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A Comparison of the Relationship Between C-Reactive Protein Levels and Cognitive Functions in Patients with Schizophrenia, First-Episode Psychosis, and Healthy Controls

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ABSTRACT

Background: There are several hypotheses on what causes schizophrenia, some of which include inflammatory responses. Additionally, it might be challenging to control and treat cognitive abnormalities, which represent the primary symptoms, and may be related to inflammation. This study aims to determine whether there is a relationship between C-reactive protein levels and cognitive abilities by assessing neuropsychological tests of drug-free patients with schizophrenia and first-episode psychosis.

Methods: The patient group consisted of 36 patients with schizophrenia or "first-episode psychosis," while the control group comprised 31 healthy people. The control group consisted of healthy participants without any medical or psychiatric diseases. Structured Clinical Interview for DSM-5 axis I disorders was applied for diagnosis, while Wisconsin card sorting test, Stroop color and word test, trail making tests, Rey auditory verbal learning test, and digit span test were applied for cognitive assessment of both groups. Clinical characteristics of patients were evaluated by using the Scale for the Assessment of Positive Symptoms, the Scale for the Assessment of Negative Symptoms, and the Calgary Depression Scale for Schizophrenia. The patient group and healthy control group were evaluated in terms of inflammation levels. The C-reactive protein levels were measured, and their relationship with cognitive status was examined. The serum samples were analyzed by the immunoturbidimetric method in C-reactive protein C8000 Architect (Abbott, Ill, USA) to measure the C-reactive protein levels.

Results: C-reactive protein levels were found to be higher in the patient group ($P = .003$), while the Scale for the Assessment of Negative Symptoms and Scale for the Assessment of Positive Symptoms scores were found to be positively correlated with C-reactive protein levels. Cognitive functions in the patient group were significantly lower compared to the healthy group. There was a statistically weak correlation between C-reactive protein and the number of word color reading errors in the Stroop test, which was associated with complex and frontal attention; however, no correlation was found with digit span test, Rey auditory verbal learning test, or Wisconsin card sorting test points.

Conclusion: Elevated peripheral levels of C-reactive protein are associated with poorer cognitive function in patients with first-episode psychosis and schizophrenia, particularly, complex attention associated with the Stroop test. Inflammation may have an impact on cognitive impairment in psychosis.

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INTRODUCTION

Schizophrenia disease might be observed in every socioeconomic class and can follow a chronic course disrupting mental, social, professional, and economic status in patients with and without treatment.[1] The number of studies on cognitive impairment in schizophrenia and the emphasis on it has increased in recent years. Cognitive problems are important factors causing a decrease in the quality of life and functions of the patients. In this respect, cognitive impairment is one of the main features that should be addressed in schizophrenia. In most patients, cognitive impairment is observed in the first psychotic episode.[2] Cognitive impairment in schizophrenia patients may be related to various factors such as age, gender, education, duration of illness, age of onset of illness, drug or substance use, and presence of negative symptoms.[3] Impairments in functions such as cognitive

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flexibility, word fluency, working memory, ability to solve complex problems, and planning have been identified in schizophrenia.[4,5] Neuropsychological studies have revealed that the most significant cognitive deficits in schizophrenia patients are attention deficit, loss of association, socially inappropriate behavior, and executive dysfunction.[6]

Recent studies have focused on inflammatory factors to reveal the etiopathology of cognitive impairment in schizophrenia patients. The inflammatory hypothesis in psychiatric disorders suggests that inflammatory processes are involved in the pathogenesis of psychiatric conditions and may support some neurobiological relationships.[7]

In schizophrenia, inflammatory reactions are caused by the brain's microvascular system due to responses to environmental stimuli, which have been suggested to cause metabolic abnormalities in the central nervous system (CNS).[8] In this respect, many studies have investigated the place of neuroinflammatory mechanisms in the etiopathogenesis of schizophrenia.[9] Based on the possible relationship between inflammation and etiopathogenesis of schizophrenia, monocyte/High-density lipoprotein (HDL) ratios,[10] interleukin levels,[11] neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios,[12] and the changes in C-reactive protein (CRP) levels have been investigated.[13] Being one of these indicators, CRP is a non-specific serum marker that plays a role in the general acute phase response.[14] It is thought that CRP is a biological indicator of aging and chronic disease; it increases chronic inflammation and is associated with a shorter life span.[15] Although studies on the relationship between CRP and psychiatric disorders have different results, CRP levels have been thought to be a psychiatric biomarker.[16]

Previous studies revealed that the CRP levels of schizophrenia patients were higher than those of the control group,[13,17] which was particularly associated with negative symptoms and impaired cognitive functions.[18] Another study found that CRP levels were significantly higher in schizophrenia patients when psychotic symptoms were exacerbated. The follow-up study on the same patients revealed that CRP levels returned to normal when the patients were in the remission period.[19] In addition, the relationship between the clinical severity of patients and CRP levels has also been researched. A study reported an association between CRP and the severity of the impairment disorder.

MAIN POINTS

- Deterioration has been detected in the cognitive skills of the patients.
- C-reactive protein (CRP) levels were associated with the clinical severity of patients with psychosis.
- Inflammatory processes may be a factor in the etiopathogenesis of cognitive impairment in psychosis.
- There was a correlation between cognitive impairment and elevated CRP in patients with psychosis.

However, no difference was observed in the CRP groups in terms of the severity of positive, negative, or general The Positive and Negative Syndrome Scale (PANSS) symptoms.[20] A study found an association between negative symptoms and CRP levels besides cognitive impairment in patients with schizophrenia.[21] Moreover, the relationship between CRP and positive symptom severity was found, and the study reported a finding that supported the inflammatory hypothesis in the etiopathogenesis of schizophrenia.[13]

It is known that cognitive impairments are present in patients with the first episode of schizophrenia. It has been revealed that there is a cognitive decline in all areas, particularly working memory, with the onset of the disease.[22] In recent years, inflammatory processes have been investigated in the etiology of cognitive impairment in patients with schizophrenia and related psychoses. There has been evidence of a correlation between cognitive deficits and inflammatory markers. Several studies investigated interleukin (IL) 1-beta, interleukin (IL)-6, transforming growth factor-beta (TGF-β), interleukin (IL)-12, interferon-gamma, tumor necrosis factor-alpha (TNF-α), and CRP in the first-episode, drug-naïve, and drug-free schizophrenia.[11,23] A meta-analysis has found that cognitive impairment was significantly correlated with CRP and Brain-derived neurotrophic factor (BDNF) levels in schizophrenia.[24]

It has been suggested that the spectrum of inflammati on-mediated cognitive impairments may primarily affect domains of executive functions, sustained attention, and working memory in schizophrenia. Inflammatory cytokines can provide an important neuronal substrate for learning and memory.[25] A study reported that the proinflammatory cytokine IL-1β seemed to be critical for normal hippocampu s-dependent learning and memory.[26] Abdel Mohsen et al[27] found a significant negative correlation between the level of serum IL-6 and visual memory. Similarly, IL-6 levels were found to have a negative correlation with general cognitive performance.[28] A cohort study revealed that higher blood IL-6 levels were predictors of smaller hippocampal volumes, and acute elevations in peripheral inflammation were also associated with changes in cognition, including memory impairment.[29]

The specificity of the cognitive effects induced by inflammatory processes in schizophrenia remains to be further elucidated. Previous studies have reported a relationship between serum CRP levels and cognitive impairments in patients with acute-phase psychosis[30] and patients with first-episode schizophrenia.[31-34] A study on patients with acute-phase psychosis reported that CRP correlated with cognitive performance.[30] A systematic review revealed cytokines and CRP alterations concerning cognitive impairment in schizophrenia.[35] High CRP levels have been associated with impairment in several cognitive domains including working memory and learning ability in patients with schizophrenia.[36] Another study reported that cognitive test scores, especially executive functions

and processing speed had a strong correlation with 5 biomarkers, including CRP levels.[37] Again, the thickness change in visual cortex areas in patients with psychotic disorder was associated with increased CRP levels and poor performance in cognitive tests. Visual cortex areas were found to be an important pathology area.[38] Studies reported that increased peripheral inflammation in patients with schizophrenia was associated with cognitive functions, particularly decreased attention and cortical thickness.[39] However, there are some contradictory results, some studies reported no significant correlation between CRP levels and cognitive impairments in patients with schizophrenia.[18]

In the literature, the results of several studies on the correlation between CRP levels and cognitive impairment are not consistent. In the literature, the following hypotheses were formulated: serum CRP levels are higher in the patient group than the control group; CRP levels are associated with worse cognitive performance in patient groups. Therefore, in the present study, we aim to investigate whether there is a difference between the patient group and control group in terms of cognitive functions and CRP levels and whether there is a correlation between serum CRP levels and cognitive impairments. Moreover, we have investigated whether there is a correlation between serum CRP levels and the clinical characteristics of the patients. This is an important issue that should be investigated to improve the treatment and follow-up process of the patients.

MATERIAL AND METHODS

Enrolment of Participants

In this study, patients with a psychotic disorder were admitted to the Bolu İzzet Baysal Mental Health and Diseases Training and Research Hospital, and healthy subjects were included in the control group. The patient group consisted of 36 patients diagnosed with schizophrenia or "first-episode psychosis" according to the DSM-5 diagnostic criteria. Their ages were between 18 and 60, and they had not used psychotropic medications for at least 1 month. We examined patients with first-episode psychosis who were drug-naïve (14 individuals), patients with schizophrenia who had not used psychiatric medication for at least 1 month (22 subjects), and healthy controls (31 subjects). The control group comprised 31 healthy people without any medical or psychiatric disease.

Patients and healthy people were not included if they were under 18 or over 60, had additional psychiatric diagnoses, were illiterate, had uncontrolled endocrine/cardiac conditions or chronic inflammatory diseases, were taking immunosuppressive or anti-inflammatory medications, were pregnant, were breastfeeding, or menstruating, had a disease of the central nervous system, were mentally retarded, had a body mass index of 30 or higher, or were heavy smokers (more than 20 cigarettes per day). Written informed consent was obtained from the patients and control subjects.

Evaluation Tools

Both patient and control groups were interviewed using the Structured Clinical Interview for DSM-5 axis I disorders Interview Inventory. Calgary Depression Scale for Schizophrenia was used for the patient group, and the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS)[40] scales were used to determine the severity of the disease. Wisconsin card sorting test (WCST),[41] Stroop color and word test (SCWT),[42] trail making tests (TMT),[43] Rey auditory verbal learning test (RAVLT),[44] and digit span test (DST)[45] were used for the patient and control groups.

Wisconsin Card Sorting Test

The test was developed by Berg in 1948, and Heaton put the finishing touches to it in 1981. The test uses 4 kinds of stimulus cards and 2 card packs of 64 response cards. Each card has a different number of shapes in a different color. The cards have the following shapes: plus, circles, stars, and triangles. Each card has 1, 2, 3, or 4 shapes in red, green, blue, or yellow. The test ends when 6 categories are completed, or 128 cards are finished. The test is used to calculate 13 types of points.[41] Wisconsin card sorting test mainly evaluates perseverative tendency and executive functions. The executive functions, conceptualization, planning, and mental flexibility are measured using the WCST.[46]

In the present study, the digital version of this test was used, and the following results were considered: the percentage of perseveration, the number of completed categories, the total number of errors, the number of errors, the number of perseverative errors, the number of non-perseverative errors, and the number of perseverative responses.

Stroop Color and Word Test: The test, which was first developed by Stroop, was then constructed into various Stroop tests.[42] The Stroop effect is obtained when the color used in the spelling of the word and the colors that the word expresses are different. This effect, which is also known as the Stroop interference, is because reading the word colors takes longer than reading the colors that express the colors.

Trail Making Tests: This test evaluates the speed of attention, mental flexibility, visual screening, and motor speed,[47] and it was used to measure executive functions such as working memory, complex attention, planning, and set switching.[48] In part A, the subject connects node 1 through node 25 drawing a continuous line; in part B, a letter is connected to a number alternately.[49] Part A measures the processing rate based on visual scanning

capability, and part B evaluates the ability to switch to the number/letter set and follow sequence.[50]

Rey Auditory Verbal Learning Test: The original form of RAVLT, which comprised word lists, was developed by Rey (1964). Rey auditory verbal learning test is a multidimensional measure of information processing processes related to verbal material. These processes include episodic verbal learning, immediate memory span, retroactive interference, free recall, recognition, and memory-related processes.[44] Rey auditory verbal learning test has 2 lists: list A and list B. Each list has 15 words. The words in list A are given in 5 consecutive sequences at a word rate. List B is given as a mixer factor after list A is given in 5 trials. Scores are obtained by measuring early and late recall scores with learning scores (number of correct words recalled in 5 trials). Rey auditory verbal learning test scores were associated with age and increased intelligence, and women were found to have higher scores.[47]

Digit Span Test: It is a subscale of Wechsler Adult Intelligence Scale-Revised (WAIS-R). The test, which is applied in 2 sections by sorting the numbers in ascending and descending orders, allows the evaluation of working memory and attention.[45]

Sociodemographics and Clinical Information Form: In the present study, a sociodemographic and clinical information questionnaire was prepared to collect data from both groups. The questionnaire asks about gender, education level, marital status, working duration, duration of disease (year), the number of hospitalization and total duration of hospitalization, smoking–alcohol–substance use, and suicide attempt.

Biochemical Analysis

5 mL of blood samples were taken from each participant to measure the CRP levels Blood samples were placed in a vacuum biochemistry tube containing a standard coagulation activator and were centrifuged at 3500 rpm for 10 minutes. Separated serum samples were stored at −70°C until analysis.

The samples were processed in a stepwise manner. Serum samples were studied by the immunoturbidimetric method in CRP C8000 Architect (Abbott, Ill, USA). (CRP: 0-5 mg/L). Smoking status and exercise were taken into consideration while collecting the blood sample.

Statistical Data Analysis

The Kolmogorov–Smirnov test was used to assess the normality of the distribution of the dataset. In cases where the dataset is not normally distributed, the Mann–Whitney *U* test was used to compare the mean and median between groups, and the *t*-test was used for variables with a normal distribution. The chi-square test of homogeneity was used to compare the categorical data. The Pearson correlation test was used for data with normal distribution, while the Spearman correlation test was used for data with a non-normal distribution. Descriptive statistics were given in terms of mean value ± standard deviation, median (25%-75%) for data with non-normal distribution, and the percentages of the categorical data were presented. $P < .05$ was considered statistically significant in all tests. Bonferroni correction was used to evaluate the differences between groups. The data were analyzed using the Statistical Package for Social Sciences (SPSS), Version 22.0 (SPSS Inc., Chicago, Ill, USA). Statistically significant differences were given in bold fonts in tables.

Informed Consent and Ethics Committee Approval

The Ethical Committee of the Faculty of Medicine of Bolu Abant İzzet Baysal University (decision no. 2015/71; dated June 10, 2015) approved this study. In addition, it was supported by the Scientific Research Projects Commission of the Bolu Abant İzzet Baysal University University (Project No: 2015.8.35.936).

RESULTS

In the study, Cronbach's alpha (α) coefficient was found to be 0.79, which is a successful result.

Sociodemographic Findings

The sociodemographic characteristics of the patient group and control group and the statistical differences between the groups were investigated. The results are given in Table 1.

In terms of sociodemographic data of the patient group and control group, no statistically significant difference was found in terms of age, gender, educational status, and smoking, while statistically significant differences were found in terms of marital status, employment status, and living alone and living areas.

Clinical Findings of the Patient Group

Of the patients, 38.1% (n=14) have first-episode psychosis, and 61.9% (n=22) patients were diagnosed with schizophrenia and had not been on medication for at least one month.

Descriptive Statistics of the Patient Group and Their Relationship with C-Reactive Protein

The clinical features of the patient group and the relationship between the CRP levels and the clinical features are given in Table 2. No correlation was found between CRP levels and duration of illness, hospital visits, and duration of hospitalization. Considering this relationship in terms of disease severity, all SANS subtypes except SANS blunting score and CRP levels were positively correlated with all SAPS scores. The interquartile range (IQR) of CRP was calculated as 9.95% for the patient group, while it was found to be 0.8% for the control group. Also, the dot plot charts in Figure 1 indicate individual values of CRP for the patient group and control group.

Table 1. Comparison of Patient and Control Groups According to Sociodemographic Features

		Patient Group	Control Group	*P*	Test
Age		37.08 (11.85)	37.94 (7.87)	.730	*t*-test
Gender	Male	27 (75%)	23 (74.1%)	.940	χ^2 cramer's V:0.009**
	Female	9 (25%)	8 (25.9%)		
Marital status	**Single**	**22(61.1%)**	**2 (6.5%)**	**.001***	**χ^2 cramer's V:0.791****
	Married	**4(11.1%)**	**28 (90.3%)**		
	Widow	**10(27.8%)**	**1 (3.2%)**		
Education	≤8 years	14 (38.8%)	17 (54.8%)	.192	χ^2 cramer's V:0.159**
	Over 8 years	22 (61.2%)	14 (45.2%)		
Smoking	Yes	21 (58.3%)	17(54.8%)	.773	χ^2 cramer's V:0.035**
	No	15 (41.7%)	14 (45.2%)		
Working status	**Yes**	**4 (11.1%)**	**27 (87.1%)**	**.001***	**χ^2 cramer's V:0.760****
	No	**32 (88.9%)**	**4 (12.9%)**		
Living place	**Rural**	**13 (36.1%)**	**1 (3.2%)**	**.001***	**χ^2 cramer's V: ****
	Urban	**23 (63.9%)**	**30 (96.8%)**		
Lives	**Alone**	**6 (16.7%)**	**0 (0%)**	**.017***	**χ^2 cramer's V:0.291****
	With family	**30 (83.3%)**	**31 (100%)**		

*$P < .05$; **Chi-square test used.

Biochemical Findings

The patient group was found to have significantly higher CRP values compared to the control group ($P = .003$). The results are presented in Table 3. Additionally, the patient group was divided into 2 subgroups First-episode psychosis (FEP) (n = 14) and schizophrenia (n = 22). FEP and schizophrenia patients were compared in terms of their CRP levels; no difference was found between first-episode psychosis and schizophrenia patients in terms of CRP levels ($P = .511$).

Table 2. Correlation Analysis Between Serum C-Reactive Protein Levels and SANS-SAPS Scores in the Patient Group

	Mean (SD)	CRP (*P*) (Spearman's Rho)	CRP (c)
SAPS total points	**38.13 (13.30)**	**.001***	**0.401**
SAPS hallucinations	**8.61 (3.81)**	**.003***	**0.360**
SAPS delusions	**14.33 (5.82)**	**.003***	**0.361**
SAPS bizarre behavior	**7.05 (3.94)**	**.003***	**0.362**
SAPS formal thought disorder	**8.13 (5.40)**	**.001***	**0.399**
SANS total points	**36.44 (21.96)**	**.003***	**0.356**
SANS affective blunting	8.83 (8.24)	.068	0.224
SANS alogia	**4.72 (4.74)**	**.002***	**0.365**
SANS avolition-apathy	**7.91 (4.08)**	**.002***	**0.376**
SANS anhedonia-asociality	**9.33 (4.95)**	**.001***	**0.384**
SANS attentional impairment	**5.63 (3.32)**	**.001***	**0.393**

*$P < .05$.
CRP, C-reactive protein; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SD, standard deviation.

Cognitive Functions

The groups were compared in terms of cognitive functions. The results are given in Table 3.

According to these results, the patient group significantly differs from the control group in terms of the RAVLT in all sub-scores, TMT A and B forms time values, DST forward and backward scores, the correct number, total error, the number of perseverative responses, and the number of completed categories of WCST. The patient group's cognitive performance was found to be lower than the control group.

C-reactive protein levels and cognitive functions were analyzed for the patient group (n = 36); CRP level was found to correlate with the word color reading error score in the Stroop test ($P = .046$; $r = 0.335$). However, CRP was found to have no significant correlation with DST, RAVLT, and WCST.

DISCUSSION

In the present study, the patient group was found to have significantly higher CRP levels and significantly poorer cognitive functions compared to the control group, and the CRP levels and clinical severity of patients were found to have a positive correlation. A weak correlation was found between cognitive performance and serum CRP levels; a correlation was found between CRP and the complex attention-related number of errors in the Stroop test; however, no correlation was found with other tests.

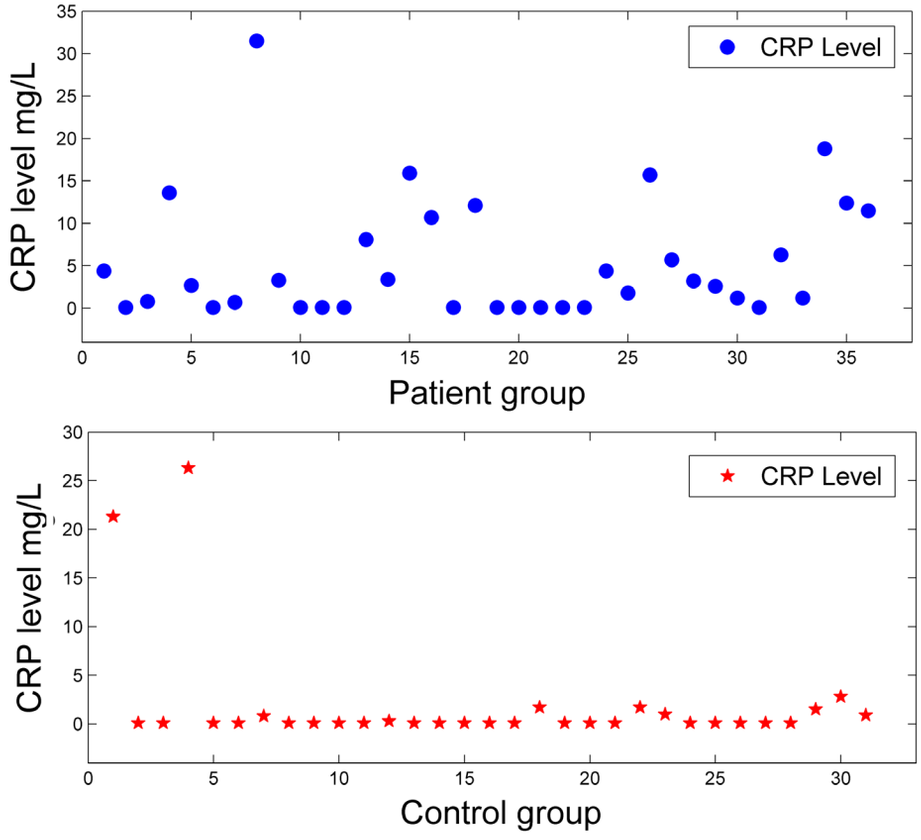

Figure 1. Dot plots, indicating individual values of C-reactive protein levels for patient and contol group.

Cognitive impairment in schizophrenia has been investigated in many studies. According to a meta-analysis including studies on drug-naïve patients, there was a decline in the cognitive performance of schizophrenia patients in all areas compared to control subjects, and the effect size was found to be wider in working memory, processing speed, and particularly verbal memory.[51] Similar results were found in patients with and without treatment regarding cognitive loss.[2] A study reported that the patient group was slower in the SCWT test, more incorrect interferences were observed in TMT,[52] and they experienced a slowdown in processing speeds,[53] attention, memory, and executive function impairment in TMT-B.[54] The literature on memory functions of patients with schizophrenia reveals deterioration in episodic memory, working memory functions,[55] data coding, and long-term memory functions.[56] In consistence with the literature, the present study found that the cognitive functions were impaired in the patient group compared to the control group; the patient group showed poorer performance in the word color reading time and the number of incorrect interferences in the Stroop test. Moreover, fewer correct numbers, more perseverative behaviors, less completion of the categories, and long test completion times in the WCST test indicate a decline in executive functions. Also, memory functions were evaluated using the RAVLT and DST. The patient group was observed to have a significantly lower performance in DST and RAVLT. As a result, psychotic patients were found to have lower executive skills such as reasoning, concluding, planning, installation, and cognitive flexibility. In addition, patients were observed to experience a slowdown in processing speed and deterioration in complex attention mediated by the frontal system and deterioration in short-term memory, long-term memory, working memory, and complex attention. All these results show that patients have global cognitive destruction.

The CRP levels of schizophrenia patients and the correlation between the CRP levels and psychosis were studied in the literature. Several studies reported that the CRP values in schizophrenia patients were higher compared to healthy individuals.[57-60] Considering the effect of drugs on inflammation, recent studies have focused on untreated schizophrenia patients and patients with first-episode psychosis.[61] Gurung et al[62] reported that the patients taking antipsychotic medication had a significantly higher level of CRP, although the difference in the psychotropic medication-free patients was not significant. A prospective birth cohort study suggested a correlation between adolescent CRP levels and adult schizophrenia diagnosis.[63] However, some meta-analyses have revealed that the difference in CRP levels between the schizophrenia group and control group was higher in young people (less than 30 years of age) regardless of the treatments administered.[64]

Table 3. Comparison of the Mean Values of Patients and Control Groups in Cognitive Tests and Groups

		Patients		Control		Difference Between Groups (*P*)	Bonferroni Correction (*P* < .0025)	Relation with CRP Levels in Patients (Spearman)		
		Mean (SD)	Median (IQR)	Mean (sd)	Median (IQR)			*P*	Bonferroni Correction (*P* < .0025)	*r*
CRP⁺	-	5.24 (7.16)	2.2 (9.95)	2.01 (5.99)	0.1 (0.80)	**.003****	0.003	-	-	-
WCST	Number correct	60.47 (17.68)	60.0 (23.75)	73.5 (17.94)	76,50 (34,50)	**.004****	0.004	.706	0.706	−0.065
	Total error	67.52 (17.68)	68.0 (23.75)	54.5 (17.94)	51.50 (34.50)	**.004****	0.004	.800	0.800	0.044
	Perseverative responses⁺	46.00 (27.38)	39.5 (26.25)	31.56 (15.72)	26.0 (21.75)	**.030***	0.030	.862	0.862	0.030
	Nonperseverative error⁺	28.94 (18.21)	23.0 (25.25)	26.56 (12.72)	24.0 (15.25)	.827	0.827	.760	0.760	−0.053
	Categories⁺	2.02 (1.87)	2.0 (1.00)	3.43 (2.32)	3.50 (4.00)	**.009****	0.009	.772	0.772	−0.050
	% perseverative error⁺	30.14 (15.73)	26.17 (16.02)	21.82 (9.87)	19.53 (15.83)	.015*	0.015	.797	0.797	0.045
	Trials to complete first category⁺	29.15 (29.83)	14.0 (16.00)	22.20 (26.85)	12.50 (11.00)	.632	0.632	.459	0.459	−0.127
	% conceptual level responses	59.68 (164.7)	29.69 (19.93)	44.66 (18.87)	46.88 (30.67)	.620	0.620	.696	0.696	−0.068
	Failures to maintain set⁺	1.47 (1.66)	1.0 (2.00)	1.46 (1.50)	1.00 (2.25)	.739	0.739	.290	0.290	−0.181
TMT-A	A form completion time⁺	84.14 (59.03)	69.50 (54.00)	42.26 (15.65)	39.00 (24.00)	**.001****	**0.001*****	.368	0.368	0.155
TMT-B	**B form completion time⁺**	**187.17 (80.7)**	167.0 (98.00)	**102.94 (37.1)**	100.00 (52.00)	**.001****	**0.001*****	.311	0.311	0.174
SCWT	Word color reading time⁺	124.75 (49.2)	109.50 (65.00)	87.06 (18.5)	82.00 (27.00)	**.001****	**0.001*****	.805	0.805	−0.043
	Word color reading error⁺	2.61 (4.06)	0,50 (5.00)	0.45 (0.81)	0.00 (1.00)	**.046***	0.046	**.046***	0.046	**0.335**
DST	Forward⁺	5.22 (0.92)	5.00 (1.00)	5.84 (7.35)	6.00 (1.00)	**.003****	0.003	.422	0.422	−0.138
	Back⁺	3.56 (1.02)	4.00 (1.00)	4.03 (0.54)	4.00 (0.00)	**.015****	0.015	.754	0.754	−0.054
RAVLT	**Instant memory⁺**	**5.11 (1.87)**	**5.00 (2.00)**	**7.52 (1.86)**	**7.00 (3.00)**	**.001****	**0.001*****	.738	0.738	−0.058
	Highest learning score⁺	**10.55 (2.44)**	**11.00 (3.00)**	**14.03 (1.16)**	**14.00 (1.00)**	**.001****	**0.001*****	.712	0.712	0.064
	LTM-free recall⁺	**8.17 (3.25)**	**8.00 (3.00)**	**13.26 (1.54)**	**14.00 (2.00)**	**.001****	**0.001*****	.663	0.663	0.075
	LTM total recall⁺	**12.06 (2.60)**	**13.00 (4.00)**	**14.48 (1.18)**	**15.00 (1.00)**	**.001****	**0.001*****	.717	0.717	0.063

***P* < .01; **P* < .05; ****P* < .003 for Bonferroni correction; ⁺Not distributed normally.

CRP, C-reactive protein; DST, digit span test; RAVLT, Rey auditory verbal learning test; SCWT, Stroop color and word test; SD, standard deviation; TMT, trail making tests; WCST, Wisconsin card sorting test.

Consistent with the literature, the present study found a significant difference between the patient group and the control group in terms of CRP levels. A Nigerian cohort study reported that the CRP values of the patients with schizophrenia increased only in the event of psychotic exacerbation, suggesting a change in nonspecific humoral immunity.[19] A meta-analysis revealed that the CRP levels were high in patients regardless of drug use, and it was associated with positive symptoms, not with negative symptoms of the disease.[64] Two other studies also found no correlation with the clinical severity of the disease.[20,65] In the present study, a positive correlation was found between the CRP levels and the positive and negative clinical severity scores except for the SANS affective blunting scores, suggesting a correlation between CRP levels and psychotic exacerbation. The correlation between the clinical severity and the CRP levels in this patient sample supports the underlying inflammatory processes in patients with schizophrenia and FEP. No correlation was found between the CRP levels and the duration of illness and the number and duration of hospitalizations. So, it can be interpreted that the inflammatory processes play a role in clinical manifestations, and CRP may play a role in clinical presentation. Follow-up studies with larger sample sizes are needed.

Recent studies suggest that inflammatory factors are among the causes of cognitive impairment in patients with schizophrenia. Therefore, the correlation between CRP levels and cognitive tests in psychotic patients has been examined in several studies. In this respect, there are different results in the literature. A study reported that elevated CRP levels were associated with the severity of cognitive impairment in schizophrenia.[66] Another study reported that it was associated with negative symptoms and impairment of cognitive function.[18] In a systematic review, the most consistent results indicate worse cognitive performance in schizophrenia patients with higher CRP.[35] A study investigated the correlation between the gating deficit and predictive attention based on the CRP level in schizophrenia patients. It was reported that the decrease in SCWT performance scores was associated with high CRP levels.[67] In terms of memory functions, the CRP level was found to have a significant correlation with processing speed, mental flexibility, visual attention, learning ability, and semantic memory, as well as working memory in particular.[68] Johnsen et al[30] revealed a negative correlation between the CRP level and delayed memory and attention in cognitive subdomain analyses. However, other studies in the literature reported that there was no correlation between CRP and cognitive impairment.[69] In a study examining cognitive functions using the National Institutes of Health (NIH) Toolbox in patients with schizophrenia, no correlation was found between CRP levels and cognitive functions.[21] Joseph et al[18] also examined cognitive functions in terms of executive functions and could not find a significant correlation in terms of CRP. In 2018, schizophrenia patients were followed up for 1 year; the researchers reported that the CRP levels were correlated with positive symptoms and general symptomatology; however, such a correlation was not found with cognitive symptoms.[70] Another study on a limited number of schizophrenia patients reported a borderline association with high CRP levels and short-term memory.[71] In the present study, the correlations between the CRP levels and cognitive functions of groups were examined, and a weak correlation was found between the CRP levels and the number of color reading errors in the Stroop test, which was associated with complex and frontal attention, in the patient group consisting of first-episode psychosis and schizophrenia patients. No correlation was found with other tests. Different results in the literature may be attributed to the small number of patients in the group or a heterogeneous patient group. It may also be because CRP is a nonspecific inflammatory marker and their levels rapidly change even within 24 hours. Therefore, follow-up studies should be carried out in larger groups and they should be supported by studies on genetic and biological fields, as well as clinical studies.

In conclusion, the present study supports the role of the inflammatory response, specific to CRP, in psychotic exacerbation in patients. Additionally, a correlation was found between CRP and cognitive impairment in the complex attention mediated by frontal function. Thus, the biological role of CRP stands out in clinical processes and frontal attention function. However, the role of serum CRP levels particularly in the development of cognitive impairment is limited because it was a cross-sectional study and the sample size was small. Therefore, further studies with larger samples should be conducted, follow-up studies should be planned, and advanced statistics should be calculated. Also, inflammatory mechanisms should be investigated at the neurobiological level to examine the potential factors that can influence the level of relationship between inflammation and cognition in schizophrenia, and whether chronic inflammation causes frontal lobe-mediated attention problems or not. Moreover, the role of anti-inflammatory strategies in pathophysiology and treatment will open new horizons.

The primary drawback of the present study is that it is a cross-sectional study, which only permits the analysis of the data using 1 measurement. The small sample of patients is a significant factor in the study's limitations. As a result, we studied the individuals who had schizophrenia or FEP in the same group. It is crucial to conduct advanced analyses by increasing the number of patients in future studies. The long application period and the use of several neuropsychological tests on individuals in 1 session may also have an impact on test performance. The fact that subjects' IQ scores could not be determined, the premorbid

status was unknown, and the reasons for the testing varied should also be stated among the limitations of the study. This study could not assess the genetic differences in CRP receptors. Another significant limitation was the inability to perform a diagnostic, it was discovered by asking whether participants had any inflammatory diseases.

In conclusion, the present research suggests that CRP levels were higher in patients with schizophrenia and FEP, which may be a sign of the inflammatory process. Clinical severity, particularly frontal attention impairment, and CRP levels were related. C-reactive protein levels in patients with schizophrenia may be a state-related biomarker of frontal complex attention. So, further research with larger samples is required. Furthermore, future research should clarify the pathways, hereditary causes of chronic inflammation, and the methods of action of CRP. More research is needed to treat cognitive impairment in schizophrenia with anti-inflammatory therapy.

Ethics Committee Approval: This study was approved by the Ethical Committee of the Faculty of Medicine of Abant Izzet Baysal University with decision no. 2015/71 dated June 10, 2015.

Informed Consent: Written informed consent was obtained from all subjects who participated in this study.

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