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Original Article

Association of Tumor Necrosis Factor-Alpha with Psychopathology in Patients with Schizophrenia

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We investigated the relationship between serum tumor necrosis factor-alpha (TNF-α) levels and psychopathological symptoms, clinical and socio-demographic characteristics and antipsychotic therapy in individuals with schizophrenia. TNF-α levels were measured in 90 patients with schizophrenia and 90 healthy controls matched by age, gender, smoking status, and body mass index. The Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of psychopathology in patients. No significant differences in TNF-α levels were detected between the patients and controls ($p = 0.736$). TNF-α levels were not correlated with total, positive, negative, general, or composite PANSS scores (all $p > 0.05$). A significant negative correlation was observed between TNF-α levels and the PANSS cognitive factor ($\rho = -0.222$, $p = 0.035$). A hierarchical regression analysis identified the cognitive factor as a significant predictor of the TNF-α level (beta = −0.258, t = −2.257, $p = 0.027$). There were no significant differences in TNF-α levels among patients treated with different types of antipsychotics ($p = 0.596$). TNF-α levels correlated positively with the age of onset ($\rho = 0.233$, $p = 0.027$) and negatively with illness duration ($\rho = -0.247$, $p = 0.019$) and antipsychotic treatment duration ($\rho = -0.256$, $p = 0.015$). These results indicate that TNF-α may be involved in cognitive impairment in schizophrenia, and would be a potential clinical-state marker in schizophrenia.

Key words: tumor necrosis factor-alpha, schizophrenia, psychopathology, immune system

Schizophrenia is a psychiatric disorder that has a profound impact on both patients and society [1]. In modern times, schizophrenia is conceptualized as a complex psychiatric syndrome with heterogeneous clinical presentation and great diversity in the patients' daily functioning [2, 3]. The pathophysiological mechanisms underlying schizophrenia have not been fully explained [2, 4]. During the last few decades, more and more evidence of the involvement of inflammation and dysfunction of the immune system in the etiopathogenesis of schizophrenia has emerged [5-7]. Schizophrenia has been associated with autoimmune processes [8], central nervous system (CNS) inflammation [9], Th1/Th2 cell imbalance [7, 10], and microglial activation [11]. Additionally, evidence of improvement in schizophrenia symptoms associated with the use of adjuvant anti-inflammatory agents has supported the role of inflammation in the etiopathogenesis of schizophrenia [12].

Cytokines are the key molecules that coordinate communication between the CNS and the immune system [13]. A number of studies suggest that individuals with schizophrenia have abnormal levels of pro-inflammatory cytokines in their peripheral blood [14-17].

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Pro-inflammatory cytokines could be involved in the pathophysiology of schizophrenia through their action on dopaminergic and glutamatergic pathways and cognitive processes [18]. They have been associated with increased oxidative stress and an increased concentration of kynurenic acid in the CNS, as well as with an increased risk of developing psychosis. However, it is still not clear whether elevated serum concentrations of pro-inflammatory cytokines have a causative role in the development of schizophrenia [19].

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine produced by various immune and non-immune cells, including neurons [20]. TNF-α affects important processes in the CNS, including neuronal maturation, neuronal survival and functioning, synaptic plasticity, and neurogenesis [21]. However, TNF-α also exerts harmful effects that induce and promote autoimmune, inflammatory, and neurodegenerative processes of the CNS [22]. Previous researches measuring peripheral TNF-α levels in patients with schizophrenia showed increased [23-25], decreased [26-28], or unchanged [29-32] results. Possible reasons for the inconsistent findings include: 1) neglecting the influence of confounding variables; 2) different sampling methods; 3) heterogeneous patient populations; 4) small sample sizes; 5) different biological media used for the TNF-α analysis; and 6) different characteristics of assay kits [33].

Two recent studies reported increased expressions of TNF-α mRNA in the postmortem brains of individuals with schizophrenia [34,35]. Another study reported an association between schizophrenia and increases in the mRNA levels of TNF-α and mRNA levels of membrane-bound receptors for TNF-α in lymphocytes [36]. A study of leukocyte gene expression also described increased mRNA levels of TNF-α in the leukocytes of individuals with schizophrenia [24]. Na and Kim (2007) documented an increased mitogen-induced production of TNF-α in individuals with schizophrenia [37]. Several genetic studies detected associations between TNF-α gene polymorphism and schizophrenia [38-40], although others suggested that this association is more specific for men and paranoid-type schizophrenia [39,41]. Lv *et al.* (2015) reported that TNF-α levels were negatively correlated with the total Positive and Negative Syndrome Scale (PANSS) score, as well as with positive and general PANSS scores [27]. A positive correlation of TNF-α with the PANSS negative score was observed in another study [42]. In light of these results, TNF-α may be important in the pathophysiology of schizophrenia.

Antipsychotics are generally considered drugs that exert immunomodulatory activity via their effects on the cytokine system [17]. However, the influence of antipsychotic drugs on the neuroimmune system as well as the mechanisms by which antipsychotics affect cytokine levels are essentially unclear [43,44]. Three meta-analyses found that the TNF-α levels did not change after antipsychotic treatment [14,16,45], which suggests that TNF-α may be a trait marker of schizophrenia [45]. On the other hand, a meta-analysis conducted by Romeo *et al.* (2018) showed that TNF-α levels decrease after antipsychotic treatment [46]. The effects of antipsychotics on TNF-α levels in individuals with schizophrenia thus requires further clarification.

Finally, it is important to note that confounding factors such as age, gender, smoking, and body mass index (BMI) have complex effects on cytokine levels [47]. The majority of the previous investigations did not control for potential confounding factors that can affect blood cytokine levels, including TNF-α [18]. Indeed, to the best of our knowledge, only a few studies have taken into account all of the aforementioned confounding variables [26,30,48]. The effect of these confounding variables on TNF-α level merits further investigation.

A considerable number of studies have suggested that pro-inflammatory cytokines such as TNF-α, interleukin (IL)-6, and IL-1β are associated with the pathophysiology of schizophrenia [6,11,14,16,33], but the data on alterations of TNF-α levels in individuals with schizophrenia are inconsistent, and the majority of the studies focused on the pathogenetic aspects of these immunological findings in schizophrenia; few studies examined the relationship between TNF-α levels and the psychopathology of schizophrenia [27]. The pro-inflammatory cytokines with replicated positive findings across multiple domains of the psychopathology of schizophrenia are IL-1β and IL-6 but not TNF-α [49]. We conducted the present study to determine the serum TNF-α levels of individuals with schizophrenia and to investigate the relationship between serum TNF-α levels and psychopathological symptoms in schizophrenia. A secondary aim of the study was to clarify the relationships between TNF-α levels and clinical and socio-demographic characteristics and antipsychotic therapy in patients with schizophrenia.

Patients and Methods

Study design. We recruited 180 subjects in this cross-sectional study. The study group consisted of 90 patients with schizophrenia recruited from the University Hospital Center (UHC) Mostar (Mostar, Bosnia and Herzegovina). The patients with schizophrenia met the following inclusion criteria: 1) age 18-65 years; 2) diagnosis of schizophrenia according to the ICD-10 criteria as confirmed by two experienced psychiatrists following the Mini-International Neuropsychiatric Interview (M.I.N.I.) [50]; 3) treatment with a stable dose of one or more oral antipsychotics for > 1 month and a parenteral antipsychotic for > 3 months before study enrollment. Subjects with comorbid psychiatric disorders were excluded. The age of onset was defined as the age at which the first symptoms of schizophrenia appeared.

These data were collected from the patients' medical records or during interviews with the patient or the patient's family members. We divided the enrolled patients into three groups based on their antipsychotic treatment: 1) typical antipsychotics; 2) atypical antipsychotics; 3) typical/atypical combination. The duration of antipsychotic treatment was calculated as the total length of treatment with any antipsychotic medication from the onset of illness. The mean antipsychotic dose was estimated as the chlorpromazine equivalent dose.

The control group consisted of 90 healthy subjects who were recruited from among the staff of UHC Mostar. Healthy subjects were also interviewed using the M.I.N.I. in order to rule out a psychiatric disorder. All of the healthy subjects had no personal or family history of psychiatric disorders. The patients and the control group were matched for age, gender, smoking status, and BMI to reduce potential confounders. A complete medical history, socio-demographic data, physical status examination, and laboratory (blood and urine) tests were obtained from all 180 subjects included in the study.

Exclusion criteria were as follows: 1) age < 18 or > 65 years; 2) elevated C-reactive protein serum concentration (> 5 mg/L); 3) obesity (BMI ≥ 30 kg/m^2); 4) the presence of an autoimmune, allergic, degenerative, rheumatic, acute or chronic infectious disease; 5) the presence of malignancy, epilepsy, pregnancy, or breastfeeding; 6) substance abuse/dependence other than tobacco; 7) treatment with antibiotics, antivirals, anti-inflammatory and immunosuppressive drugs.

Psychopathology assessment. The psychopathology of the patients with schizophrenia was assessed with the PANSS questionnaire [51]. The assessment was made by two psychiatrists who attended the PANSS training session prior to starting the study. The PANSS consists of 30 items, and each item is rated on a seven-point severity scale that represents increasing levels of psychopathology: 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate severe, 6 = severe, and 7 = extreme. The symptoms are categorized into three subscales: a positive scale (7 items), negative scale (7 items), and general psychopathology scale (16 items). Possible PANSS score ranges are 7-49 for the positive and negative scales, and 16-112 for the general psychopathology scale.

The PANSS composite scale score (range from –42 to +42) is a bipolar index that is scored by subtracting the negative score from the positive score; the composite scale score reflects the degree of the predominance of positive or negative syndrome. According to some factor-analytic studies, a five-factor model better reflects the dimensional structure of the PANSS data compared to the original three-subscale classification [52, 53]. For this reason, we used a consensus PANSS five-factor model proposed by Wallwork *et al*. (2012) [54] in the present study. This model includes 20 items from the original PANSS grouped into the following factors: positive, negative, cognitive, excitement, and depression.

TNF-α measurement in serum. Blood samples were taken from the cubital vein into serum separation tubes between 8:00 and 9:00 a.m. after a 12-hr overnight fast, and the tubes were left at room temperature for 30 min. Serum was obtained by centrifugation at 3,000 rpm for 15 min, and the serum samples were stored at ≤ –20°C until the assay was performed. TNF-α levels were measured in one sample with an enzyme-linked immunosorbent assay (ELISA) kit (Quantikine ELISA Human TNF-α Immunoassay; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The optical densities were measured using an ELISA reader (iMark; BioRad, Hercules, CA, USA) at 450 nm. In accordance with the manufacturer's instructions, a four-parameter curve was made, and the TNF-α levels were calculated by Microplate Manager Software (BioRad). The minimal detection sensitivity was 4 pg/mL. Assays for each subject were performed by the same investigator, who was blinded to

the subject information and the study design.

Anthropometric measurements. The height of subjects was measured with a telescopic measuring rod, and weight was measured with a spring balance placed on a horizontal surface. Subjects were in their underwear and without shoes for these measurements, all of which were performed three times in a row; the mean values were then calculated. BMI was calculated as body weight in kilograms divided by the height in meters squared (kg/m^2).

Ethics. This study was approved by the Ethics Committee of UHC Mostar (approval no. 3830/15). It was conducted in accordance with the Declaration of Helsinki and the principles of high-quality clinical practice. All subjects gave written informed consent prior to participating in the study.

Statistical analyses. Data were analyzed using descriptive statistics methods. Categorical variables are presented as the frequency and percentage, and continuous variables are presented as arithmetic mean ± standard deviation (SD). The normality of the distributions was tested with the Shapiro–Wilk test. The Mann–Whitney *U*-test was used to analyze differences between pairs of groups, and the Kruskal–Wallis test was used to analyze differences among three groups. We performed a hierarchical regression analysis to examine the predictive value of socio-demographic variables, BMI, and the PANSS cognitive factor for the TNF-α level in the patients with schizophrenia. Correlations between variables were analyzed by Spearman correlation coefficients. The probability level $p < 0.05$ was considered significant. SPSS statistics software, ver. 20.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

The socio-demographic characteristics of the 90 patients with schizophrenia and the 90 healthy controls are summarized in Table 1. There were significant between-group differences in employment and marital status ($p < 0.001$) but no significant between-group differences in age, gender, education level, residence, or smoking status.

The mean age of the schizophrenia group was 44.45 ± 12.19 years. The mean age at the onset of schizophrenia was 24.23 ± 7.31 years, with a mean illness duration of 20.13 ± 12.26 years. The mean duration of antipsychotic treatment was 14.12 ± 11.64 years, with a mean antipsychotic dose of 675.00 ± 387.82 mg/day. There were no significant between-group differences in BMI ($p = 0.581$). Forty-two patients were being treated with a combination of typical and atypical antipsychotics (46.7%), 19 (21.1%) with an atypical antipsychotic, and 29 patients (32.2%) with a typical antipsychotic.

There were no significant differences in serum TNF-α levels between the individuals with schizophrenia and the controls ($p = 0.736$) (Table 2). The TNF-α levels did not differ significantly according to the type of antipsychotics used ($p = 0.596$) (Table 3).

The serum TNF-α levels did not differ significantly between the male and female patients ($p = 0.396$), or between the smokers and nonsmokers ($p = 0.316$). There were no significant differences in serum TNF-α levels among the underweight, normal weight, and overweight patients ($p = 0.714$). The TNF-α levels did not differ significantly between the patients with predominantly positive syndrome and those with predominantly negative syndrome ($p = 0.761$).

However, there was a significant negative correlation between TNF-α levels and the duration of illness, as well as between the TNF-α levels and the duration of antipsychotic treatment. We also observed a significant positive correlation between TNF-α levels and the age of onset. There were no significant correlations between the TNF-α levels and age, BMI, or antipsychotic dose (Table 4).

TNF-α levels were not correlated with the total PANSS score or with positive, negative, general, or composite PANSS scores (Table 5), but a significant negative correlation was identified between TNF-α levels and the PANSS cognitive factor score (Table 6). The hierarchical regression analysis with the TNF-α level as the dependent variable and age, gender, BMI, and PANSS cognitive factor score as the independent variables revealed that the PANSS cognitive factor was the only significant factor for predicting the TNF-α level (beta = −0.258, t = −2.257, $p = 0.027$).

Discussion

The first main finding of this study was that serum TNF-α levels did not differ significantly between individuals with schizophrenia and healthy control subjects. Several earlier studies also failed to find differences in serum TNF-α levels among individuals with schizophrenia without antipsychotic treatment [48] and indi-

Table 1 Sociodemographic data of the patients with schizophrenia and healthy controls

	Group				test	*P*-value
	Schizophrenia		Control			
Age ($\bar{X} \pm SD$)	44.45 ± 12.191		44.13 ± 12.324		t = 0.176	0.860
Gender N (%)					$\chi^2 = 0$	< 1
Male	59	65.6	59	65.6		
Female	31	34.4	31	34.4		
Education level N (%)					$\chi^2 = 0.051$	0.997
Elementary school	6	6.7	6	6.7		
High school	67	74.4	66	73.3		
College	6	6.7	6	6.7		
University degree	11	12.2	12	13.3		
Employment N (%)					$\chi^2 = 126.664$	< 0.001*
Unemployed	52	57.8	3	3.3		
Employed	9	10.0	77	85.6		
Student	2	2.2	4	4.4		
Retired persons	27	30.0	6	6.7		
Marital status N (%)					$\chi^2 = 52.885$	< 0.001*
Married	12	13.3	58	64.4		
Unmarried	65	72.2	28	31.1		
Divorced	9	10.0	4	4.4		
Widow/er	4	4.4	0	0		
Residence N (%)					$\chi^2 = 3.137$	0.077
Urban area	56	62.2	68	75.6		
Countryside	34	37.8	22	24.4		
Smoking status N (%)					$\chi^2 = 0$	< 1
Smoker	59	65.6	59	65.6		
Non smoker	31	34.4	31	34.4		

*Fisher's exact test

Table 2 Serum TNF-α levels in the schizophrenia group and healthy control group

	Group				Z	*P*-value
	Schizophrenia		Control			
	C	Q	C	Q		
TNF-α	10.91	3.456	11.46	3.062	−0.338	0.736

Mann–Whitney *U*-test.

viduals with schizophrenia with and without antipsychotic treatment and healthy controls [29]. Similar findings were also reported in studies of individuals with schizophrenia in acute exacerbation phase [30] and individuals with chronic schizophrenia [31,32,55,56]. According to some researchers, this absence of differences in TNF-α levels could be a consequence of the non-acute profile of individuals with schizophrenia [56] or the effect of drugs [32]. However, some earlier studies reported increased TNF-α levels among patients with first-episode psychosis [14,16,24], acutely relapsed individuals with schizophrenia [14,16,23], and individuals with chronic schizophrenia [16,25]. Other studies have described decreased TNF-α levels

Table 3 Comparison of TNF-α levels among individuals with schizophrenia being treated with a typical antipsychotic, an atypical antipsychotic, or a typical/atypical antipsychotic combination

	Antipsychotics						χ^2	*P*-value
	Typical		Atypical		Typical + Atypical			
	C	Q	C	Q	C	Q		
TNF-α	10.18	2.093	10.91	4.44	11.71	3.68	1.034	0.596

Kruskal–Wallis test.

Table 4 Correlations between the demographic and clinical characteristics of patients with schizophrenia and their serum TNF-α levels

	TNF-α	
	ρ	*P*-value
Age	0.067	0.528
BMI	−0.068	0.365
Duration of illness	−0.247	0.019
Age of onset	0.233	0.027
Duration of antipsychotic treatment	−0.256	0.015
Antipsychotic dose	0.098	0.360

Spearman correlation coefficients.

Table 5 Correlations between PANSS scores and TNF-α levels

PANSS	TNF-α	
	ρ	*P*-value
Total score	−0.096	0.371
Positive score	−0.160	0.131
Negative score	−0.050	0.643
General psychopathology score	−0.104	0.328
Composite score	−0.047	0.662

Spearman correlation coefficients.

Table 6 Correlations between scores of the PANSS five-factor model and TNF-α levels

PANSS five-factor model	TNF-α	
	ρ	*P*-value
Positive factor	−0.004	0.969
Negative factor	0.014	0.893
Cognitive factor	−0.222	0.035
Excitement	−0.164	0.123
Depression	0.010	0.922

Spearman correlation coefficients.

among individuals with schizophrenia in the acute exacerbation phase [26] and individuals with chronic schizophrenia [27,28]. The differences in the aforementioned studies may be a consequence of several factors, such as the use of different methodologies for measuring TNF-α, the recruitment of patients in different stages or types of schizophrenia, and the use of different antipsychotic drugs.

The second main finding of this study was that the serum TNF-α levels were not significantly correlated with the PANSS subscores or total score. In agreement with our findings, two previous studies that observed no differences in TNF-α levels between individuals with schizophrenia and healthy controls also reported that TNF-α levels were not correlated with the PANSS subscores or total score [32,48]. It should be pointed out that in some of the studies that observed increased TNF-α levels in patients with schizophrenia, no correlations were observed between TNF-α levels and the PANSS subscores or total score [23], or between the TNF-α levels and the PANSS total, negative, or positive scores [25]. In addition, a research group that reported

decreased TNF-α levels in individuals with schizophrenia also noted that there were no correlations between the TNF-α levels and PANSS subscores of subjects [57].

In contrast, two studies that observed decreased TNF-α levels in individuals with schizophrenia reported negative correlations between TNF-α levels and the PANSS total, positive, and general scores [27] and between TNF-α levels and the PANSS total score [28]. An investigation describing increased TNF-α levels in individuals with chronic schizophrenia reported a positive correlation between TNF-α and the PANSS negative score [42]. Given the inconsistent results of these studies, it is not possible to reach a definitive conclusion about the relationship between TNF-α and psychopathology in individuals with schizophrenia. Moreover, cytokines most likely exert their effects on the CNS as a complex system [37], which limits the observation of TNF-α as an individual agent.

Our present analyses demonstrated that TNF-α levels were negatively correlated with the PANSS cognitive factor, which was also shown to be a significant factor for predicting the TNF-α level after we controlled for confounding variables. According to this result, TNF-α may be associated with cognitive impairment, which is a key feature of schizophrenia. Cognitive deficits in schizophrenia are linked to inflammatory processes and immune dysfunction that affect neurodevelopment [58]. One of the possible mechanisms underlying this process is the microglial activation that leads to the release of inflammatory cytokines [11]. TNF-α has been shown to have many roles in neurodevelopment and neurodegeneration, including regulation of neuronal proliferation and survival [59], regulation of synaptic plasticity and cognitive processes [60], mediation of oxidative stress [61], and induction of neuronal apoptosis [62].

Previous studies linking TNF-α levels and cognitive functioning in individuals with schizophrenia have shown inconsistent results. Specifically, poorer cognitive functioning was observed to be associated with increased TNF-α levels in patients with first-episode schizophrenia [63] and individuals with non-acute schizophrenia [64]. TNF-α levels were also shown to be negatively correlated with the processing speed and attention in patients with chronic schizophrenia [65]. Two studies found no significant correlations between TNF-α levels and cognitive functioning in individuals with schizophrenia [66,67]. In agreement with our present results, only two studies reported that schizophrenia patients with higher levels of TNF-α had better cognitive functioning. In the study by Lv *et al*. (2015), there was a significant negative correlation between TNF-α and the PANSS cognitive factor in individuals with chronic schizophrenia [27]. Similarly, a significant negative effect of the interaction between levels of brain-derived neurotrophic factor (BDNF) and TNF-α on the PANSS cognitive factor score was described [68]. Taken together, these results may indicate that there are variations in the associations between TNF-α levels and cognitive functioning among different groups of individuals with schizophrenia.

Given that increased peripheral TNF-α levels have generally been perceived as detrimental to cognitive functioning [63,64], our results seem paradoxical. However, it has been postulated that TNF-α may exert beneficial rather than detrimental effects on the symptomatic improvement of individuals with chronic schizophrenia under long-term drug treatment when the effects of the antipsychotics reach their stabilized plateau [28]. Given that the patients in our study had experienced an average of 20 years of illness and 14 years of drug treatment, this explanation could also apply to our results.

Disease-heterogeneity genetic factors, inadequately considered possible confounding factors [69], and the heterogeneity in cognitive measures used in previous studies may also have contributed to the inconsistent results. It should be noted that the use of the PANSS cognitive factor has limitations, given that there is no broad consensus on its psychometric characteristics. The PANSS cognitive factor is a general measure of cognitive functioning and does not refer to specific cognitive domains [27]; rather, it refers to verbal skills [70]. More specific neuropsychological tests should be used for a better assessment of the relationship between TNF-α levels and the cognitive status in individuals with schizophrenia.

Previous studies have not sufficiently accounted for the confounding effects of antipsychotics on TNF-α levels in individuals with schizophrenia. Although antipsychotics have an immunomodulatory effect [43], in most of the previous studies the antipsychotics had no effect on TNF-α levels in patients with schizophrenia [14,43,45]. Our present analyses showed that TNF-α levels did not differ significantly according to the type of antipsychotics used. Several other research groups found no significant differences in TNF-α levels

between patients taking typical and atypical antipsychotics [26-28], and another study detected no differences in TNF-α levels among patients taking clozapine, typical antipsychotics or both [31]. In our present study, some of the patients in either the typical or atypical group had not received monotherapy. Some of the patients in the typical group had been treated with two typical antipsychotics simultaneously (*e.g.*, haloperidol and promazine), and some patients in the atypical group had received two atypical antipsychotics simultaneously (*e.g.*, risperidone and clozapine), which may have affected TNF-α levels.

Interestingly, amisulpride has been reported to reduce the mitogen-induced production of TNF-α [37], and clozapine has been shown to increase TNF-α levels [71]. Clozapine has also been reported to decrease TNF-α levels in individuals with schizophrenia [72]. Future studies should further investigate the effect of monotherapy on TNF-α levels. In accord with several prior studies [25,27,28,56], we observed no correlation between the antipsychotic dose and TNF-α levels; however, in contrast with some reports [24,26-28], we identified a significant negative correlation between TNF-α levels and the duration of antipsychotic treatment. It is important to note that our subjects with schizophrenia were not observed longitudinally, and the duration of their treatment could not be estimated with certainty. This result must therefore be interpreted with caution considering that medication nonadherence is common among patients with schizophrenia [73].

Previous investigations have not consistently addressed age, gender, smoking status, and BMI, each of which could affect serum TNF-α levels. We matched the present patients with schizophrenia and healthy controls based on these variables in order to achieve greater homogeneity of the sample and to reduce the influence of these variables on the TNF-α level. Increasing activity of the TNF-α system with aging has been described [47,74], and the production of TNF-α has been significantly positively correlated with age in individuals with schizophrenia [37]. However, as in other studies [25,26,30,31,55,75], we observed no correlation between age and TNF-α levels. These findings would appear to run counter to the process of immunosenescence [75], at least in terms of the role of the TNF-α system in the immunosenescence of individuals with schizophrenia.

The effect of gender on TNF-α levels in individuals with schizophrenia has rarely been exmined, but gender-related differences in TNF-α levels were not observed in several investigations [25,30,48,75] including the present study. In contrast, only a single study reported higher serum levels of TNF-α in the female than in the male patients with schizophrenia [55], and higher serum levels of TNF-α in the male than in the female patients with schizophrenia were also reported [76].

The prevalence of smoking is higher among individuals with schizophrenia compared to those with other mental disorders and the general population [77]. Smoking tobacco exerts immunomodulatory effects through the effect of nicotine on the immune response system, the inhibition of cytokine production, and increased glucocorticoid release [78]. The results of our present analyses demonstrated that smoking did not affect the serum TNF-α levels of the patients with schizophrenia, as in other studies [26,30,31,37,48].

No correlation between BMI and serum TNF-α levels was observed in the present schizophrenia group, confirming previous findings [16,24,26,30]; these studies used different BMI criteria for their recruitment of subjects, which is a limitation for comparing the results. It is necessary to mention that although BMI is the most widely accepted index of adiposity, it cannot differentiate body lean mass and body fat mass, which is the reason that a patient with a high BMI may still have a very low fat mass [79]. We excluded obese subjects from the present investigation and matched the patients and controls based on their BMI in order to minimize the effect of potential abdominal fat on serum TNF-α levels, but for the above-mentioned reasons this effect could not be completely excluded.

The duration of illness has been reported to be correlated with the levels of IL-6 [25,80] but not those of TNF-α [25-27,30,32,55,75]. The present investigation revealed a significant negative correlation between the TNF-α level and the duration of illness in the schizophrenia group, and this result may support the hypothesis of the predominance of the type-2 response in the later stages of schizophrenia [81]. However, this finding could also be explained by the longer duration of antipsychotic treatment. We also observed a positive correlation between the TNF-α level and the age of schizophrenia onset, which is in contrast to earlier findings [25,27]. Further studies are necessary to determine the precise relationships between TNF-α levels and

these clinical characteristics of schizophrenia.

Finally, an earlier age of onset and longer duration of illness accompanied the decrease in the level of TNF-α in the present work, while a decrease in the level of TNF-α accompanied the deterioration of cognitive functioning in the individuals with schizophrenia. A defect in the induction of inflammatory pathways or the active inhibition of TNF-α due to long-term drug treatment may be associated with a decrease in TNF-α levels [28]. Severe cognitive deficits have been reported to be linked with an earlier age of onset of schizophrenia [82] and in some patients with a longer duration of the illness as well [83]. We therefore postulate that TNF-α-related pathophysiological processes may underlie the cognitive impairment associated with an earlier onset and longer duration of illness in individual patients.

Several methodological limitations of this study should be mentioned. First, the relatively small sample size (90 subjects in each group) may have limited the detection of actual relationships between TNF-α and psychopathology. Future studies with larger sample sizes will be needed to confirm our results. Second, we assessed only TNF-α, which is a limitation considering that different cytokines are interrelated and act in a complex cytokine system [84]. Moreover, we measured the TNF-α levels in serum, but not in cerebrospinal fluid; it is not known whether peripheral TNF-α reflects similar changes in the CNS [28]. Third, we examined individuals with schizophrenia with different stages and disease subtypes, and these differences could have been confounding factors [26, 37]. Fourth, we did not examine the influences of stress [85], diet [86], physical activity [87], or the freezer storage time of blood samples [48], all of which can affect cytokine levels. Fifth, the subjects with schizophrenia were exposed to different types of antipsychotic drugs before their enrollment in the study. Given that previous studies have obtained contradictory results, this could be a confounding factor. Future studies in drug-naïve patients with long-term antipsychotic monotherapy plus serial measurements of TNF-α levels are necessary to establish the association between antipsychotics and TNF-α.

In summary, the results of this study demonstrated that the serum TNF-α levels in patients with schizophrenia are not significantly different from those of healthy controls if confounding variables such as age, gender, smoking, and BMI are taken into account. Regarding the association between TNF-α and psychopathology, our findings support the possible involvement of TNF-α in cognitive impairment in schizophrenia. We observed that clinical parameters such as the age of onset and the duration of illness were correlated with TNF-α levels, which suggests that TNF-α is a potential marker of the clinical state in schizophrenia. Further prospective studies in drug-naïve individuals with schizophrenia will be needed to confirm the present findings.

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