi.org/10.3390/biom13020297.

Sandberg, A.A., Steen, V.M., Torsvik, A., 2021. Is elevated neutrophil count and neutrophil-to-lymphocyte ratio a cause or consequence of schizophrenia? A scoping review. Front. Psychiatry. 12, 728990. https://doi.org/10.3389/fpsyt.2021.728990.

Sellgren, C.M., Gracias, J., Watmuff, B., Biag, J.D., Thanos, J.M., Whittredge, P.B., Fu, T., Worringer, K., Brown, H.E., Wang, J., Kaykas, A., Karmacharya, R., Goold, C.P., Sheridan, S.D., Perlis, R.H., 2019. Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. Nat. Neurosci. 22, 374–385. https://doi.org/10.1038/s41593-018-0334-7.

Soares, C.L.R., Wilairatana, P., Silva, L.R., Moreira, P.S., Barbosa, N.M.M.V., da Silva, P. R., Coutinho, H.D.M., de Menezes, I.R.A., Felipe, C.F.B., 2023. Biochemical aspects of the inflammatory process: a narrative review. Biomed. Pharmacother. 168, 115764. https://doi.org/10.1016/j.biopha.2023.115764.

Song, M., Graubard, B.I., Rabkin, C.S., Engels, E.A., 2021. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. Sci. Rep. 11, 464. https://doi.org/10.1038/s41598-020-79431-7.

Truong, T.T.T., Liu, Z.S.J., Panizzutti, B., Kim, J.H., Dean, O.M., Berk, M., Walder, K., 2024. Network-based drug repurposing for schizophrenia. Neuropsychopharmacology. https://doi.org/10.1038/s41386-024-01805-6. Advance online publication.

Wallwork, R.S., Fortgang, R., Hashimoto, R., Weinberger, D.R., Dickinson, D., 2012. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr. Res. 137 (1–3), 246–250. https://doi.org/10.1016/j.schres.2012.01.031.

Wang, X., Chen, X., Guan, X., Li, Z., 2024. The neutrophil-to-lymphocyte ratio is associated with clinical symptoms in first-episode medication-naïve patients with schizophrenia. Schizophrenia 10 (1), 13. https://doi.org/10.1038/s41537-024-00437-5.

Wolfers, T., Doan, N.T., Kaufmann, T., Alnæs, D., Moberget, T., Agartz, I., Buitelaar, J.K., Ueland, T., Melle, I., Franke, B., Andreassen, O.A., Beckmann, C.F., Westlye, L.T., Marquand, A.F., 2018. Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. JAMA Psychiatry 75 (11), 1146–1155. https://doi.org/10.1001/jamapsychiatry.2018.2467.

World Medical Association, 2025. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human participants. JAMA 333 (1), 71–74. https://doi.org/10.1001/jama.2024.21972.

Zhang, L., Lizano, P., Guo, B., Xu, Y., Rubin, L.H., Hill, S.K., Alliey-Rodriguez, N., Lee, A. M., Wu, B., Keedy, S.K., Tamminga, C.A., Pearlson, G.D., Clementz, B.A., Keshavan, M.S., Gershon, E.S., Sweeney, J.A., Bishop, J.R., 2022. Inflammation subtypes in psychosis and their relationships with genetic risk for psychiatric and cardiometabolic disorders. Brain Behav. Immun. Health 22, 100459. https://doi.org/10.1016/j.bbih.2022.100459.

Zhang, G., Yao, Q., Long, C., Yi, P., Song, J., Wu, L., Wan, W., Rao, X., Lin, Y., Wei, G., Ying, J., Hua, F., 2025. Infiltration by monocytes of the central nervous system and its role in multiple sclerosis: reflections on therapeutic strategies. Neural Regen. Res. 20 (3), 779–793. https://doi.org/10.4103/NRR.NRR-D-23-01508.

Zhu, X., Zhou, J., Zhu, Y., Yan, F., Han, X., Tan, Y., Li, R., 2022. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in schizophrenia. Australas. Psychiatry 30 (1), 95–99. https://doi.org/10.1177/10398562211022753.