NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2024;61:275–280
https://doi.org/10.29399/npa.28663

Evaluation of the Correlation Between Peripheral Inflammatory Markers and Suicide Risk in Drug-Naive First-Episode Schizophrenia

Ümit Haluk YEŞİLKAYA[1,3], Meltem ŞEN[1], Yasin Hasan BALCIOĞLU[1], Hasan GÖKÇAY[2], Pınar ÇELİKKIRAN[1], Simge KIRLIOĞLU BALCIOĞLU[4], Nesrin KARAMUSTAFALIOĞLU[1]

[1]Department of Psychiatry, Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Istanbul, Turkey
[2]Department of Psychiatry, Bagcilar Training and Research Hospital, Istanbul, Turkey
[3]Regenerative and Restorative Medicine Research Center (REMER), Institute for Health Sciences and Technologies (SABITA), İstanbul Medipol University, Istanbul, Turkey
[4]Department of Psychiatry, Hamidiye Faculty of Medicine, University of Health Sciences, Istanbul, Turkey

ABSTRACT

Introduction: Patients with schizophrenia have a higher lifetime prevalence of suicidal behavior (SB) compared to the general population. Therefore, understanding the possible neurobiology of suicide and predicting the risk of suicide in schizophrenia is a solemnly critical issue.

Methods: 31 drug-naïve first episode schizophrenia (FES) patients with current SB (FES-S), 69 drug-naive patients with first episode schizophrenia without SB (FES-NS), and 69 drug-naïve non-psychotic patients with current SB (NPS) who were diagnosed according to The Diagnostic and Statistical Manual of Mental Disorders - 5 (DSM-5) participated the study. The control group (HC) consisted of 127 individuals matched with the patients. Symptoms at the time of evaluation were assessed using The Positive and Negative Syndrome Scale (PANSS) and Columbia Suicide Severity Rating Scale (CSSRS). Blood samples were collected from all participants to determine White blood cell (WBC), neutrophil, monocyte, albumin, C-reactive protein (CRP), Lymphocyte, and Platelet levels and to measure this protein ratio.

Results: The blood levels of WBC, neutrophil, monocyte, albumin, CRP, and Neutrophil/Albumin Ratio (NAR) were higher in all patient groups compared to HC. CRP/Albumin Ratio (CAR) value was observed to be highest in the NPS group. Monocyte/Lymphocyte Ratio (MLR) value was significantly higher in patients with FES compared to HC. There were no significant differences between the FES-S group and the FES-NS and NPS groups.

Conclusion: It can be suggested that although inflammation is not a predictor for suicide attempts in schizophrenia, it is associated with the degree of suicide risk in schizophrenia. In addition, the strong relationship between suicide and psychiatric disorders can be the main reason for high peripheral inflammation levels in suicidal patients.

Keywords: C-reactive protein/albumin ratio, first-episode schizophrenia, inflammation, neutrophil/albumin ratio, schizophrenia, suicide

Cite this article as: Yeşilkaya ÜH, Şen M, Balcıoğlu YH, Gökçay H, Çelikkıran P, Kırlıoğlu Balcıoğlu S et al. Evaluation of the Correlation Between Peripheral Inflammatory Markers and Suicide Risk in Drug-Naive First-Episode Schizophrenia. Arch Neuropsychiatry 2024; 61:275–280.

INTRODUCTION

Schizophrenia is a progressive chronic mental disorder that generally appears in late adolescence and young adulthood, affecting approximately 1% of the population. In longitudinal follow-up studies, one-third of this patient group showed good prognosis in terms of improvement and functionality; regrettably, around sixty percent of patients were observed to have clinical exacerbation accompanied by relapses and poor prognosis (1). Suicidal behavior is a paramount consequence stemming from an unfavorable prognosis among individuals diagnosed with schizophrenia and suicide represents one of the most important causes of premature death in schizophrenia patients. (2). There are many factors for suicidal risk in patients with schizophrenia. While psychotic disorganization, delusional beliefs, or hallucinatory behaviors may trigger suicidal acts, as a byproduct of psychosis, disappointment reactions or demoralization may also contribute to suicidality (3).

Highlights

- **Peripheral inflammatory markers are higher in all patient groups compared to healthy individuals.**
- **Severity of positive symptoms in schizophrenia correlates with increased peripheral inflammation.**
- **Suicidal behavior risk is linked to inflammation, independent of psychotic status.**

In recent years, research into the risk and identification of suicidal behavior (SB) with psychotic patients has blossomed. Neuroanatomical, genetic, environmental, and molecular aspects of SB have been

Correspondence Address: Ümit Haluk Yeşilkaya, Bakırköy Prof. Dr. Mazhar Osman Ruh Sağlığı ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Psikiyatri Anabilim Dalı, 34147, Istanbul, Turkey • **E-mail:** halukyesilkaya@gmail.com
Received: 16.11.2023, **Accepted:** 05.04.2024, **Available Online Date:** 20.08.2024

investigated, while all aspects might contribute to the pathogenesis via different dysregulations within (4). A possible association between neurotransmitter pathways and neuroimmune mechanisms has piqued interest in the research of SB neurobiology. According to the literature, cytokines and immune system regulators may be associated with suicidal behavior; amid high levels of peripheral inflammatory markers. Increased gene expression of several interleukins (IL), such as IL-4, IL-3, IL-6, and IL-13, were observed in the CSF of suicide attempters (5).

In recent years, extensive research has examined peripheral biomarkers of inflammation obtained from complete blood counts (CBC) in the context of schizophrenia. These studies have suggested that such biomarkers may reflect the underlying mechanisms involved in the pathogenesis of schizophrenia. Several peripheral biomarkers of inflammation have been investigated in psychosis such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) which are easily measured, relatively inexpensive and could be obtained retrospectively (6,7).

In patients with first-episode psychosis, monocyte and neutrophil-to-lymphocyte ratios were found to be higher than controls. In addition, one study found increased WBC (white blood cell) and neutrophil counts compared to controls. It has also been suggested that monocytosis may be associated with more severe psychotic symptomatology (6,7). In addition, it has been reported that NLR, MLR, and PLR values were high in patients with schizophrenia both during the relapse period compared to the control group and during the remission period of the patients (8).

On the other hand, emerging evidence hints at the potential of NLR as a biomarker for suicide vulnerability in patients struggling with bipolar disorder or major depressive disorder (MDD) (8,9). Notably, studies have revealed significantly elevated NLR levels in suicidal individuals with depression compared to those not experiencing suicidal thoughts and healthy controls. One research team even incorporated NLR and a history of suicide attempts into a predictive model for suicidal status with promising results (9).

Furthermore, immune system alterations might be present with various psychiatric conditions regardless of the patient's suicidal status, while most suicide attempters have several different psychiatric disorders as comorbidities. Increased levels of peripheral inflammatory markers have become progressively documented in individuals with chronic schizophrenia and those experiencing their initial psychotic episode within schizophrenia cohorts (10). An imbalance that promotes a proinflammatory state has been implicated in the development of schizophrenia, both during periods of vulnerability and at earlier stages of the disorder, such as the psychosis high-risk state (11).

The strong association between suicidal behavior and primary psychiatric disorders makes it challenging to distinguish whether neurobiological abnormalities are specifically related to suicidal behavior or are inherent to the underlying psychiatric illness. While inflammation may play significant roles in the pathogenesis of psychosis and suicidal behavior, it remains unclear whether inflammation has a specific role in psychotic patients with suicidal behavior. Therefore, the main aim of this study was to delineate the distinctions in peripheral inflammatory markers among individuals with first-episode schizophrenia (FES), distinguishing between those with and without SB, non-psychotic patients who exhibited SB, and healthy controls. The hypothesis driving this study postulates that FES patients with suicidal behavior would demonstrate an elevated peripheral inflammatory status compared to the other groups.

METHODS

Participants and Study Setting

The current study included thirty-six drug-naïve patients with first-episode schizophrenia (FES) and current suicidal behavior (FES-S), 72 drug-naïve patients with first-episode schizophrenia without suicidal behavior (FES-NS), and 69 drug-naïve non-psychotic patients (49 major depressive disorder cases, 3 nonpsychotic bipolar disorder cases, and 17 impulse control disorders and personality disorders cases) with current suicidal behavior (NPS). These patients were recruited from the psychiatric emergency or outpatient units and diagnosed according to SCID-5 criteria between May 2020 and April 2023. The individuals with FES-S were identified among the patients who presented to the hospital after suicidal attempts.

All patients underwent a follow-up evaluation after two months to confirm the diagnosis. Five patients were excluded from the FES-S group, and three patients were excluded from the FES-NS group due to the absence of a schizophrenia diagnosis. Furthermore, the non-psychotic patients with current suicidal behavior were confirmed to have a non-psychotic diagnosis. The control group (healthy control; HC) consisted of 127 individuals matched for age, gender, and body mass index (BMI) with the patients. HCs were selected from individuals who visited the polyclinic for administrative procedures or from the hospital staff who underwent routine examinations within the scope of occupational health and safety laws. All participants were between 18 and 50 years old. All groups have been equalized in terms of BMI. All participants were literate and had no known mental disabilities that would prevent them from participating in the study.

None of the participants were diagnosed with chronic systemic diseases or neuropsychiatric diseases (relevant to the HC group only) or had a history of neurodegenerative disorders. Furthermore, the patients who used any medication when they applied to the hospital were also excluded. Participants who met the DSM-5 criteria for substance or alcohol use were excluded from the study. Urine tests were performed on all participants to exclude any potential incidence of substance or alcohol abuse. The sample size was calculated by evaluating the effect size as 0.3, α-error as 0.05, and power as 0.85 using G Power version 3.1.9.

Ethical Supproval

All participants were informed about the study procedures before the start of the study, and written consent was obtained. Only individuals who agreed to participate in the study were included in the final cohort. Ethical approval for the study was obtained from the Hamidiye Scientific Research Ethics Committee of the University of Health Sciences (IRB Date/Number: October 1, 2019-364)

Data Collection Tools

Sociodemographic and Clinical Data Form

The researchers prepared two different data forms. They included questions on sociodemographic characteristics such as age, gender, level of education, marital status, income level, and clinical features such as duration of illness, height, and weight. The patient and control groups filled out both forms.

Positive and Negative Syndrome Scale (PANSS)

Positive and negative syndrome scale (PANSS) was used to assess the severity of the disease in patients with first episode psychosis (FES). The scale, which was developed by Kay et al., is a semi-structured interview scale that consists of 30 components and a severity evaluation of 7 points. It consists of 3 fundamental sub-groups: 7 out of 30 components are for positive symptoms, 7 for negative symptoms, and 16 for general psychopathology subscale (Kay, Fiszbein, and Opler 1987).

Columbia Suicide Severity Scale (CSSRS)

It is a semi-structured clinician-rated interview to quantify the severity of suicidal ideation and behavior, both current and lifetime. The scale consists of four different constructs: the severity of ideation, the intensity of ideation, and the behavior and lethality sub-scales. This novel suicide risk assessment tool uses three key questions to pinpoint and measure the threat of self-harm. It probes whether the patients are at risk for suicide, assesses the severity and immediacy of that risk, and gauges the level of support that the patient needs. The present study utilizes the first three constructs of the scale (12,13). The reliability and validity study of its Turkish version was conducted by Kiliçaslan et al. in 2018, and ordinal alpha values were 0.89 and 0.91(14).

Blood Sample Collection

After the patients applied to the emergency service and after psychiatric examination, venous blood samples (5 mL) were collected in gel-coagulant tubes during the general examination. The blood samples were left to clot at room temperature for 2 hours and then centrifuged at 3000 rpm at 4°C for 20 minutes to obtain the serum. The samples were separated into 0.5 mL aliquots and stored at –80°C until use.

Laboratory Data

The serum levels of albumin were measured using a Siemens automated biochemistry analyzer (Germany) and albumin test kits (Roche Diagnostics GmbH, Mannheim, Germany) using a bromocresol green colorimeter. Hemogram tests were measured using Abbott Cell Dyne 3700 (Abbott Diagnostic Systems, Illinois, USA). Serum CRP was measured using kinetic nephelometry with an immunochemical system (IMMAGE®; Beckman, Marburg, Germany).

Statistical Analysis

Data were analyzed with the Statistical Package for Social Sciences for Windows (SPSS) version 25.0. The study data were evaluated with various descriptive statistical methods such as frequency, percentage, mean, and standard deviation. The Kolmogorov-Smirnov test determined whether the variables conformed to a normal distribution. Categorical variables were compared using the Pearson chi-square test. Independent samples t-test and one-way ANOVA were used for comparisons between groups of quantitative variables. The homogeneity of distribution of the data was evaluated with the Levene test. Post hoc analyses were conducted with the Tukey test when the data were homogeneously distributed. Correlations between variables were determined with the Pearson correlation test. A p-value of less than 0.05 was statistically significant.

RESULTS

Demographic and Clinical Data

The study population comprised 169 males (57.1%) and 127 females (42.9%). The average age of the participants of FES-S, FES-NS, NPS, and HC groups were 31.61±9.6, 31.02±9.5, 30.3±10.6, 30.2±8.5 years, respectively. There was no significant difference in age (p=0.89), gender ratio (p=0.60), level of smoking (p=0.1), and BMI (kg/m^2) (p=0.69). Detailed clinical data and demographic information are shown in Table 1.

Comparison of the Peripheral Inflammatory Markers Between All Patient Groups and HC

Table 2 shows a comparison of the peripheral inflammatory markers between the patients with FES-S, FES-NS, NPS, and HC. The blood levels of WBC, neutrophil, monocyte, albumin, and CRP were detected to be higher in all patient groups compared to HC (p<0.001, p<0.001, p<0.001, p<0.0001, p=0.04, respectively).

Evaluation of the Value of the Peripheral Inflammatory Markers' Ratios Between All Patient Groups and HC

Table 3 shows a comparison of the balance of the peripheral inflammatory markers between patients with FES-S, FES-NS, NPS, and HC. While the value of Neutrophil/Albumin Ratio (NAR) was observed to be higher in all patient groups, Monocyte/Lymphocyte Ratio (MLR) was detected to be higher in both FES-S and FES-NS groups compared to HC (p<0.001, p<0.001, p<0.001, p<0.001, p=0.04 respectively). Also, although the value of CRP/Albumin Ratio (CAR) was higher in the NPS group compared to both FES groups, it was lower in NPS compared to the HC group (p<0.001, p<0.001, p<0.001, respectively).

Correlation of Biochemical Markers, Ratio of Biochemical Markers, PANSS, and CID Scores

Statistical evaluation of the relationship between PANSS scores, CSSRS scores, and biochemical markers, the ratio of biochemical markers is shown in Table 4. Firstly, a negative correlation was found between lymphocytes and both PANSS positive and PANSS negative scores. Additionally, there was a negative correlation between PANSS negative scores and the levels of monocytes and albumin. Moreover, the analysis revealed positive correlations between PANSS positive scores and two markers: NLR and SII (Systemic Immune-Inflammation Index). Similarly, the CSSRSSB-L t score displayed positive correlations with NAR and SIRI. Furthermore, a positive correlation was observed between the CSSRSSB-C score and NAR.

Table 1. Sociodemographic data of all study groups (mean ± standard deviation)

	FES-S (n: 31)	FES-NS (n: 69)	NPS (n: 69)	HC (n: 127)	df	p
Age	31.61±9.6	31.02±9.5	30.3±10.6	30.2±8.5	3	0.89
Gender (%)	Male: 16(51%) Female: 15(49%)	Male: 43(63%) Female: 26(37%)	Male: 40(57%) Female: 29(43%)	Male: 69(54%) Female: 58(46%)	3	0.60
Education Level (year)	10.62±4.2[a]	11.51±4.2[a]	12.24±2.5	13.97±1.8	2	0.001*
Smoking	Yes: 20(66%)	Yes: 44(64%)	Yes: 36(52%)	Yes: 63(50)	3	0.1
BMI (kg/m^2)	23.6±4.6	24.7±5.2	24.3±3.7	22.8±6.6	3	0.69

* p<0.05, ** p<0.01. one way-ANOVA test was performed. Bonferroni correction was applied and p value was taken as 0.05.
FES-NS: first episode schizophrenia patients without suicidal behavior; FES-S: first episode schizophrenia patients with current suicidal behavior; HC: healthy control Bonferroni correction was applied and p value was taken as 0.05; NPS: nonpsychotic patients without current suicidal behavior.
a: p<0.05 or 0.05 when compared with HC; b: p<0.05 or 0.05 when compare with NPS; c: p<0.05 or 0.05 (when compare with FES-NS).

Table 2. Comparison of the peripheral inflammatory markers between the all groups (mean ± standard deviation)

	FES-S (n: 31)	FES-NS (n: 69)	NPS (n: 69)	HC (n: 127)	df	p
WBC	9.18±2.93[a]	8.51±2.55[a]	8 0.43±2.3[a]	7.05±1.7	3	<0.001*
Neutrophil	5.75±2.6[a]	5.18±2.3[a]	5.07±2.1[a]	3.89±1.22	3	<0.001*
Lymphocyte	2.53±0.78	2.3±0.83	2.5±0.8	2.39±0.6	3	0.61
Monocyte	0.72±0.3[a]	0.66±0.22[a]	0.63±0.25[a]	0.55±0.18	3	<0.001*
Platelet	257.64±57.5	268.75±68.1	269.1±76.5	251.2±60.1	3	0.2
Albumin	4.22±0.4[a]	4.21±0.2[a]	4.1±0.38[a]	15.5±16.1	3	<0.001*
CRP	3.47±4.2[a]	4.08±5.38[a]	3.24±3.69[a]	1.2±1.01	3	<0.001*

* p<0.05, ** p<0.01. one way-ANOVA test was performed. Bonferroni correction was applied and p value was taken as 0.05.
CRP: C reactive protein; FES-NS: first episode schizophrenia patients without suicidal behavior; FES-S: first episode schizophrenia patients with current suicidal behavior; HC: healthy control; NPS: nonpsychotic patients without current suicidal behavior; WBC: white blood cells.
a: p<0.05 or 0.05 when compared with HC; b: p<0.05 or 0.05 when compared with NPS; c: p<0.05 or 0.05 (when compared with FES-NS).

Table 3. Comparison of ratio of biochemical markers between the all groups (mean ± standard deviation)

	FES-S (n: 31)	FES-NS (n: 69)	NPS (n: 69)	HC (n: 127)	df	p
NLR	2.55±1.63	2.79±3.35[a]	2.10±1.19	1.85±0.95	3	0.002*
PLR	113.24±47.31	128.44±67.94	118.42±46.87	114.15±39.99	3	0.434
MLR	0.31±0.14[a]	0.31±0.20[a]	0.27±0.12	0.23±0.07	3	<0.001**
NAR	1.38±0.67[a]	1.23±0.55[a]	1.27±0.61[a]	0.90±0.31	3	<0.001**
CAR	0.8±0.11[b]	0.13±0.23[b]	1.25±1.79[a]	0.243±242	3	<0.001**

* p<0.05, ** p<0.01. one way-ANOVA test was performed. Bonferroni correction was applied and p value was taken as 0.05.
CAR: CRP-albumin ratio; FES-NS: first episode schizophrenia patients without suicidal behavior; FES-S: first episode schizophrenia patients with current suicidal behavior; HC: healthy control Bonferroni correction was applied and p value was taken as 0.013; MLR: monocyte-to-lymphocyte ratio; NAR: neutrophil-albumin ratio; NLR: neutrophil-lymphocyte ratio; NPS: nonpsychotic patients with current suicidal behavior; PLR: platelet-to-lymphocyte ratio.
a: p<0.05 or 0.05 when compared with HC, b: p<0.05 or 0.05 when compare with NPS, c: p<0.05 or 0.05 (when compare with FES-NS)

Table 4. Correlation between biochemical markers, ratio of biochemical markers to PANSS Scores, and C-SSRS scores

r	CSSRSSI-Lt[a]	CSSRSSI-C[a]	CSSRSII-Lt[a]	CSSRSII-C[a]	CSSRSSB-Lt[a]	CSSRSSB-C[a]	CSSRST-Lt[a]	CSSRST-C[a]	PANSS Total[b]	PANSS Positive[b]	PANSS Negative[b]	PANSS Global[b]
Wbc	0.083	0.048	0.102	0.113	0.163	0.146	0.127	0.095	-0.005	0.053	-0.182	0.027
Lym	-0.103	-0.082	-0.020	-0.022	-0.066	-0.074	-0.050	-0.035	-0.195	-0.275**	-0.257*	-0.124
Neu	0.118	0.075	0.108	0.121	0.202	0.187	0.148	0.107	0.046	0.166	-0.112	0.052
Crp	-0.106	-0.190	-0.039	-0.081	0.079	0.065	-0.014	-0.076	0.279*	0.090	0.181	0.200
Alb	-0.085	-0.106	-0.059	-0.071	-0.067	-0.076	-0.064	-0.081	-0.178	-0.146	-0.254*	-0.111
Mnc	0.065	0.019	0.070	0.053	0.076	0.054	0.089	0.061	-0.044	-0.068	-0.276**	-0.019
Plt	0.005	-0.024	-0.012	-0.030	-0.021	0.024	0.0012	-0.020	0.104	-0.041	0.062	0.064
CAR	-0.100	-0.189	-0.025	-0.069	0.098	0.085	-0.001	-0.062	0.290**	0.095	0.184	0.206
NLR	0.138	0.111	0.088	0.101	0.182	0.181	0.130	0.092	0.57	0.287**	0.027	0.026
NAR	0.156	0.118	0.147	0.161	0.230*	0.215*	0.185	0.148	0.64	0.184	-0.065	0.079
PLR	0.117	0.090	0.001	0.002	0.086	0.094	0.038	0.025	0.172	0.196	0.228*	0.069
SII	0.135	0.085	0.078	0.085	0.189	0.184	0.124	0.083	0.141	0.224*	0.082	0.083
SIRI	0.132	0.078	0.079	0.089	0.208*	0.189	0.142	0.089	0.075	0.202	-0.062	0.056
MLR	0.144	0.098	0.051	0.048	0.141	0.132	0.105	0.067	0.063	0.180	-0.076	0.051

* p<0.05, ** p<0.01. Pearson (rho) correlation analysis test was performed. Bonferroni correction was applied and p value was taken as 0.05.
Alb: albumin; CAR: CRP-albumin ratio; CSSRS: Columbia suicide severity rating scale; CSSRSII-C: Columbia suicide severity rating scale intensity of ideation, current; CSSRSII-Lt: Columbia suicide severity rating scale intensity of ideation, lifetime; CSSRSSB-C: Columbia suicide severity rating scale suicidal behavior, current; CSSRSSB-Lt: Columbia suicide severity rating scale suicidal behavior, lifetime; CSSRSSI-C: Columbia suicide severity rating scale - suicidal ideation, current; CSSRSSI-Lt: Columbia suicide severity rating scale - suicidal ideation, lifetime; CSSRST-C Columbia suicide severity rating scale total, current; CSSRST-Lt: Columbia suicide severity rating scale total, lifetime; Lymp: lymphocyte; MLR: monocyte-to-lymphocyte ratio; Mnc: monocyte; NAR: neutrophil-albumin ratio; NLR: neutrophil-lymphocyte ratio; PANSS: positive and negative syndrome scale; PLR: platelet-to-lymphocyte ratio; WBC: white blood cells.
[a] Correlation analysis was performed between First Episode Schizophrenia patients with current suicidal behavior, First episode schizophrenia patients without suicidal behavior, and Nonpsychotic patients without current suicidal behavior groups; [b] Correlation analysis was performed between First Episode Psychosis patients with current suicidal behavior and Nonpsychotic patients without current suicidal behavior groups; The p-value was taken as <0.05.

DISCUSSION

In the present study, plasma levels of peripheral inflammatory markers and ratios in the drug-naïve FES-S, drug-naïve FES-NS patients, NPS patients, and HC were compared to investigate whether inflammation has a role in suicide in FES. In our study, four separate groups were selected to demonstrate whether different diagnoses affect suicide through inflammation differently. As we know, it is the first study to investigate this association with four different groups. Our first result is that the levels of peripheral inflammation were higher in all patient groups compared to the control group. Additionally, an important finding was that although

inflammation is not a predictor for suicide attempts in schizophrenia, it is associated with the degree of suicide risk in schizophrenia.

The serum acute phase reactants such as WBC, neutrophil, monocyte, albumin, and CRP levels were found to be higher in all patients compared to HC; also, while the NAR value was higher in all patients compared to the HC, the CAR value was higher in NPS group.

In the last ten years, many studies intensified the role of inflammation in psychosis pathogenesis, and much evidence was obtained on increased pro-inflammatory cytokines, upregulated gene expression, and increased inflammation levels in post-mortem areas. Also, a growing body of evidence suggests a link between peripheral inflammation and schizophrenia. A meta-analysis by Jackson and Miller involving 24 studies and 3132 participants (1604 schizophrenia patients, 1528 controls) demonstrated significantly elevated WBC, monocyte, and neutrophil counts in the schizophrenia group, suggesting potential associations between inflammatory parameters and disease pathophysiology (15). Similarly, Karageorgiou et al. reported higher NLR values in schizophrenia patients. (16). Balcioglu et al. obtained CAR and NAR values in schizophrenia, especially in the acute exacerbation phase. The study concludes that CAR and NAR are reliable biomarkers of inflammation and can reflect increased inflammatory status in schizophrenia, regardless of relapse or remission. In the present study, we also observed higher WBC, neutrophil, monocyte, CRP, and NAR values in patients with psychosis and compatible results with previous studies (17).

Moreover, two studies observed elevated NLR, MLR, PLR, NAR, and CAR values in schizophrenia patients compared to controls (8,18). Similar findings were observed in first-episode schizophrenia patients. Steiner et al. found elevated neutrophil, NLR, monocyte, and CRP levels in the patient groups compared to controls (19). In the present study, we found that all patients with schizophrenia had increased inflammation, which is consistent with the literature.

Research indicates a close relationship between psychiatric disorders, particularly mood disorders, and inflammation, with various components of inflammation being implicated in conditions such as depression and bipolar disorder. Elevated levels of inflammatory markers such as IL1, IL6, TNF alpha, and CRP, as well as increased neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), suggest inflammation's involvement in both manic and depressive phases of bipolar disorder, potentially indicating bipolar disorder as a more inflammatory condition than depression. These findings suggest inflammation may play a significant role in the pathogenesis of not only psychotic disorders but also other psychiatric conditions. (20).

According to previous studies, one of the significant risk factors for suicide is the presence of psychiatric disorders (19). Unfortunately, such a close relationship makes it difficult to understand the complicated main reasons for suicide. Numerous studies have linked inflammation to suicidal behavior and ideation, with higher levels of inflammatory markers such as IL-1, IL-6, TNF, and others observed in suicidal individuals compared to controls. Meta-analyses have shown significantly elevated immune and inflammatory profiles in suicidal patients, particularly those with suicide attempts. Elevated levels of inflammatory markers, including neutrophils, NLR, monocytes, and MLR, have been associated with increased suicide risk, suggesting a potential role of inflammation in neurotoxicity and decreased neuroprotection. (21–23).

In current studies, while we detected higher WBC, neutrophil, monocyte, CRP levels, and value of NAR in patients with suicide compared to HC, there is no significant difference between the FES-NS group and the FES-S group. Nevertheless, CAR values were higher in NPS compared to FES-S and NPS groups. It can be explained by lower albumin levels in NPS.

The NPS group primarily comprised depressed patients, with studies indicating that depression often correlates with low albumin levels, a known suicide risk factor. This could stem from irregular eating habits and weight loss associated with depression. Moreover, inflammation in depression has been linked to increased suicide risk, suggesting a direct relationship between inflammation severity and suicide risk (24). In addition, a positive relationship has been found between suicide risk and inflammation in patients with depression, and it has been shown that the degree of inflammation can increase suicide risk. In our current study, we also found a positive relationship between suicide severity and inflammation severity in patients with schizophrenia, which is consistent with the literature. This finding suggests that inflammation may be a significant factor in suicide risk in first-episode psychotic patients.

NAR values correlate positively with all CID score subscales, indicating inflammation's role in both suicidal behavior and ideation. The correlation between inflammation and long-term ideation suggests a link with disease sub-thresholds. High inflammation may exacerbate clinical severity, potentially triggering high-risk suicide, although it may not directly cause suicide in individuals with FES. Furthermore, inflammatory status in FES individuals with suicidal behavior does not significantly differ from other disorders with suicidal behavior, suggesting that the strong association between suicide and psychiatric disorders causes high inflammation levels in suicidal patients.

The current study has some limitations that must be considered while evaluating the results. Although our sample size was enough according to g power analysis, the size of the FES-S group is smaller than other groups. Also, we collected the blood samples once the patients came to the hospital. We did not apply any particular time procedure for blood sample collection. The time of blood collection can affect blood values, which is also a limitation of our study. Studies investigating the association between protein levels and behaviors, like the current study, should have a more significant size cohort. Although we aimed to study using affordable and reproducible marker levels, these results should be tested with other inflammatory markers because inflammation is a multifaceted condition, and it involves many different pathways. Although detailed medical history, personal background information, and mental state and physical examination were obtained from patients during admission, the inability to completely rule out possible factors that could affect blood values remains a potential limitation.

This study's primary finding is that two acute phase reactants significantly differed in favor of high inflammation in both FES and NPS. However, levels of inflammation are not different in FES patients with SB than in non-suicidal FES patients and NPS patients with SB. It suggests that although inflammation is not a predictor for suicide attempts in schizophrenia, it may be associated with the degree of suicide risk in schizophrenia. In addition, the strong relationship between suicide and psychiatric disorders may be the main reason for high inflammation levels in suicidal patients.

Acknowledgments: This study's preliminary data was presented as a poster and a poster jam presentation. It won an Excellence Award at the 34th European College of Neuropsychopharmacology (ECNP) Congress, October 2–5, 2021.

Ethics Committee Approval: Ethical approval for the study was obtained from the Hamidiye Scientific Research Ethics Committee of the University of Health Sciences (IRB Date/Number: October 1, 2019-364)

Informed Consent: All participants were informed about the study procedures before the start of the study, and written consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- ÜHY, MŞ; Design- UHY; Supervision- NK; Resource-(-); Materials- YHB, HG, PÇ, SKB; Data Collection and/or Processing- YHB, HG, PÇ, SKB; Analysis and/or Interpretation- ÜHY, YHB; Literature Search- ÜHY, MŞ; Writing- ÜHY; Critical Reviews- NK.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia -an overview. JAMA Psychiatry. 2020;77(2):201–210. [Crossref]
2. Girgis RR. The neurobiology of suicide in psychosis: a systematic review. J Psychopharmacol. 2020;34(8):811–819. [Crossref]
3. David Klonsky E, Kotov R, Bakst S, Rabinowitz J, Bromet EJ. Hopelessness as a predictor of attempted suicide among first admission patients with psychosis: a 10-year cohort study. Suicide Life Threat Behav. 2012;42(1):1–10. [Crossref]
4. Bernard R, Kerman IA, Thompson RC, Jones EG, Bunney WE, Barchas JD, et al. Altered expression of glutamate signaling, growth factor, and glia genes in the locus coeruleus of patients with major depression. Mol Psychiatry. 2011;16(6):634–646. [Crossref]
5. Ernst C, Mechawar N, Turecki G. Suicide neurobiology. Prog Neurobiol. 2009;89(4):315–333. [Crossref]
6. Garcia-Rizo C, Casanovas M, Fernandez-Egea E, Oliveira C, Meseguer A, Cabrera B, et al. Blood cell count in antipsychotic-naive patients with non-affective psychosis. Early Interv Psychiatry. 2019;13(1):95–100. [Crossref]
7. Moody G, Miller BJ. Total and differential white blood cell counts and hemodynamic parameters in first-episode psychosis. Psychiatry Res. 2018;260:307–312. [Crossref]
8. Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res. 2019;271:131–135. [Crossref]
9. Ekinci O, Ekinci A. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. Nord J Psychiatry. 2017;71(8):574–580. [Crossref]
10. Russell A, Ciufolini S, Gardner-Sood P, Bonaccorso S, Gaughran F, Dazzan P, et al. Inflammation and metabolic changes in first episode psychosis: preliminary results from a longitudinal study. Brain Behav Immun. 2015;49:25–29. [Crossref]
11. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer. 2016;122(14):2158–2167. [Crossref]
12. Anyanwu EO. Implementing the Columbia-Suicide Screening Scale to Improve Identification of Suicidal Inpatients. Grand Canyon University; 2021.
13. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266–1277. [Crossref]
14. Kilincaslan A, Gunes A, Eskin M, Madan A. Linguistic adaptation and psychometric properties of the Columbia-Suicide Severity Rating Scale among a heterogeneous sample of adolescents in Turkey. Int J Psychiatry Med. 2019;54(2):115–132. [Crossref]
15. Jackson AJ, Miller BJ. Meta-analysis of total and differential white blood cell counts in schizophrenia. Acta Psychiatr Scand. 2020;142(1):18–26. [Crossref]
16. Karageorgiou V, Milas GP, Michopoulos I. Neutrophil-to-lymphocyte ratio in schizophrenia: a systematic review and meta-analysis. Schizophr Res. 2019;206:4–12. [Crossref]
17. Balcioglu YH, Kirlioglu SS. C-reactive protein/albumin and neutrophil/albumin ratios as novel inflammatory markers in patients with schizophrenia. Psychiatry Investig. 2020;17(9):902. [Crossref]
18. Ranzani OT, Zampieri FG, Forte DN, Azevedo LCP, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013;8(3):e59321. [Crossref]
19. Steiner J, Frodl T, Schiltz K, Dobrowolny H, Jacobs R, Fernandes BS, et al. Innate immune cells and C-reactive protein in acute first-episode psychosis and schizophrenia: relationship to psychopathology and treatment. Schizophr Bull. 2020;46(2):363–373. [Crossref]
20. Bulut NS, Yorguner N, Carkaxhiu Bulut G. The severity of inflammation in major neuropsychiatric disorders: comparison of neutrophil-lymphocyte and platelet-lymphocyte ratios between schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and obsessive compulsive disorder. Nord J Psychiatry. 2021;75(8):624–632. [Crossref]
21. Black C, Miller BJ. Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. Biol Psychiatry. 2015;78(1):28–37. [Crossref]
22. Courtet P, Giner L, Seneque M, Guillaume S, Olie E, Ducasse D. Neuroinflammation in suicide: toward a comprehensive model. World J Biol Psychiatry. 2016;17(8):564–586. [Crossref]
23. Vasupanrajit A, Jirakran K, Tunvirachaisakul C, Maes M. Suicide attempts are associated with activated immune-inflammatory, nitro-oxidative, and neurotoxic pathways: a systematic review and meta-analysis. J Affect Disord. 2021;295:80–92. [Crossref]
24. Ambrus L, Westling S. Inverse association between serum albumin and depressive symptoms among drug-free individuals with a recent suicide attempt. Nord J Psychiatry. 2019;73(4-5):229–232. [Crossref]