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Effects of 6-week olanzapine treatment on serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels in drug-naive individuals with first-episode schizophrenia

Xiaofeng Zhao^{1*†}, Wenli Zhu^{2*†}, Yangying Bu^{2†}, Junwei Li², Yihui Hao¹ and Yuxiao Bi¹

Abstract

Background Schizophrenia is a complex neuropsychiatric disorder. Growing evidence indicates that the activation of the inflammatory response system with interleukin (IL)-2, IL-4, IL-8, IL-10, and tumor necrosis factor-alpha (TNF- α) plays an important role in the pathogenesis of schizophrenia. However, clinical data on cytokine levels in patients with schizophrenia treated with antipsychotics are inconsistent or inconclusive. In this study, we have examined inflammatory factors' alterations and their relationship to changes in clinical symptoms before and after olanzapine treatment of drug-naive patients with first-episode schizophrenia.

Methods We recruited 142 hospitalized patients with first-episode schizophrenia as a study group; blood samples were collected, and the patients were assessed for clinical symptoms at baseline and after 6 weeks of olanzapine treatment. One hundred individuals with no history of mental illness were also recruited as healthy controls. Blood samples were collected, and the serum levels of IL-2, IL-4, IL-8, IL-10, and TNF- α were determined using an enzyme cycling assay. The severity of clinical symptoms was assessed according to the Positive and Negative Syndrome Scale (PANSS).

Results Individuals with schizophrenia had lower IL-8 levels and higher IL-10 levels than healthy controls ($P < 0.001$). Positive correlations were detected between serum IL-2 and IL-10 concentrations and each subscale of the PANSS (all $P < 0.05$). Moreover, a negative correlation existed between the serum IL-8 concentration and the PANSS negative score ($r = -0.172$, $P = 0.040$). After 6 weeks of treatment, serum IL-8 levels in the patient group were lower than at baseline ($P < 0.001$), whereas serum IL-10 and TNF- α levels were higher than at baseline (all $P < 0.05$). Therefore, serum IL-10 can be determined as an independent risk factor for outcome in patients with first-episode schizophrenia ($P = 0.02$, $OR = 2.327$). Furthermore, serum IL-2, IL-10, and TNF- α levels were significantly lower, whereas the serum

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IL-8 level was significantly higher ($P < 0.001$) in the healthy control group than in the “response” and “no-response” treatment groups respectively.

Conclusions Our results indicate that serum IL-2, IL-8, IL-10, and TNF- α levels may be involved in the pathophysiological mechanisms of schizophrenia and correlate with the effects of olanzapine.

Keywords Interleukin-2, Interleukin-8, Interleukin-10, Tumor necrosis factor-alpha, Schizophrenia

Background

Schizophrenia is a psychiatric disorder with a high incidence rate and a prolonged recurrent course, which not only jeopardizes the physical health of patients and increases their risk of cardiovascular disease and death, but also imposes a heavy economic burden on families and society [1, 2]. The weighted lifetime prevalence of schizophrenia and other mental disorders in China is reported to be 0.7% [3]. Although many studies have been conducted on schizophrenia over the years, yet its pathogenesis has not been clarified. Therefore, it is often difficult to achieve satisfactory results when treating such patients in the clinics. However, growing evidence indicate that dysregulation of the immune and inflammatory response systems is gradually becoming a feature of the disease [4, 5]. Numerous studies suggest that abnormal levels of cytokines, hyperactivation of the complement system in immune responses, activation of microglial cells in the central nervous system, neuroinflammation, dysbiosis of the gut microbiota, and polymorphisms in immune-related genes may all increase the risk of developing schizophrenia [6–8]. Accumulating evidence suggest that cytokines play a major role in mediating signal communications between innate and adaptive immune cells and thus guarantee the antipsychotic response in patients with schizophrenia [5, 9]. Among cytokines, previous studies have focused on interleukin (IL)-2, IL-4, IL-8, IL-10, and tumor necrosis factor (TNF)- α , which are involved in the antipsychotic response [10]. Meta-analyses from multiple studies on patients with schizophrenia reported elevated levels of IL-6, TNF- α , IL-1 β , sIL-2R (soluble interleukin receptor), IL-12, IFN- γ (interferon γ) in the peripheral blood implying the presence of low-grade systemic inflammation [11–13].

Earlier studies have shown that elevated levels of IL-8 are associated with a poor response to antipsychotic treatment. Moreover, the increased levels of the cytokines IL-8, IL-10, and TNF- α are positively correlated with negative symptoms in patients with schizophrenia [10].

We know that olanzapine can reduce pro-inflammatory cytokines such as IL-2 and IL-6, suggesting anti-inflammatory properties [14]. However, the response may vary based on metabolic health, such that patients without metabolic syndrome show decreased levels of cytokines like IFN- γ and IL-1 β , while those with metabolic

syndrome experience increased levels of IFN- α 2 and IL-1 α [15]. Additionally, baseline levels of IL-6 and IL-27 were found to regulate the severity of negative symptoms, hinting at their role in the clinical response to olanzapine [16]. Yuan et al. detected an abnormal expression of serum cytokines, such as IL-2 and TNF- α , in patients with schizophrenia treated with clozapine in comparison to healthy participants [17]. Similarly, in an ex vivo study, the mRNA levels of TNF- α were decreased, which resulted in diminished TNF- α protein concentration in primary human peripheral blood mononuclear cells conditioned with olanzapine and aripiprazole [18]. Further, a clinical study demonstrated that increased IL-2 levels may be involved in the psychopathology and cognitive impairments of patients with schizophrenia [19]. Ajami et al. compared the peripheral blood levels of TNF- α and IL-10 in patients with schizophrenia before and after treatment with risperidone and clozapine, revealing a significant decrease in TNF- α and an increase in IL-10 levels [18, 20]. After 4 weeks of treatment with aripiprazole, the levels of TNF- α and IL-4 were significantly reduced and those of IL-10 significantly elevated as compared to baseline [21]. Zhang et al. [22] found that, compared to the control group, the olanzapine group showed increased levels of pro-inflammatory cytokines—tumor necrosis factor α (TNF α), IL-1 β , and IL-6 in the hypothalamus, white adipose tissue, and brown adipose tissue. The study further indicated that peripheral low-grade inflammation occurs during olanzapine treatment and is closely associated with obesity. Furthermore, Li et al. [23] discovered that long-term olanzapine treatment induces different inflammatory cytokine responses in peripheral fat and the central nervous system. The prolonged treatment with olanzapine significantly elevated plasma levels of pro-inflammatory cytokines, including IL-1 β , IL-6, IL-8, and TNF α , leading to metabolic symptoms [23].

Accordingly, clinical data on cytokine levels in patients with schizophrenia treated with antipsychotic drugs have been inconsistent or inconclusive due to different ethnic backgrounds, sample sizes, and antipsychotic drugs. Therefore, we performed a case-control study to verify whether (1)-serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels are associated with the severity of schizophrenia and to determine whether (2)-the antipsychotic response is associated with serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels in patients with schizophrenia at baseline

and after 6 weeks of olanzapine treatment in comparison with healthy controls.

Methods

Participants and samples

Before conducting the formal study, we recruited 20 hospitalized patients with first-episode schizophrenia and 20 healthy participants at the Fourth People's Hospital in Wuhu, China. We selected $\alpha=0.05$ (bilateral), with a certainty of $1 - \beta=0.9$, combined the means and standard deviations of the cytokines IL-2, IL-4, IL-8, IL-10, and TNF- α , and used PASS 15.0 for sample size estimation [24]. TNF- α was found to be the indicator requiring the largest sample size (with a mean \pm standard deviation (SD) of 6.94 ± 2.39 for healthy participants and 11.17 ± 11.11 for patients), at which point the sample size required for each group was approximately 78 cases. Considering a shedding rate of 20%, the final sample size was calculated to be approximately 98 cases per group.

From May 2022 to May 2023, 171 patients were recruited with first-episode schizophrenia diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) from the Fourth People's Hospital of Wuhu City, China. The Positive and Negative Syndrome Scale (PANSS) was adopted to evaluate schizophrenia severity [25]. During the same period, 100 healthy participants who met the inclusion criteria were recruited through volunteers from the Fourth People's Hospital of Wuhu City. All participants'

investigations were conducted by trained researchers and contained general information, medical history, PANSS ratings, and laboratory tests. This study finally included 142 patients with first episode of schizophrenia who were not receiving medication, mean age (39.04 ± 10.82) years, mean age at onset (27.26 ± 9.83) years, mean duration of illness (136.46 ± 111.43) months, and 132 patients (92.96%) were born in towns. In the healthy control group, there were 100 patients with a mean age of (41.31 ± 12.39) years, and 92 (92%) were born in towns. There was a difference in HDL levels between the two groups in terms of demographic and clinical characteristics ($p < 0.05$). There were no significant differences in age, place of birth, body mass index, blood glucose, HDL, LDL, total cholesterol, total calories, alcohol consumption, and smoking ($P > 0.05$). See Table 1 for details. Written informed consent was obtained from all participants prior to their participation in the study. The study protocol was approved by the Ethics Committee of the Fourth People's Hospital of Wuhu City, and the experiments were conducted in accordance with the Declaration of Helsinki.

The inclusion criteria for the patient group were as follows: (1) first onset of illness; (2) meeting the diagnostic criteria for schizophrenia spectrum disorders in the DSM-5; (3) no antipsychotic medication prior to enrollment; (4) a total score of ≥ 60 on the PANSS; and (5) age between 18 and 60 years.

Table 1 Demographics and clinical characteristics of the sample

Characteristics	Patient group (<i>n</i> = 142)	Healthy control (<i>n</i> = 100)	X ² or F (<i>P</i>)
Age (years, mean \pm SD)	39.04 (10.82)	41.31 (12.39)	7.11 (0.131)
Birthplace (town), <i>n</i> (%)	132 (92.96)	92 (92)	0.08 (0.807)
BMI (kg/m ² , mean \pm SD)	22.56 (3.38)	23.18 (3.15)	0.47 (0.214)
Glu (mmol/L, mean \pm SD)	4.71 (0.92)	4.81 (0.54)	5.70(0.329)
HDL (mmol/L, mean \pm SD)	1.23 (0.86)	1.42 (0.32)	0.28(0.039)
LDL (mmol/L, mean \pm SD)	2.8 (1.08)	2.78 (0.78)	5.39(0.863)
TG (mmol/L, mean \pm SD)	1.23 (0.68)	1.27 (0.79)	0.38(0.666)
TC (mmol/L, mean \pm SD)	4.48 (1.24)	4.62 (0.97)	2.12(0.321)
Alcohol drinking, <i>n</i> (%)			0.01 (1.000)
No	127 (89.44)	89 (89)	
Yes	15 (10.56)	11 (11)	
Smoking, <i>n</i> (%)			0.64 (0.547)
No	123 (86.62)	90 (90)	
Yes	19 (13.39)	10 (10)	
Age of onset (years, mean \pm SD)	27.26 (9.83)	NA	NA
Duration of illness (months, mean \pm SD)	136.46 (111.43)	NA	NA
PANSS total score (mean \pm SD)	98.88 (19.32)	NA	NA
P subscore	28.48 (6.87)	NA	NA
N subscore	22.23 (8.34)	NA	NA
G subscore	48.17 (10.41)	NA	NA

Note: BMI, body mass index; GLU, Blood glucose; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; TG, Triglyceride; TC, total cholesterol; PANSS, Positive and Negative Syndrome Scale; P, positive symptom; N, negative symptom; G, general psychopathology; NA, not applicable. The data are expressed as mean \pm standard deviation. Significant differences ($P < 0.05$) are indicated in bold

The exclusion criteria for the patient group were: (1) severe somatic diseases, such as diabetes mellitus, hypertension, heart disease, and malignant tumors; (2) severe central nervous system disorders, immune disorders, and recent administration of any immunomodulators; and (3) drug or alcohol dependence or use of illegal drugs, such as marijuana, within the last 30 days.

The inclusion criteria for healthy participants were as follows: (1) no history of psychiatric problems; (2) no serious physical illnesses, such as diabetes mellitus, hypertension, cardiac disease, and malignant tumors; (3) no immunologic disorders; (4) no drug or alcohol dependence and no use of illegal drugs, such as marijuana, in the past 30 days; and (5) age between 18 and 60 years.

Peripheral blood was collected from patients with schizophrenia and healthy controls at baseline. In addition, peripheral blood was collected from patients with schizophrenia after 2, 4, and 6 weeks of treatment with olanzapine. Serum IL-2, IL-4, IL-8, IL-10, and TNF- α were measured using ELISA kits for humans according to the manufacturer's instructions (Jiangsu Meimian Industrial Co., Ltd).

Patients were considered in the "response" group if their total PANSS score decreased by 30% from baseline to week 6; otherwise, they were considered as a "non-response" group [26].

Statistical analysis

The obtained data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS), version 25.0. For descriptive analyses, the data were presented as continuous and categorical variables and expressed as mean \pm SD. According to the Kolmogorov-Smirnov test, serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels were not normally distributed in the control group and in the pre- and post-treatment schizophrenia groups; therefore, nonparametric analyses were carried out. The Mann-Whitney test was performed on baseline serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels in the schizophrenia and control groups to determine whether there was a significant difference between the two groups. Spearman's correlation coefficients were used to assess the correlation between baseline serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels in the schizophrenia group and the PANSS scores. The Wilcoxon signed-rank test was then employed to determine whether there were any differences in the serum levels of IL-2, IL-4, IL-8, IL-10, and TNF- α at baseline and after 6 weeks of treatment in the schizophrenia group, and then serum baseline values that differed were log-transformed to perform binary logistic analyses with the presence of efficacy as the dependent variable. Finally, to compare the differences in serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels among the response, non-response, and control groups, the Kruskal-Wallis test and

multiple comparisons were used. Statistical significance was set at $P < 0.05$. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$.

Results

Serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels in patients with schizophrenia and healthy controls

According to the Kolmogorov-Smirnov test ($P < 0.001$), serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels were non-parametrically distributed both in patients with schizophrenia and healthy controls, and the data were analyzed using the Mann-Whitney U test. IL-8 levels were found significantly lower in patients with schizophrenia than in the healthy control group, whereas IL-10 levels were depicted higher in patients with schizophrenia than in the healthy control group ($P < 0.001$) (Fig. 1). IL-2, IL-4 and TNF- α levels were not statistically different between the two groups ($P > 0.05$).

Correlations between IL-2, IL-4, IL-8, IL-10, and TNF- α serum concentrations and clinical symptoms

Spearman's correlation analysis showed that the serum IL-2 concentration was positively associated with the PANSS positive subscale, general psychopathology subscale, and total scores (all $P < 0.05$) (as shown in Fig. 2a and d, and 2e). A negative correlation was observed between serum IL-8 levels and the PANSS negative subscale score ($r = 0.172$, $P = 0.040$) (as shown in Fig. 2b). There was also a positive correlation between serum IL-10 concentrations and each of the PANSS subscale scores (all $P < 0.05$) (as shown in Fig. 2a, c and e). However, there was no significant association between the levels of IL-4 and TNF- α and the PANSS symptom scores (all $P > 0.05$), see Fig. 2f.

Comparison of serum IL-2, IL-4, IL-8, IL-10, and TNF- α levels at baseline and post-therapy

After 6 weeks of olanzapine treatment, the serum IL-8 level was found significantly lower in patients with schizophrenia than at baseline ($P < 0.001$) (as shown in Fig. 3c), whereas the serum IL-10 level was determined significantly higher ($P < 0.001$) (as shown in Fig. 3d). The post-therapy serum TNF- α level was increased in patients with schizophrenia as compared to their levels at baseline ($P < 0.01$) (as shown in Fig. 3e). However, there was no statistically significant difference between the post-therapy and baseline levels of serum IL-2 and IL-4 (all $P > 0.05$) (as shown in Fig. 3a and b).

Binary logistic regression analysis affecting treatment outcomes in patients with schizophrenia

The baseline values of serum IL-4, IL-8, IL-10, and TNF- α , which were statistically significant factors compared before and after treatment, were logarithmically transformed and included in a logistic regression equation

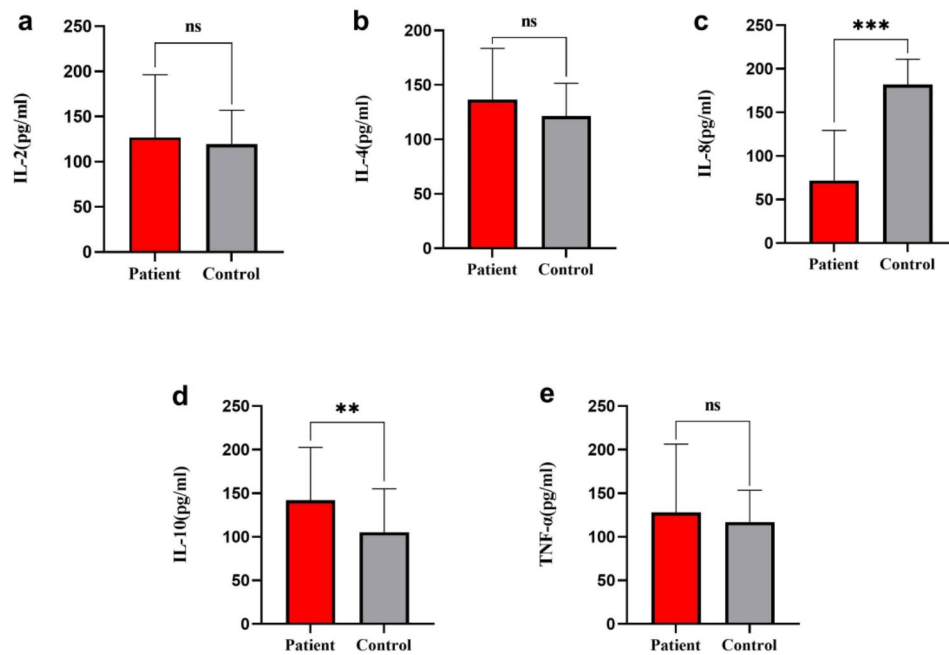


Fig. 1 Serum levels of IL-2, IL-4, IL-8, IL-10, and TNF-α in patients with schizophrenia and in healthy controls. ****P* < 0.001, ***P* < 0.01, and ^{NS}*P* > 0.05

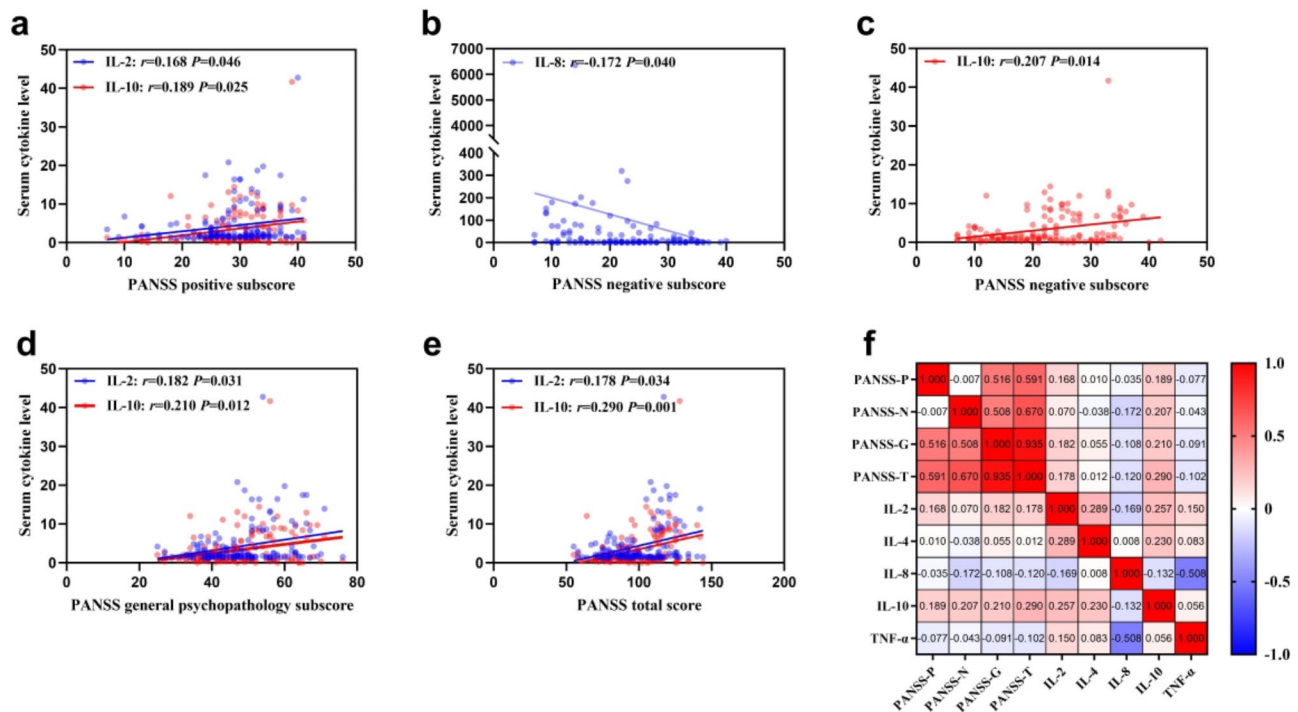


Fig. 2 Spearman correlations between IL-2, IL-4, IL-8, IL-10, TNF-α, and PANSS subscale scores in schizophrenia patients at baseline. **(a)** correlation between IL-2, IL-10 and PANSS positive subscore in schizophrenia patients at baseline; **(b)** correlation between IL-8 and PANSS negative subscore in schizophrenia patients at baseline; **(c)** correlation between IL-10 and PANSS negative subscore in schizophrenia patients at baseline; **(d)** correlation between IL-2, IL-10 and PANSS general psychopathology subscore in schizophrenia patients at baseline; **(e)** correlation between IL-2, IL-10 and PANSS total score in schizophrenia patients at baseline; **(f)** correlation between correlation heat map of IL-2, IL-4, IL-8, IL-10, TNF-α, PANSS positive subscore, PANSS negative subscore, PANSS general psychopathology subscore and PANSS total score in schizophrenia patients at baseline (Red indicates a positive correlation, whereas blue indicates a negative correlation, only f). *P* positive subscore, *N* negative subscore, *G* general psychopathology subscore, *T* total score

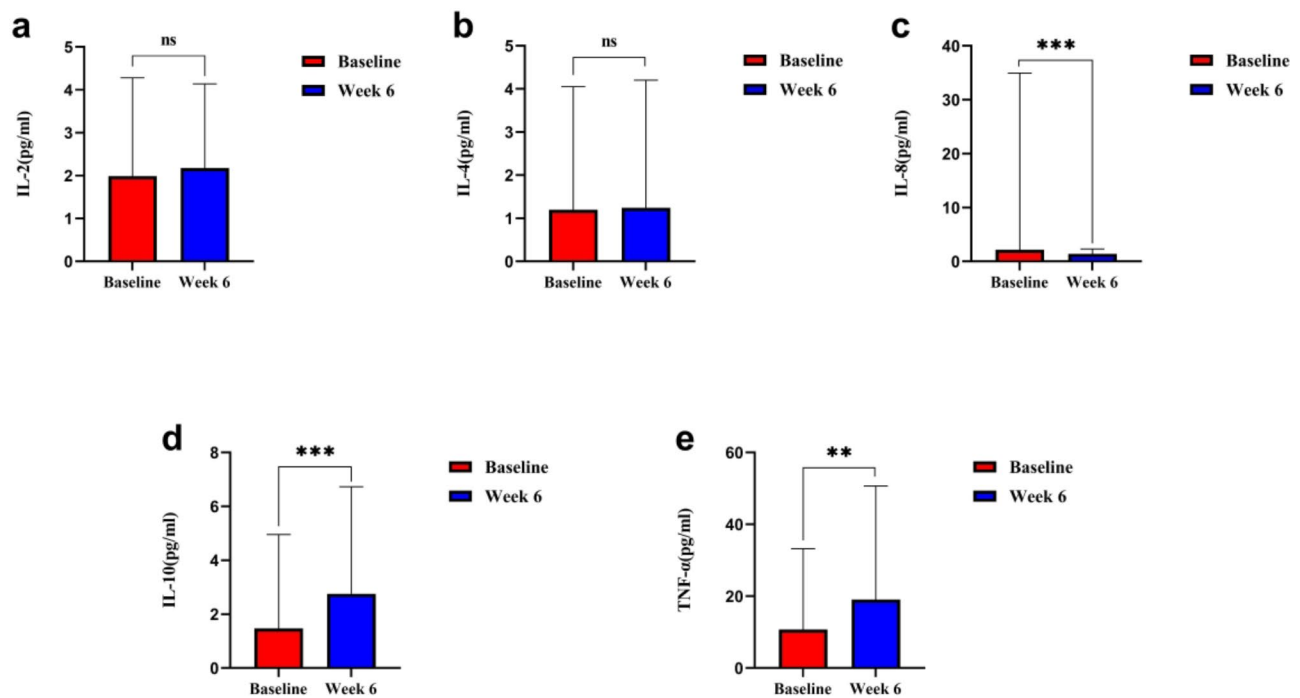


Fig. 3 Serum levels of IL-2, IL-4, IL-8, IL-10, and TNF-α in schizophrenia patients at baseline and after 6 weeks of treatment. (a) Serum levels of IL-2 in schizophrenia patients at baseline and after 6 weeks of treatment. (b) Serum levels of IL-4 in patients with schizophrenia at baseline and after 6 weeks of treatment. (c) Serum levels of IL-8 in patients with schizophrenia at baseline and after 6 weeks of treatment. (d) Serum levels of IL-10 in patients with schizophrenia at baseline and after 6 weeks of treatment. (e) Serum levels of TNF-α in patients with schizophrenia at baseline and after 6 weeks of treatment. *** $P < 0.001$, ** $P < 0.01$, and ^{NS} $P > 0.05$

Table 2 Binary logistic regression analysis affecting treatment outcomes in patients with schizophrenia

Variables	β	S.E.	Wald	df	P	OR
IL-4	0.013	0.356	0.001	1	0.971	1.013
IL-8	-0.122	0.179	0.470	1	0.493	0.885
IL-10	0.845	0.364	5.369	1	0.020	2.327
TNF-α	0.009	0.310	0.001	1	0.977	1.009

Note: IL, Interleukin; TNF, tumor necrosis factor

with efficacy after 6 weeks of treatment as the dependent variable (no-responder group=0, responder group=1). The results showed that serum IL-10 was an independent risk factor for outcome in patients with first-episode schizophrenia ($P=0.02$, the $OR=2.327$). The binary logistic analysis affecting the treatment outcome of patients with schizophrenia is shown in Table 2.

Comparison of serum IL-2, IL-4, IL-8, IL-10, and TNF-α levels among the response and no-response groups of patients with schizophrenia and healthy controls

The Kruskal-Wallis test showed statistically significant differences in serum IL-2, IL-8, IL-10, and TNF-α levels among the healthy control, response, and no response groups (all $P < 0.05$). Moreover, serum IL-2, IL-10, and TNF-α levels were significantly lower in the healthy control group than in the no-response group, whereas the serum IL-8 level was significantly higher (all $P < 0.05$).

Further, there were statistically significant differences in serum IL-8, IL-10, and TNF-α levels between the healthy control and response groups ($P < 0.001$). Serum IL-10 levels in the response group were also lower than those in the no-response group ($P < 0.001$). However, there was no statistically significant difference in the serum IL-4 level between the response and no-response groups (all $P > 0.05$), see Fig. 4.

Discussion

The present study demonstrated lower IL-8 levels and higher IL-10 levels in patients with schizophrenia as compared to healthy controls ($P < 0.001$). Moreover, it showed positive correlations between serum IL-2 and IL-10 concentrations and each subscale of the PANSS ($P < 0.05$) as well as a negative correlation between the serum IL-8 concentration and PANSS negative score ($r = -0.172$, $P = 0.040$). After 6 weeks of olanzapine treatment, serum

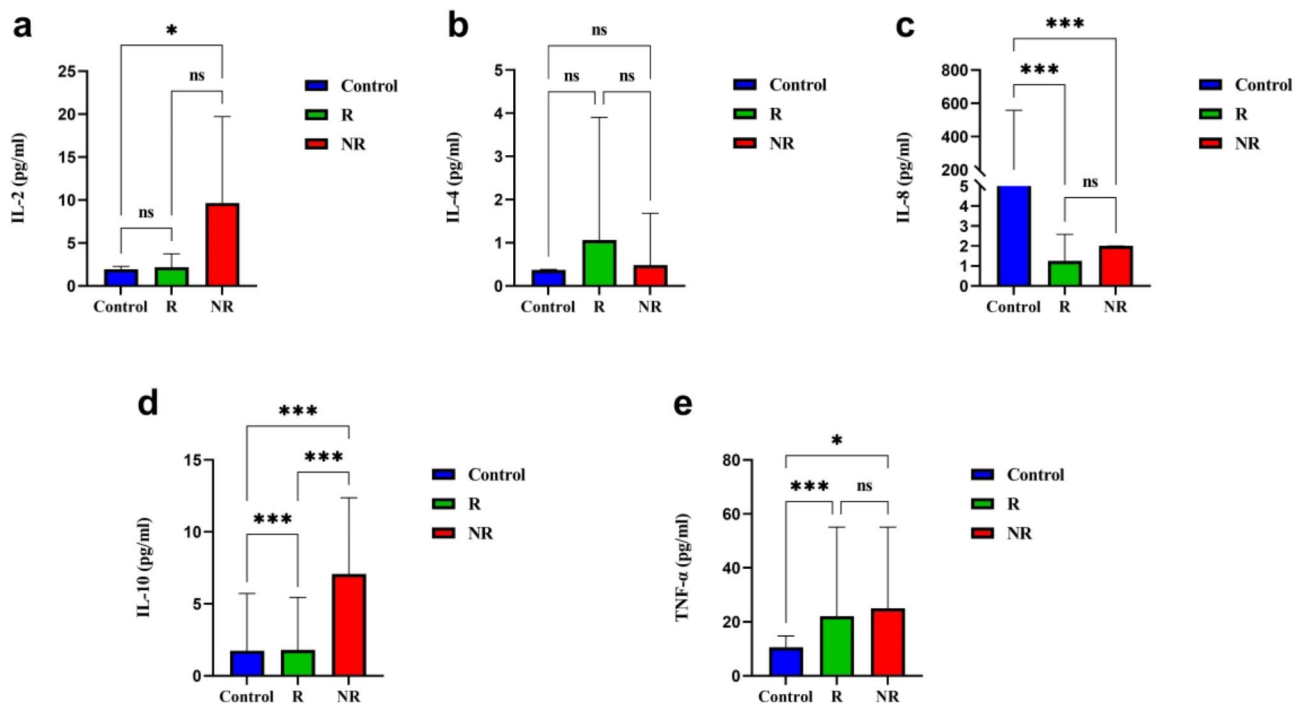


Fig. 4 Comparison of IL-2, IL-4, IL-8, IL-10, and TNF- α in the response and no-response groups of patients with schizophrenia and healthy controls. R: response group; NR: no-response group. *** $P < 0.001$, ** $P < 0.01$, and ^{NS} $P > 0.05$

IL-8 levels were lower than IL-8 levels at baseline in the patient group ($P < 0.001$), whereas serum IL-10 and TNF- α levels were higher in patients treated with olanzapine, compared with their levels at baseline (all $P < 0.05$). Serum IL-10 may be an independent risk factor for treatment outcomes in patients with first-episode schizophrenia ($P = 0.02$, the $OR = 2.327$). Furthermore, serum IL-2, IL-10, and TNF- α levels were significantly lower in the healthy control group than in the response and non-response groups, whereas serum IL-8 levels were significantly higher in the control group than in the response and non-response groups ($P < 0.001$). Trait or state markers were adopted to categorize the involvement of cytokine factors in the etiology of schizophrenia. IL-8, IL-10, and TNF- α can be considered trait markers, while the IL-2, IL-4, and IL-12 may be potential state markers. Of the proposed trait markers, IL-8, IL-10, and TNF- α are associated with major pro-inflammatory functions by triggering inflammatory cascade signaling response. IL-2 activity might be involved in low-grade inflammation response caused by pro-inflammatory cytokines with a homeostatic anti-inflammatory response. Similarly, IL-10 plays a major role in suppressing T-cell activation and communication by reducing the secretion of pro-inflammatory cytokines from macrophages and T-helper-1 lymphocytes. Illness-related factors such as medical comorbidities, acute or chronic state of illness, and antipsychotic treatment may also influence the levels

of IL-2, IL-4, IL-8, IL-10, and TNF- α as compared to subgroups of schizophrenia patients [27–31].

Olanzapine is considered a first-line pharmacological treatment for schizophrenia [18]. However, to date, few studies have explored alterations in inflammatory cytokines levels between response and non-response groups after 6 weeks of olanzapine treatment. Our findings are consistent with the literature that shows antipsychotics, particularly olanzapine, reduce pro-inflammatory cytokine levels, thereby playing a significant role in ameliorating immune dysfunction in schizophrenia patients [32, 33]. Olanzapine's effect on cytokines, such as IL-2, IL-6, and TNF- α , suggests a dual anti-inflammatory and immunomodulatory action. Specifically, IL-2's role in supporting regulatory T cell (Treg) survival and proliferation could be critical in reducing neuroinflammation associated with schizophrenia [34–36]. Furthermore, the decrease in IL-8 and the increase in IL-10 and TNF- α after olanzapine treatment highlights the drug's potential to restore immune balance. Olanzapine's antagonism of dopamine D2 receptors may intersect with cytokine signaling, particularly influencing IL-2 and its effects on dopaminergic pathways [37, 38]. Inflammatory processes that negatively impact neurogenesis, as demonstrated in preclinical studies, might also explain the broader impact of olanzapine on both inflammatory markers and clinical symptoms in schizophrenia [39–41].

The main finding of this study reveals that the levels of several proinflammatory cytokines were decreased after

treatment (a significant decrease in IL-1 β and IFN- γ levels, IL-6 and TNF- α levels were decreased compared to pre-treatment levels), whereas the levels of several anti-inflammatory cytokines were increased after treatment (significant increases in sTNF-R2 and sIL2-R levels). Additionally, in some cases, the kinetics of cytokine levels could be impacted by the diagnosis and/or type of antipsychotic used.

Antipsychotics may exert major anti-inflammatory effects in patients with schizophrenia. Previous research has demonstrated that antipsychotic treatment can reduce the levels of pro-inflammatory cytokines and therefore plays a major role in normalizing the immune dysfunction in patients with schizophrenia [42, 43]. For example, IL-2 has an important function in the anti-inflammatory response due to its capacity to support the survival and proliferation of Treg cells, which can produce multiple anti-inflammatory agents and alleviate neuroinflammation [44, 45], such as in schizophrenia.

A pre-clinical study demonstrated that injecting mice with IL-2 led to a significant change in stereotypical behavior that could be explained by IL-2's effect on the pruning process, resulting in an elimination of dopaminergic synapses and receptors. Since second-generation antipsychotics are dopamine D2 receptor antagonists, this observation can also explain the involvement of IL-2 in the antipsychotic response. This finding was verified in a clinical study by Capuzzi et al. [34] that detected decreased IL-2 levels in patients with schizophrenia after antipsychotic treatment.

Regarding inflammation, a previous pre-clinical study demonstrated increased activity of mesolimbic dopamine (DA) neurons, which are involved in the etiology and antipsychotic response in schizophrenia, in the offspring of rodents exposed to a prenatal inflammatory insult [46]. Further, inflammatory processes have been shown to negatively impact adult neurogenesis and are thus involved in neurodegenerative processes. Moreover, dysregulation of N-methyl D-aspartate receptor agonist downstream products, such as quinolinic acid, has been implicated in the pathophysiology of cognitive deficits in patients with schizophrenia [47]. This can explain the involvement of certain inflammatory factors in the etiology of schizophrenia and antipsychotic treatment response.

GWAS findings have indicated the presence of a close relationship between the immune system and schizophrenia, identifying new therapeutic strategies for the improved treatment of schizophrenia. Researchers have also focused on human umbilical cord-derived mesenchymal stem cells (hUC-MSCs), which have been associated with an immunomodulatory effect [48, 49]. You et al. [48] demonstrated that hUC-MSCs inhibited schizophrenia-relevant and neuroinflammatory changes.

Further, hUC-MSCs were associated with Treg induction and anti-inflammatory cytokine IL-10 production in the periphery and thus with the induction of an anti-inflammatory response. From these considerations, it can be concluded that the effect of antipsychotic treatment is improved by modulating the immune system and producing an anti-inflammatory response.

Besides their effects on inflammatory processes, antipsychotics also exert a major effect on neurotrophic factor-related pathways, leading to modulation of neuronal activity. A randomized controlled trial performed by Jena et al. [49, 50] found an increase in serum BDNF, NGF, and NT3 levels with olanzapine monotherapy. Yang et al. [51] demonstrated that serum neuregulin-1 beta 1 (NRG1 β 1) levels were increased significantly in responders following 4 weeks of antipsychotic treatment, while non-responders showed no such effect. As for patients with an acute term of schizophrenia, there was a statistically significant increase in BDNF after 20 days of treatment [52]. Previous studies have also implicated increased levels of BDNF, NRG1 β 1, NGF, and NT3 in inflammation processes in the pathogenesis and antipsychotic response in schizophrenia. These findings can explain the ability of antipsychotics to limit inflammatory processes by enhancing anti-inflammatory signaling, affecting neurotrophic factor-related pathways, and influencing changes mediated by inflammatory factors [52].

Inconsistencies and differences between our current study and previously published studies can be explained by several factors that may contribute to different results, such as race, disease duration, disease processes, disease severity, and control group selection. Interestingly, TNF- α can be considered a trait marker of schizophrenia [13]. Alterations in cytokine profiles may prominently occur during the early stages of schizophrenia, even before the initiation of antipsychotic treatment. Recent studies have shown significant elevations in TNF- α levels in antipsychotic-naive patients with first-episode psychosis (AN-FEP) [32, 53].

Although a pilot study was conducted to estimate the sample size before the formal start of this study, it is not known whether reductions in plasma inflammatory cytokines are present early in the disease course and in patients with different subtypes and mild to severe symptoms, and whether they are influenced by treatment or disease progression. Thus, in a future studies, large samples of drug-naive patients with first-episode schizophrenia should be considered.

Conclusion

Our current study highlights a correlation between the levels of the cytokines IL-2, IL-8, IL-10, and TNF- α and the severity of schizophrenia. The therapeutic effect of olanzapine in patients can be achieved through

modulation of the immune system to limit the inflammatory response, suggesting that inflammatory cytokine levels should be highly prioritized in the course of schizophrenia. These revelations provide new perspectives for the discovery of therapeutic options in order to improve the treatment of this disorder. In addition, the role of the immune and inflammatory response can further be implicated in understanding the detailed pathogenesis of schizophrenia.

Abbreviations

TNF	αTumor Necrosis Factor-alpha
PANSS	Positive and Negative Syndrome Scale
SD	Standard Deviation
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
BMI	Body mass index
GLU	Blood glucose
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
TG	Triglyceride
TC	Total cholesterol
SPSS	Statistical Package for the Social Sciences
DA	Dopamine
NRG1β1	Neuregulin-1 beta 1
AN-FEP	Antipsychotic-naïve patients with first episode psychosis

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12888-024-06163-7>.

Supplementary Material 1

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Author contributions

XZ reviewed literature, designed the study, drafted the original manuscript, provided financial support and was responsible for the supervision and coordination of research as a whole. WZ recruited subjects, collected clinical data, evaluated scale, was responsible for the supervision and coordination of research as a whole and provided financial support. YB recruited subjects, collected clinical data, evaluated scale, and did preliminary data analysis. JL and YB assisted in clinical data acquisition. YH Provide experimental equipment, technology and financial support. All the authors reviewed the various drafts of the manuscript and have approved the final version of the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files. Raw data supporting the obtained results are available at the corresponding author.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all the participants and their legal guardians. The present study was approved by the Institutional Review Board of Ethical Committee of the Fourth People's Hospital of Wuhu City (Approval No. [2020]—KY—17).

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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