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Relationship Between Exposure to Emotional Neglect and the Inflammatory Biomarkers Neutrophil-to-Lymphocyte, Monocyte-to-Lymphocyte, and Platelet-to-Lymphocyte Ratios in Patients With First-Episode Psychosis

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Abstract

Aim: To assess whether exposure to childhood traumatic experiences is linked to the inflammatory markers neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) in people with a first-episode psychosis.

Methods: A cross-sectional study was performed in 83 patients (21 females and 62 males) with a diagnosis of a first psychotic episode. All participants completed the self-reported Spanish version of the Childhood Trauma Questionnaire (CTQ). NLR, MLR, and PLR were calculated in each patient.

Results: Highest CTQ scores were noted on the emotional neglect and abuse domains (mean ± SD = 10.92 ± 4.41; mean ± SD = 10.93 ± 4.78, respectively), being lowest for the sexual abuse domain (mean ± SD = 6.12 ± 2.41). Backward stepwise linear regressions showed that high emotional neglect significantly predicted increased PLR (β = 0.452, *P* = .036), older age and high emotional neglect predicted increased NLR (β = 0.483, *P* = .036; β = 0.442, *P* = .06, respectively), and high emotional neglect, low physical neglect, high total Positive and Negative Syndrome Scale (PANSS) score, and cannabis and alcohol use predicted increased MLR (β = 0.698, *P* = .003; β = 0.672, *P* = .033; β = 0.296, *P* = .027; β = 0.390, *P* = .069; β = 0.560, *P* = .078, respectively).

Conclusions: Our results highlight the relationship between the exposure to emotional neglect and the inflammatory biomarkers NLR, MLR, and PLR in patients with a first-episode psychosis. This study has benefitted from controlling for confounders such as body mass index, smoking status, symptom severity, and alcohol and cannabis use.

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A large body of evidence supports the association between childhood traumatic experiences and an increased risk of developing schizophrenia[1–5] later in life.[6] Childhood trauma (CT) is a significant factor in the dysregulation of the immune system in individuals with schizophrenia. This is supported by the increased levels of circulating interleukin-6 (IL-6), interferon regulatory factor 1, toll-like receptor 4, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) observed in these patients.[7–10]

Studies performed in individuals with a first-episode psychosis (FEP) have demonstrated elevated levels of CRP,[11] IL-1b, IL-6, IL-8, and TNF-α[12,13] and decreased levels of brain-derived neurotrophic factor[14] in patients exposed to CT when compared to healthy controls. Specific types of CT have varying effects on the expression of unique immunity markers.[8]

The mechanisms linking CT and psychosis through proinflammatory phenotypes are mostly unclear. CT

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Clinical Points

- Traumatic events in childhood and dysregulation of the immune system are factors that have been shown to be involved in the onset of psychosis, but their correlation in these patients has not yet been studied.
- The existence of a link between the immune system and childhood traumatic events in patients with a first-episode psychosis, as well as its exploration in clinical practice, may promote the use of alternative therapies or approaches.

seems to trigger long-lasting disruptions in the hypothalamic-pituitary-adrenal axis,[15] which is responsible for the reactivity of the hippocampal function and dopaminergic neurotransmitter systems that are widely described in schizophrenia.[16–18] Inflammatory signaling pathways seem to impact a network of biological systems that are extensively involved in psychosis, including neuroendocrine, monoaminergic, oxidative, nitrosative, and neurotrophic pathways.[19,20] These lines of evidence point to the activation of the immune and inflammatory system as one of the biological mechanisms underlying the pathogenesis of mental illness in vulnerable individuals, especially in the context of early-life stress.[8]

Many studies focus on the neutrophil-to-lymphocyte ratio (NLR) as a systemic inflammation biomarker as it provides a balance between the innate (neutrophil) and adaptive (lymphocyte) immune systems.[21] An increased NLR has been associated not only with a worse clinical prognosis[22–24] but also with a higher prevalence of mental disorders.[25] Monocytes and platelets play a key role in immunity through various pathways, including the secretion of proinflammatory substances. An increase in both monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocytes ratio (PLR) has also been described as novel inflammatory parameters.[21]

Establishing a normal range of these parameters is difficult due to various factors such as age, race, treatment, or chronic diseases (heart diseases, obesity, anemia, diabetes, and cancer). In Zahorec's review,[26] a normal NLR range between 1 and 2 was determined. An NLR between 2.3 and 3 may indicate a pathological process such as a psychiatric disorder.[26]

There are fewer studies that determine a normal range for PLR or MLR in a healthy population. A study conducted in South Korea found that healthy subjects had a mean PLR of 132.4 and a mean lymphocyte-to-monocyte ratio of 5.31.[27]

Multiple meta-analyses and systematic reviews have shown that chronic schizophrenia and early-onset psychosis are associated with an increased NLR.[28,29] Mazza's meta-analysis[28] also provides evidence that patients with nonaffective psychosis have an increased MLR. The severity of negative symptoms in patients with schizophrenia is positively correlated with both NLR and MLR.[21] Although there are fewer studies linking PLR and schizophrenia, Mazza's meta-analysis[28] also found an increased trend of PLR in patients with nonaffective psychosis compared to healthy controls. Finally, a recent study found an increased PLR in patients with early-onset psychosis.[30] In addition to their potential relationship with psychosis, markers such as NLR, MLR, and PLR are valuable due to their low cost, ease of measurement, and widespread availability, and they provide inexpensive, easily measurable, and widely available parameters in routine clinical practice.[28,29,31]

The aim of this study was to assess whether exposure to childhood traumatic experiences is linked to the inflammatory markers NLR, MLR, and PLR in individuals with a FEP.

METHODS

Study Sample

We performed a descriptive, cross-sectional analysis. The sample was recruited as part of the PROFEP study, which began in 2013 and is still active, and it is a longitudinal study focusing on describing factors and variables that may influence the onset and evolution of patients with FEP. The study sample included 83 patients at baseline (21 females and 62 males) with a diagnosis of FEP. All patients were recruited at Parc Sanitari Sant Joan de Déu (Barcelona).

The inclusion criteria for patients required them to be between the ages of 13 and 46 years and to have suffered a FEP as defined by the presence of at least one of the following symptoms: delusional ideas, hallucinations, disorganized language, and catatonic or disorganized behavior for at least 1 week and <5 years of development. These symptom criteria include patients diagnosed with the F20-F29 (except F21) according to the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*),[32] as well as those diagnosed with affective psychosis (major depressive disorder or bipolar disorder). Moreover, they have not been taking medication for more than 15 days. Patients diagnosed with intellectual disabilities (premorbid IQ < 70), traumatic brain injury, or well-known pathology of the central nervous system (tumor, HIV, and radiotherapy) were excluded from the study. Other exclusion criteria are fully described elsewhere.[28,33] All patients received verbal and written information about the study and signed the informed consent.

Clinical Variables

We administered a sociodemographic questionnaire to collect data on age, gender, and days in treatment. The

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psychiatrist provided the duration of untreated psychosis (DUP) based on the information provided by the patients and their relatives.

All participants completed the self-reported Spanish version of the Childhood Trauma Questionnaire (CTQ), which identifies the presence or absence of childhood traumatic events and the level of CT.[29,30,34,35] The CTQ instrument evaluates 5 commonly recognized forms of maltreatment through different domains: emotional abuse, physical abuse, emotional neglect, physical neglect, and sexual abuse. Scores for each domain are based on a 4-point Likert scale, ranging from 1 (absence) to 4 (severe). The total CTQ score is calculated by summing the scores from all 5 subscales and ranges between 25 and 75 points. Also, we used a cutoff for each CTQ domain, which corresponds to a "moderate-to-severe" CT. Thus, a score ≥15 in the emotional neglect subscale, a score ≥13 in the emotional abuse subscale, a score ≥10 in the physical abuse and physical neglect subscales, and ≥8 in the sexual abuse subscale were considered to be positive for that particular domain.[31,36,37] These categories were used only to describe the sample, analyzing CTQ scores as a continuous variable to provide greater statistical power.

Symptom severity was assessed through the Positive and Negative Syndrome Scale (PANSS),[38,39] which evaluates the positive, negative, and general symptoms of patients with schizophrenia. Each item is scored on a Likert scale of 7 of severity [ranging from 1 (no symptoms) to 7 (presence with extreme gravity)].

Alcohol use, cannabis use, and nicotine use were assessed by a semistructured interview. A urinalysis was also performed upon admission to detect recent cannabis use. For this study, alcohol use was defined as consuming three or more standard drink units per week for at least the last 3 months. Any weekly cannabis use or daily nicotine use during the same period was rated as "substance users."

Anthropometric and Biochemical Analyses

Body mass index (BMI = weight in kg/height squared) was determined by a trained nurse. Peripheral blood samples were collected between 8 and 10 AM. Blood cell counts were performed at the Department of Clinical Chemistry, Hospital Sant Joan de Déu (Esplugues de Llobregat, Barcelona, Spain). NLR, MLR, and PLR were calculated from absolute neutrophil, monocyte, lymphocyte, and platelet values (NLR: absolute neutrophil/absolute lymphocyte count, MLR: absolute monocyte/absolute lymphocyte count, and PLR: absolute platelet/absolute lymphocyte count).

Statistical Analyses

The different analyses were performed using the statistical program SPSS version 20.0 (IBM Corp; Armonk, NY). Statistical significance was established at $P < .05$. Frequencies and percentages were reported for categorical variables.

Potential associations between CT exposures and NLR, MLR, and PLR levels were assessed using a backward stepwise linear regression analysis. The dependent variables were NLR, MLR, and PLR levels. Age, sex, symptom severity (total PANSS), BMI, and alcohol, nicotine, and cannabis use in the last 3 months and CTQ subscale scores were entered together as independent variables or potential predictors.

NLR and MLR do not follow a normal distribution. To compare mean differences, a Mann-Whitney *U* test was performed for these parameters instead of a Student *t* test. To perform linear regression analysis, the raw data were transformed to logarithmic equivalents for these 2 variables.

Table 1.
Sociodemographic, Clinical, and Inflammatory Biomarkers in FEP Subjects

		FEP N = 83
Age, y		24.70 ± 7.80
Gender, %	Male	74.7%
	Female	25.3%
BMI, kg/m² (mean; SD)		24.58 ± 21.32
Consumption in the last 3 months (% yes)	Nicotine	59.5%
	Alcohol	43.4%
	THC	30.3%
Years of education (%)	5–8	15.7%
	9–12	55.4%
	>12	28.9%
People who live with (%)	Own	8.5%
	Couple	6%
	Family origin	66.3%
	Own family	2.4%
	Other relatives	6%
	Others	10.8%
Inflammatory biomarkers (mean; SD)	NLR	2.31 ± 1.01
	MLR	0.23 ± 0.10
	PLR	104.71 ± 36.84
CTQ domains (mean; SD)	Emotional abuse	10.93 ± 4.78
	Physical abuse	6.87 ± 3.18
	Sexual abuse	6.12 ± 2.41
	Emotional neglect	10.92 ± 4.41
	Physical neglect	7.75 ± 3.11
	Total CTQ score	51.15 ± 12.97
Naïve (% yes)		45.8%
DUP in months (median; IQR)		5 (1–13.5)
Days in treatment (mean; SD)		1.79 ± 2.37
PANSS scores (mean; SD)	Positive subscale	25.32 ± 4.48
	Negative subscale	19.43 ± 7.80
	General subscale	43.90 ± 12.06
	PANSS total score	88.08 ± 19.42

Abbreviations: BMI = body mass index, CTQ = Childhood Trauma Questionnaire, DUP = duration of untreated psychosis, FEP = first-episode psychosis, IQR = interquartile range, MLR = monocyte-to-lymphocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PANSS = Positive and Negative Syndrome Scale, PLR = platelet-to-lymphocyte ratio, THC = Δ9-tetrahydrocannabinol.

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Ethical Standards

This study was approved by the Research and Ethics Committee of the Parc Sanitari Sant Joan de Déu (reference number is PIC-148-17). It was carried out in accordance with the Declaration of Helsinki in its recent review.

RESULTS

Characteristics of the Sample

Table 1 shows the sociodemographic and clinical variables and inflammatory biomarkers of the sample. The mean age of our patients was 24.7 years, indicating a young population in our sample. Over half of the subjects had received 9–12 years of education, lived with their parents, and reported nicotine use within the past 3 months.

Within our sample, patients were either antipsychotic-naïve (45.8%) or had been on antipsychotic treatment for a very short period (1.79 days). Although the doses of antipsychotics and their duration of use were low, we compared the biomarker levels between naïve and non-naïve patients, as antipsychotics can affect them. We did not find any differences between these 2 groups for MLR (Z = −0.079; $P = .937$) and NLR ($Z = -0.652$; $P = .514$). However, we found that naïve patients had significantly higher PLR levels than treated patients ($t = 3.582$; $P = .001$).

Mean total CTQ and subscale scores are presented in Table 1. The emotional neglect and abuse domains had the highest scores, while the sexual abuse domain had the lowest. Based on the previously described cutoff values, we found that 30.1% of the patients reported emotional abuse, 21.9% reported physical neglect, 19.8% reported emotional neglect, 17% reported sexual abuse, and 11.5% reported physical abuse. There were no significant differences between men and women in the percentage of positivity for each CTQ domain, except for sexual abuse, where women have suffered significantly more ($P = .006$).

Positive significant correlations were found between the physical neglect domain and PANSS positive ($r = 0.251$; $P = .013$), PANSS general ($r = 0.243$; $P = .017$), and total scores ($r = 0.224$; $P = .029$). Significant correlations are found between the physical abuse domain and PANSS positive ($r = 0.324$; $P = .001$), general ($r = 0.244$; $P = .016$), and total scores ($r = 0.324$; $P = .001$). Finally, the emotional abuse domain showed a significant correlation with the PANSS positive subscale ($r = 0.227$; $P = .026$). Men showed a significant correlation between emotional abuse and PANSS positive ($r = 0.303$; $P = .013$), as well as between emotional abuse and DUP ($r = 0.233$; $P = .043$). There were significant correlations found between physical abuse and PANSS positive ($r = 0.618$; $P < .001$), general ($r = 0.460$; $P = .012$), and total scores ($r = 0.561$; $P = .002$) in women.

Table 2.
Multivariate Predictors of Inflammatory Status (NLR, PLR, and MLR) in FEP Patients[a]

	Standardized coefficient β	*P* value[b]
PLR[c]		
High emotional neglect	β = 0.452	*P* = .036
	Overall model: *F* = 7.177, *P* = .012	
NLR[c]		
Older age	β = 0.483	*P* = .036
High emotional neglect	β = 0.442	*P* = .06
	Overall model: *F* = 4.838, *P* = .016	
MLR[c]		
High total PANSS score	β = 0.296	*P* = .27
High emotional neglect	β = 0.698	*P* = .003
Low physical neglect	β = −0.672	*P* = .033
Alcohol use (yes)	β = 0.560	*P* = .078
Cannabis use (yes)	β = 0.390	*P* = .069
	Overall model: *F* = 3.603, *P* = .014	

[a]Stepwise (backward) linear regression.
[b]Bonferroni correction for multiple testing was performed.
[c]Dependent variables: PLR, NLR, and MLR.
Abbreviations: FEP = first-episode psychosis, MLR = monocyte-to-lymphocyte ratio, NLR = neutrophil-to-lymphocyte ratio, PANSS = Positive and Negative Syndrome Scale, PLR = platelet-to-lymphocyte ratio.

Prediction Models of Inflammatory Status

We performed backward stepwise linear regressions using PLR, NLR, and MLR as dependent variables. Regarding independent variables, the CTQ subscales have been included as variables of interest. Age, BMI, and the use of nicotine, cannabis, and alcohol have been included as confounding variables because they can modify the inflammatory factors.[28,29,31,40,41] It is important to note that the severity of psychotic symptoms and gender can modify CTQ scores and are therefore considered confounding factors as well.[42,43] Significant predictors, standardized coefficient, and *P* values are shown in Table 2.

The model obtained for PLR explained 17.6% of the variance, with high emotional neglect predicting an increase in PLR. The model obtained for NLR explained 20.9% of the variance, with older age as a statistically significant predictor of increased NLR. Emotional neglect also showed a tendency toward significance in explaining the increase in NLR. The significant model obtained for MLR explained 31% of the variance. High emotional neglect and low physical neglect were statistically significant predictors of increased MLR, while alcohol and cannabis use tended to be significant.

DISCUSSION

This study is the first to investigate the associations between CT and the inflammatory markers NLR, MLR, and PLR in individuals with FEP. We report for the first time an association between high emotional neglect and increased PLR, NLR, and MLR in patients with FEP.

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Research has shown that childhood traumatic events can cause long-term changes in the human inflammatory response,[10] suggesting that stress experienced during periods of high immune system plasticity can affect the functioning of cells that regulate inflammation. Furthermore, exposure to inflammation during the early stages of brain development may interfere with processes such as cell differentiation, creating a common pathway between early genetic and/or environmental factors and the development of psychosis.[44]

The impact of different types of childhood adversities on inflammatory mediators is an important issue, as the response to similar adversities may depend on the subject's resilience and vulnerability. Sexual abuse is usually linked to slight increases in TNF-α, but not CRP or IL-6 levels, and exposure to physical abuse is associated with slight elevations of TNF-α and IL-6, but not CRP levels.[8] Emotional abuse seems to be at the core of the associations with neurobiological stress markers seen in schizophrenia,[45] such as reduced hippocampal volume and lower morning cortisol.[15]

In our study, we found that high emotional neglect was the type of CT that significantly predicted increased levels of NLR, PLR, and MLR, and therefore a more severe inflammatory status. Interestingly, this specific type of CT is associated with a higher prevalence of nonaffective psychosis.[46] This may be due to a family environment that fails to provide security and appreciation, hindering the development of strategies for adequate emotional management.[47] As a result, individuals who have experienced emotional neglect may exhibit reduced empathy in both social inclusion and exclusion scenarios,[48] potentially leading to misinterpretation of certain situations.

Physical and emotional neglect may also significantly affect the course of symptoms,[49,50] probably due to compromised emotion regulation strategies which makes individuals less able to deal with the stress of psychotic symptoms.[51] In our study, the domains of physical and emotional abuse, as well as physical neglect, are significantly correlated with greater symptom severity, except for negative symptomatology.

Leukocytes play a primary role in mediating inflammatory response, where changes in its populations may reflect the answer of the immune system during inflammation.[52] Inflammatory ratios promise more accurate information than other single leukocyte parameters or other commonly used markers of inflammation.[53] To date, several studies have shown increased MLR, PLR, and NLR in patients with schizophrenia.[28,29] There is little evidence available on individuals with a FEP, as only 5 studies have included FEP patients[31,54–57] and only 1 of them was performed in drug-naive patients.[31] None of these studies included information about CT. Four studies reported high NLR values,[54–57] while 1 study did not.[31] High MLR values were reported in the 3 studies.[55,56] To our knowledge, no study has yet reported PLR values in FEP patients.

When studying childhood traumatic events and their relationship with inflammatory biomarkers NLR, PLR, and MLR, it is important to control for several confounding factors that may affect either variable.[28,29] These factors are age, gender, treatment status, smoking, alcohol and cannabis use, and BMI and will be briefly discussed in relation to our results.

CT seems to be linked to an increased risk of obesity, possibly due to increased energy intake and storage, reduced energy expenditure, and higher calorie intakes.[58] This finding is not explained by antipsychotic exposure and is likely to involve both biological and psychological mechanisms.[59] Additionally, obesity is accompanied by low-grade inflammation leading to a stress-induced cytokine response.[60] Four of the 5 studies on ratios and FEP have reported BMI values ranging from 22 to 25,[31,54–56] which is in line with the BMI values reported in the present study. However, none of these studies considered BMI as a confounding factor in their statistical analyses. In our study, we found that increased BMI did not affect NLR, MLR, and PLR values, possibly because of the wide BMI values.

Studies with healthy subjects have shown a positive correlation between NLR and age.[61,62] Metaregression has also demonstrated the influence of age on the relationship between nonaffective psychosis and MLR.[28] Our mean age of 25 years was similar to the age range (15–29 years) reported in studies on ratio values in FEP.[54,56,57] As expected, our study found that older age significantly predicted inflammatory biomarkers.

The effect of antipsychotic medication was not assessed in our study, but we can rule out its impact. When comparing biomarker ratios, we found a possible effect of antipsychotic medication on PLR levels. Therefore, we can infer that patients in treatment could be considered naïve, as there were no differences between patients with and without antipsychotic treatment on NLR and MLR values. This is an important issue as antipsychotic medications might influence inflammatory biomarkers.[28]

Although a recent meta-analysis[43] found that the occurrence of adverse or traumatic childhood events was associated with greater severity of positive symptoms, studies on ratios in schizophrenia have not shown an association between NLR and clinical severity.[29] In our study, symptom severity predicts an increased MLR but not NLR or PLR, which is consistent with current literature.

Cannabis use has a differential relationship with inflammatory biomarkers, depending on the relative concentration of Δ9-tetrahydrocannabinol (THC), with proinflammatory effects, and cannabidiol (CBD), with

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anti-inflammatory effects. The prevalence of cannabis use in our study (30.3%) is similar to the results found in the literature, which is around 33.7% in FEP patients.[63] We found that cannabis use predicts an increased MLR, but not other inflammatory ratios. This can be explained by the impossibility to determine the use of THC and CBD in each patient. On the other hand, our finding confirms previous evidence of monocyte activation and altered humoral and cellular immunity caused by alcohol, which can lead to infection and inflammation in many tissues.[40] This is supported by our reported association between alcohol use and impaired MLR levels.

Although an association between smoking and monocyte count has been described in FEP patients 31, we did not find an association between the 2 variables in our study.

Concerning nicotine use, numerous studies have reported the association between nicotine and psychosis, involving epidemiologic, genetic, and neuroimaging explanations.[64] Furthermore, nicotine triggers the neutrophil release of reactive oxygen species and DNA fibers from their own nuclei, causing tissue damage in several inflammatory diseases.[65] In our study, 59.5% of the patients were smokers, a prevalence similar to that found in a meta-analysis.[66] Although an association between smoking and monocyte count has been described in FEP patients,[31] we did not find an association between these 2 variables in our study.

Strengths and Limitations

Several limitations of this study should be considered. First, the cross-sectional design of our study implied that no conclusions could be drawn about causality and prevented the assessment of a temporal association between the age of exposure to the traumatic event and both inflammatory status and psychosis outcome. Recording when the traumatic event occurred appears to be important in terms of brain development, as certain brain regions seem to be particularly sensitive to the effects of stressors depending on the time frame.[67] This limitation has been acknowledged in most studies on CT, as they lack information on the frequency, duration, timing, impact, and distress of the traumatic event.

In addition, retrospective CT assessment is susceptible to memory bias and underestimation, as participants are asked to recall events that occurred a long time ago. However, there is no bias due to current psychopathology when using a retrospective assessment.[68] Secondly, although we evaluated our patients for confounding factors, other important confounders were not recorded, such as inflammatory diseases (antiallergens and antirheumatic treatment, tumor, HIV, thyroid disease, and alterations of the pituitary gland and ovaries), the active use of anti-inflammatory drugs. However, we can assume that these drugs are not widely used in young adults.[69] Thirdly, like most studies of life events, we examined a relatively small sample and lacked a healthy subject control group comparison, which would improve the internal validity of our work. Future studies should include this to provide further strength. Finally, our sample is mostly male, a fact that may bias our results, although it was taking into account in the linear regression analysis.

Our findings highlight the relationship between exposure to emotional neglect type of CT and an increase in inflammatory biomarkers such as NLR, MLR, and PLR. Although we found that the treatment received in non-naïve patients could affect PLR levels, it would not affect MLR or NLR levels, which is a strength of our study. Unlike other studies of NLR, PLR, and MLR in FEP, this study benefitted from controlling for confounders such as BMI, smoking status, symptom severity, and alcohol and cannabis use. However, future research should investigate this relationship through longitudinal studies. It might also be helpful for future research to take gender differences into account. Moreover, future research should include more information about childhood traumatic events, such as the frequency, duration, timing, impact, and distress of the traumatic event.

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