

Monocyte to Lymphocyte Ratio as the Sole CBC-Derived Inflammatory Index Associated with PANSS EC Agitation Severity in a Large Psychiatric Cohort

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ABSTRACT

Agitation is a clinically important manifestation across severe mental disorders, yet its routine assessment remains predominantly symptom-based. Complete blood count (CBC)-derived inflammatory indices offer an inexpensive opportunity to complement clinical assessment with an objective biological signal. This study investigated the association of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) with agitation severity measured using the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC). An analytical observational cross-sectional study was conducted using 1,571 psychiatric patient records from Mutiara Sukma Hospital in 2025. Secondary data comprised CBC results and PANSS-EC scores; the four inflammatory indices were evaluated using stepwise multiple linear regression. Moderate agitation was the most frequent category (58.24%), followed by severe (22.92%) and mild agitation (18.84%). Mean NLR, PLR, MLR, and SII values showed an upward tendency across increasing agitation severity. In the final regression model, MLR was the only inflammatory index significantly associated with PANSS-EC score ($p < 0.001$), with a positive regression coefficient ($\beta = 3.374$), explaining 1.1% of score variance ($R^2 = 0.011$); NLR, PLR, and SII were not significant in the final model. The selective association of MLR supports a potentially distinct role of monocyte-linked innate immune activity in behavioral excitation. However, the small explained variance indicates that MLR should be interpreted as a complementary rather than stand-alone marker. These findings highlight MLR as a simple, low-cost candidate biomarker for further prospective evaluation in agitation assessment.

INTRODUCTION

Psychomotor agitation is a clinically important state characterized by excessive motor activity, tension, hostility, uncooperativeness, and impaired impulse control. It may occur across psychotic, affective, substance-related, and other severe psychiatric conditions, and is clinically relevant because escalating agitation can increase the risk of aggression, coercive interventions, injury, and prolonged hospitalization. The Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) is a brief five-item instrument that has demonstrated reliability, responsiveness, and convergent validity for quantifying agitation in acute psychiatric settings (Montoya et al., 2011). Nevertheless, PANSS-EC remains an observer-rated clinical measure, and biological parameters capable of complementing symptom assessment are still needed.

Immune-inflammatory dysregulation has increasingly been implicated in severe mental disorders, particularly psychotic disorders. A recent comprehensive meta-analysis showed elevations in circulating leukocytes, neutrophils, monocytes, and several leukocyte-derived ratios among people with psychotic disorders, supporting the presence of broad peripheral immune activation (Clausen et al., 2024). This has encouraged investigation of inexpensive hematological indices derived from routine complete blood counts. Among the most frequently studied are the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). These indices integrate changes in innate immune cells, adaptive

immune cells, and, for SII, platelet activity, thereby providing accessible proxies of systemic inflammatory balance.

Evidence linking these indices to psychiatric symptom severity is emerging but remains inconsistent. NLR is generally elevated in schizophrenia compared with controls (Karageorgiou et al., 2019), while meta-analytic evidence also supports alterations in MLR and PLR across non-affective psychosis (Mazza et al., 2020). More recent clinical studies have reported associations between CBC-derived inflammatory indices and PANSS symptom dimensions (Mojadadi et al., 2024; Zhou et al., 2024). Importantly, Cavaleri et al. (2024) found that MLR, but not NLR or PLR, was independently related to positive and negative symptom severity in schizophrenia spectrum disorders, suggesting that monocyte-related inflammatory activity may carry information not captured by other ratios.

However, most available studies focus on diagnosis-specific PANSS domains rather than acute behavioral excitation measured with PANSS-EC, and many involve relatively modest sample sizes. The present study addresses this gap by directly comparing four routinely obtainable CBC-derived inflammatory indices against PANSS-EC severity in a large real-world psychiatric cohort. The primary objective was to determine whether NLR, PLR, MLR, and SII were associated with PANSS-EC scores and to identify which index retained the strongest relationship when evaluated simultaneously. The novelty of this study lies in its large transdiagnostic clinical dataset and its focus on agitation severity as a clinically actionable behavioral phenotype rather than on diagnostic status alone.

MATERIALS/METHODS

This study used an analytical observational cross-sectional design based on secondary clinical data from patients treated at Mutiara Sukma Hospital during 2025. A total of 1,571 eligible psychiatric patient records were included using purposive sampling. The analysis used records containing complete blood count parameters required to derive hematological inflammatory indices and a documented PANSS-EC assessment. Records with insufficient data for calculation of the indices or analysis of PANSS-EC were not included.

The hematological inflammatory indices were derived from routine complete blood count parameters using conventional formulas: $NLR = \text{absolute neutrophil count} / \text{absolute lymphocyte count}$; $PLR = \text{platelet count} / \text{absolute lymphocyte count}$; $MLR = \text{absolute monocyte count} / \text{absolute lymphocyte count}$; and $SII = \text{platelet count} \times \text{absolute neutrophil count} / \text{absolute lymphocyte count}$. Because the study used secondary data, no additional blood collection was performed for research purposes.

Agitation severity was assessed using the PANSS-EC, which consists of five items: excitement, tension, hostility, uncooperativeness, and poor impulse control. The total PANSS-EC score was used as the continuous outcome in regression analysis. Descriptive categories recorded in the study dataset were mild, moderate, and severe agitation.

Descriptive statistics were used to summarize agitation categories and the pattern of inflammatory indices. The relationship between NLR, PLR, MLR, and SII and PANSS-EC score was evaluated using multiple linear regression with a stepwise variable-selection procedure. Statistical significance was set at $p < 0.05$. The final model was interpreted using the regression coefficient, p -value, and coefficient of determination (R^2).

Patient confidentiality was maintained throughout the analysis of secondary clinical data. The study was conducted in accordance with the ethical requirements applicable to the original research protocol.

RESULTS AND DISCUSSION

A total of 1,571 psychiatric patient records were analyzed. Moderate agitation represented the largest proportion of the cohort (58.24%), followed by severe agitation (22.92%) and mild agitation (18.84%). Thus, more than four-fifths of the analyzed patients were in the moderate-to-severe categories, indicating that the dataset predominantly represented clinically meaningful agitation rather than minimally symptomatic presentations.

Table 1. Distribution of agitation severity based on PANSS-EC categories

Agitation category	Proportion (%)
Mild	18.84
Moderate	58.24

Severe	22.92
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The mean values of NLR, PLR, MLR, and SII demonstrated an increasing tendency across higher agitation categories. This overall pattern is biologically plausible because acute psychiatric excitation can coexist with autonomic activation, neuroendocrine stress, altered innate immune signaling, and shifts in circulating leukocyte subpopulations. However, an apparent gradient across categories does not establish that all four indices contribute independent information. Their cellular components overlap substantially; for example, NLR and SII share neutrophil and lymphocyte counts, while MLR and NLR both use lymphocytes as the denominator. Multivariable modeling is therefore important to identify the index that retains an association when the markers compete for explanatory value.

Table 2. Final stepwise regression model for PANSS-EC score

Index	Final-model status	Regression information	Interpretation
MLR	Retained	beta = 3.374; $p < 0.001$; model $R^2 = 0.011$	Significant positive association
NLR	Not retained	$p > 0.05$ in final model	No independent association detected
PLR	Not retained	$p > 0.05$ in final model	No independent association detected
SII	Not retained	$p > 0.05$ in final model	No independent association detected

The principal finding was that MLR was the only inflammatory index retained as a significant correlate of PANSS-EC score in the final regression model ($p < 0.001$; $\beta = 3.374$). The positive coefficient indicates that higher MLR values were associated with higher agitation scores. This result is especially noteworthy because all four indices showed an increasing descriptive tendency with agitation severity, yet only MLR remained statistically informative in the multivariable selection process. The finding therefore suggests that the monocyte-lymphocyte balance may capture a component of immune dysregulation that is more closely related to behavioral excitation than neutrophil- or platelet-dominant composite measures in this cohort.

This interpretation is supported by recent literature. Cavaleri et al. (2024), using structural equation modeling in 266 inpatients with schizophrenia spectrum disorders, reported significant relationships between MLR and both positive and negative symptom severity, while NLR and PLR were not significantly related in the same model. Similarly, Atkaya et al. (2024) observed that MLR remained elevated in patients with schizophrenia even during remission compared with healthy controls, leading the authors to propose MLR as a potential trait-related inflammatory marker. These observations provide a biologically coherent context for the present result and strengthen the argument that monocyte-linked innate immune activity deserves specific attention in psychiatric biomarker research.

Monocytes are central components of innate immunity and are capable of producing pro-inflammatory cytokines and interacting with endothelial and neuroimmune pathways. In psychotic disorders, meta-analytic evidence demonstrates increased circulating monocyte counts as part of a broader pattern of immune activation (Clausen et al., 2024). By combining monocyte abundance with lymphocyte status, MLR may reflect a balance between innate inflammatory activation and adaptive immune regulation. A higher ratio can therefore arise from increased monocyte activity, relatively reduced lymphocyte counts, or both. In the context of agitation, such a ratio may be responsive to inflammatory and stress-related processes that accompany acute behavioral dysregulation.

The absence of an independent association for NLR, PLR, and SII should not be interpreted as evidence that these markers are biologically irrelevant. Previous studies have shown elevated NLR in schizophrenia (Karageorgiou et al., 2019) and associations of NLR, PLR, MLR, and SII with broader PANSS symptom scores (Mojadadi et al., 2024). Differences between studies may arise from diagnostic composition, medication exposure, smoking, obesity, metabolic comorbidity, recent infection, stress at blood sampling, and the clinical outcome being modeled. The present study specifically examined agitation measured by PANSS-EC in a broad psychiatric cohort; this phenotype is narrower than total psychosis severity and may have a different inflammatory signature.

The distribution of agitation severity also deserves clinical interpretation. Moderate agitation accounted for 58.24% of records and severe agitation for 22.92%, meaning that 81.16% of the cohort had at least moderate behavioral excitation. This concentration of clinically relevant agitation

strengthens the usefulness of the dataset for examining biological correlates of acute behavioral dysregulation. At the same time, it may limit extrapolation to stable outpatients or individuals with minimal agitation. The predominance of moderate-to-severe cases may also increase the probability of concomitant physiological stress, disturbed sleep, restraint exposure, dehydration, smoking, or recent psychotropic administration, all of which can alter circulating leukocyte subsets. Therefore, the observed hematological gradient should be interpreted as reflecting the biological milieu of real-world acute psychiatric care rather than a disease-specific inflammatory signature alone.

The finding that MLR was retained while NLR, PLR, and SII were excluded from the final model is consistent with evidence that different CBC-derived ratios are not biologically interchangeable. Cavaleri et al. (2024) reported that MLR was significantly related to both positive and negative symptom severity in schizophrenia spectrum disorders, whereas NLR and PLR were not significant within the same structural model. Similarly, Hu et al. (2025) found higher monocyte counts and MLR in first-episode schizophrenia than in healthy controls and reported a positive independent effect of MLR on an arousal-related symptom score. These findings are particularly relevant because arousal and behavioral activation overlap conceptually with several PANSS-EC domains, including excitement, tension, hostility, and poor impulse control. Taken together, the present results add to an emerging pattern in which monocyte-related indices may be more closely linked to symptom expression than to diagnosis alone.

A plausible explanation for this selectivity involves the functional role of monocytes in peripheral-to-central immune communication. Activated monocytes can release pro-inflammatory mediators, interact with vascular endothelium, and influence cytokine signaling that may affect neurotransmission and stress-response systems. The MLR simultaneously reflects the monocyte compartment and the relative availability of lymphocytes; consequently, it may capture a shift toward innate immune predominance more effectively than a single leukocyte count. This interpretation is compatible with the meta-analysis by Clausen et al. (2024), which documented increased circulating monocytes as part of a broader immune-cell alteration in psychotic disorders. It is also compatible with the observation of Atkaya et al. (2024) that MLR remained elevated in schizophrenia during remission compared with healthy controls, raising the possibility that MLR may contain both trait-related and state-related information.

The present result should nevertheless be contrasted with studies in which neutrophil-dominant indices showed stronger associations. Mojadadi et al. (2024) found that NLR, MLR, PLR, and SII were positively correlated with multiple PANSS domains, while adjusted analyses identified NLR as a predictor of several symptom scores. More recently, Pavlovic et al. (2025) reported higher NLR in schizophrenia and positive correlations with PANSS negative, general psychopathology, total, and excitement factor scores. Such findings do not necessarily contradict the current analysis. Those studies focused primarily on schizophrenia and broader PANSS symptom dimensions, whereas the present study used a transdiagnostic psychiatric cohort and modeled PANSS-EC as the specific behavioral outcome. In addition, differences in age, sex distribution, body mass index, smoking, illness stage, medication exposure, and exclusion of infectious or metabolic conditions may alter which leukocyte ratio appears most informative.

Evidence from inflammatory biomarkers outside the CBC further supports the biological relevance of inflammation to agitation. Kachouchi et al. (2020) reported higher C-reactive protein levels in agitated patients with schizophrenia, with reductions in both CRP and PANSS excitement following treatment. Li et al. (2021) likewise identified inflammatory and biochemical parameters associated with agitation measured using PANSS-EC. More recently, Wang et al. (2024) demonstrated significantly higher plasma TNF-alpha in first-episode schizophrenia patients with agitation than in those without agitation, and TNF-alpha concentrations were positively correlated with PANSS-EC scores. These studies indicate that agitation may be accompanied by measurable inflammatory activation across several biological levels. The present MLR finding therefore fits within a broader inflammatory framework, while offering the practical advantage that MLR can be calculated from an inexpensive routine CBC without an additional biomarker assay.

The non-significant final contribution of PLR and SII also warrants explanation. Platelet-related indices may reflect inflammatory and thrombo-inflammatory processes, but platelet counts are influenced by a wide range of physiological and clinical factors and may be less sensitive to short-term behavioral excitation. SII combines neutrophils, lymphocytes, and platelets and is often

described as a broader marker of systemic inflammation. However, greater biological breadth does not automatically translate into greater specificity for a psychiatric phenotype. Because SII mathematically incorporates the same neutrophil-to-lymphocyte relationship represented by NLR, collinearity and shared variance among the candidate indices may reduce its independent contribution when all markers are considered together. Thus, exclusion from a stepwise model should be interpreted as lack of incremental explanatory value in this dataset, not as evidence that platelet- or neutrophil-linked inflammation is absent.

Another important consideration is the distinction between statistical significance and clinical discrimination. The positive regression coefficient for MLR indicates directionality, but the model R^2 of 0.011 shows that the ratio accounts for only a small fraction of variation in PANSS-EC scores. Agitation is a multidimensional clinical phenomenon driven by psychotic symptoms, affective instability, substance effects, environmental stress, sleep disruption, pain, medication adherence, and interpersonal context in addition to biological inflammation. A single hematological ratio would therefore not be expected to explain a large proportion of its variance. Rather than weakening the finding, the low R^2 helps define an appropriate clinical role: MLR may function as an adjunctive biological signal that contributes to multimodal risk characterization when interpreted alongside structured behavioral assessment and clinical history.

The large sample size of 1,571 records is an important strength but also changes the interpretation of p values. In a cohort of this size, relatively small effects can reach strong statistical significance. Accordingly, the $p < 0.001$ result should be considered together with the magnitude of the regression coefficient, the narrow purpose of the model, and the low explained variance. For future clinical translation, measures of discrimination, calibration, clinically useful cut-off values, and incremental predictive value beyond demographic and clinical variables would be more informative than statistical significance alone. Prospective analyses could compare models containing PANSS-EC clinical predictors with and without MLR to determine whether MLR meaningfully improves prediction of severe agitation, need for rapid tranquilization, restraint, or prolonged hospitalization.

Medication and acute-care context are particularly relevant potential confounders. Antipsychotic drugs can influence immune activity indirectly through changes in weight, glucose metabolism, prolactin, sedation, and illness stabilization; conversely, severe agitation may lead to emergency medication before laboratory sampling. Cavaleri et al. (2024) demonstrated that antipsychotic treatment was meaningfully connected with symptom severity and obesity within their structural model, illustrating how treatment variables may intersect with inflammatory measurements. Without precise information on medication timing relative to CBC collection and PANSS-EC assessment, the present cross-sectional analysis cannot determine whether elevated MLR precedes agitation, arises as part of the acute stress response, or changes following treatment. Temporal standardization should therefore be a priority in subsequent studies.

The transdiagnostic composition of the cohort is both a strength and a limitation. Agitation occurs across schizophrenia, bipolar disorder, substance-related disorders, organic psychiatric conditions, and other severe mental illnesses; therefore, a marker associated with PANSS-EC across diagnoses could have broader acute-care relevance. On the other hand, different diagnoses may involve distinct inflammatory mechanisms and treatment exposures. Diagnostic stratification in future analyses could determine whether the MLR association is consistent across schizophrenia-spectrum, affective, and substance-related conditions or whether it is driven by a particular subgroup. Interaction analyses by sex and age would also be valuable because prior studies have reported sex-dependent relationships between CBC-derived inflammatory indices and psychiatric symptom severity.

Overall, the comparison with previous literature suggests that the main contribution of this study is not simply the observation that inflammation accompanies psychiatric illness. Rather, its contribution is the identification of MLR as the only CBC-derived index that retained an independent association with PANSS-EC agitation severity when four readily available indices were evaluated in the same large real-world cohort. This specificity, together with convergent evidence linking monocyte-related measures to psychiatric symptom severity and arousal, provides a focused hypothesis for future validation. The findings support moving from broad statements about 'inflammation in psychiatry' toward testing whether particular immune-cell relationships map onto particular behavioral phenotypes.

A particularly important aspect of the present finding is the effect size. Although MLR was statistically robust, the model explained only 1.1% of the variance in PANSS-EC score ($R^2=0.011$). With a sample of 1,571 records, small associations can be detected with high statistical power. Therefore, the clinical message should not be that MLR can replace PANSS-EC or independently determine agitation severity. Rather, MLR may serve as an objective complementary parameter that adds a small amount of biological information to clinical assessment. This restrained interpretation increases the translational credibility of the finding and avoids overstatement of biomarker utility.

The study has several strengths. First, the sample size is substantially larger than many prior single-center studies of hematological inflammatory markers in psychiatric populations. Second, the simultaneous comparison of four commonly accessible indices provides a pragmatic test of which marker may be most informative when laboratory resources are limited. Third, the focus on PANSS-EC links the biomarker analysis to a clinically actionable outcome relevant to acute care. The main limitations are the cross-sectional design, use of secondary data, potential diagnostic heterogeneity, and the absence in the available dataset summary of detailed adjustment for important confounders such as age, sex, body mass index, smoking, infection, medication type and dose, substance use, and metabolic disease. These factors can influence CBC-derived ratios and should be incorporated into future prospective multivariable models.

Future studies should validate the MLR-PANSS-EC relationship prospectively, record blood sampling in close temporal proximity to agitation assessment, and adjust for major inflammatory and treatment-related confounders. Repeated measurements before and after clinical de-escalation would be especially informative because they could distinguish whether MLR behaves as a state marker of acute agitation, a trait marker of psychiatric illness, or a combination of both. Comparative models incorporating C-reactive protein and cytokine measures may also clarify whether MLR provides incremental value beyond conventional inflammatory biomarkers.

CONCLUSIONS

Among four CBC-derived inflammatory indices evaluated in 1,571 psychiatric patients, MLR was the only index significantly associated with PANSS-EC agitation severity in the final stepwise regression model. Higher MLR was associated with higher PANSS-EC scores ($\beta=3.374$; $p<0.001$), whereas NLR, PLR, and SII did not retain significant associations. The finding supports MLR as a low-cost candidate marker of monocyte-linked inflammatory activity relevant to agitation. However, because MLR explained only 1.1% of PANSS-EC variance, it should be considered an adjunct to, not a replacement for, structured clinical assessment. Prospective studies with diagnostic stratification and adjustment for inflammatory, metabolic, and treatment-related confounders are needed before clinical implementation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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