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ORIGINAL PAPER

The relationship between inflammatory markers, clinical characteristics, and cognitive performance in drug-naïve patients with schizophrenia

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Abstract

Increasing evidence implicates that inflammatory factors do play a crucial role in the pathophysiology of schizophrenia. However, the association between inflammatory markers and different symptom dimensions and cognitive function of schizophrenia remains unclear. A total of 140 drug-naïve patients with schizophrenia and 69 healthy controls matched for age and gender were enrolled. Peripheral blood plasma concentrations of S-100 calcium-binding protein B (S100B), neutrophil gelatinase-associated lipocalin (NGAL), and interferon-γ (IFN-γ) were detected by enzyme-linked immunosorbent assay (ELISA). Psychotic symptoms were measured using the Positive and Negative Syndrome Scale (PANSS), and cognitive function was assessed by the MATRICS Consensus Cognitive Battery (MCCB). Compared with healthy controls, patients with schizophrenia had significantly worse cognitive function and lower levels of NGAL and IFN-γ ($P < 0.001$). In schizophrenia, plasma NGAL and IFN-γ levels negatively correlated with positive symptom scores (all $P < 0.05$). There was a positive correlation between plasma levels of NGAL and IFN-γ with visual learning, neurocognition, and MCCB total score (all $P < 0.05$). We found that NGAL levels ($\beta = 0.352$, $t = 5.553$, 95% CI 0.228–0.477, $P < 0.001$) and negative symptoms subscale scores ($\beta = -0.321$, OR = 0.725, 95% CI 648–0.811, $P < 0.001$) were independently associated with the MCCB total score. Further, binary logistic regression analysis indicated that the concentrations of NGAL ($\beta = -0.246$, OR = 0.782, 95% CI 0.651–0.939, $P = 0.008$) were independently associated with the diagnosis of schizophrenia. There was a positive correlation between NGAL and IFN-γ levels and MCCB total score in schizophrenia. NGAL level was an independent protective factor for cognitive function and an independent risk factor for the diagnosis of schizophrenia.

Keywords NGAL · S100B · IFN-γ · Inflammatory marker · Schizophrenia · Drug naïve · Cognition

Introduction

Schizophrenia is a high-burden psychiatric disorder with abnormal levels of inflammation [1, 2]. As early as a century ago, Alexander Rosenblum proposed the hypothesis of an association between mental illness and the immune system. In recent years, substantial evidence has supported the role of the immune system in the pathogenesis of depression and schizophrenia [3–5]. It is mainly involved in the activation and aggregation of microglia, cytokine expression imbalance, and astrocyte changes [6]. Moreover, epidemiological studies have found that maternal pregnancy infections and childhood autoimmune diseases may be risk factors for schizophrenia [7].

Clinical trials of anti-inflammatory drugs for schizophrenia and the anti-inflammatory effects of antipsychotic medications have demonstrated a strong relationship between schizophrenia and inflammation from a pharmacological perspective [8, 9]. Earlier studies have shown that patients with schizophrenia can achieve clinical improvement from anti-inflammatory treatment, especially in subgroups with elevated levels of inflammation [10]. This finding stimulated in-depth studies to explore the use of inflammatory markers to assess the clinical severity and efficacy of schizophrenia. The current findings suggest that inflammatory markers

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influence the development of schizophrenia, but the results of studies on the relationship between inflammatory markers and schizophrenia are inconsistent [11]. The reasons for this inconsistency may be the relatively small sample size, the duration of schizophrenia, and the choice of inflammatory indicators.

NGAL has been associated with various psychiatric disorders, including schizophrenia, obsessive–compulsive disorder (OCD), depression, and Alzheimer's disease [12–14]. The formation of diverse tissue types, embryonic development, apoptosis, inflammatory immunological responses, and lipid metabolism are all impacted by NGAL. Breast cancer, esophageal cancer, and other tumor cells may proliferate as a result [12–14]. And only one study of NGAL and schizophrenia is currently available, indicating significantly higher levels of NGAL in patients with schizophrenia [15]. So, it is worth exploring the role of NGAL in the development of schizophrenia. Interferon-γ (IFN-γ) is a nonspecific inflammatory marker, and its potential pathogenic role in schizophrenia has been extensively studied [16]. There may be a correlation between IFN-γ and response to medication and cognitive function in patients with schizophrenia [17, 18]. Current findings are fraught with conflicting results due to subject sampling differences and the effects of antipsychotic medications [19, 20]. For example, a recent meta-analysis showed no significant difference in IFN-γ levels between schizophrenic patients and healthy controls [21]. S100B is a Ca2+-binding protein secreted by glial cells [22]. The activation of microglial production of COX-2 and iNOS by increased S100B release, which is mediated by astrocytes and oligodendrocytes, may result in neuroinflammatory processes and cause neuronal dysfunction and apoptosis [23]. S100B expression was linked to immune checkpoint genes, chemokines/chemokine receptors, and the invasion of many immune cells in tumors. Additionally, immune cells, particularly NK (Natural Killer) cells, are the main hosts of S100B expression [24]. It has been gradually investigated in schizophrenia and depression [25]. Studies have found elevated levels of S100B in plasma and cerebrospinal fluid during acute psychotic episodes in schizophrenia [26, 27], which positively correlated with negative symptoms [28].

Previous studies have provided preliminary insight into the changes in the levels of NGAL, IFN-γ, and S100B in schizophrenic patients, but few studies have examined the associations between inflammation markers and psychiatric symptoms or cognition in schizophrenia. The objectives of this study were: (1) to explore the differences between NGAL, IFN-γ, and S100B levels in patients with schizophrenia compared to healthy controls; (2) to analyze the relationship between NGAL, IFN-γ, and S100B and clinical symptoms; and (3) to explore the association between NGAL, IFN-γ, and S100B levels and cognitive function in schizophrenia.

Methods

Subjects

In this case–control study, 140 patients with schizophrenia were recruited from Tianjin Anding Hospital. The patients in this study met the following inclusion criteria: (1) aged from 18 to 65 years; (2) met the criteria of DSM-5 for schizophrenia or schizophreniform disorder by two experienced psychiatrists; (3) illness duration ≤ 5 years; (4) never received antipsychotics treatment. Exclusion criteria included: (1) patients who met the diagnosis of DSM-5 except for schizophrenia or schizophreniform disorder; (2) patients with combined severe and unstable physical diseases, especially a history of immune system-related diseases or immunotherapy; (3) patients who received physical intervention of mental symptoms, such as repetitive transcranial magnetic stimulation or modified electroconvulsive therapy; (4) pregnant and lactating women.

Sex- and age-matched healthy controls were recruited from the local community through advertising. Participants were also excluded if they had a personal or family history of mental disorders.

This study complied with the basic principles of the Helsinki Declaration, and the investigation and sampling were examined and approved by Tianjin Anding Hospital Ethics Committee (approval number: 2017-03). All participants provided written informed consent.

Clinical and cognitive assessments

The Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of psychotic symptoms [29]. The Chinese version of MATRICS Consensus Cognitive Battery (MCCB) was used to assess cognitive function, including seven dimensions: speed of processing, attention, vigilance, working memory, verbal learning, visual learning, reasoning and problem-solving, and social cognition. The reliability and validity of the Chinese version of MCCB have been confirmed [30]. To ensure consistency and reliability, each evaluator attended training in using PANSS and MCCB. After training, repeated assessment showed that the inter-rater correlation coefficient [31] was more significant than 0.8.

Laboratory measurements

Venous blood (5 ml) was collected from subjects in a fasting state on the day of enrollment. All blood samples were centrifuged at 1000*g* for 15 min at 4 °C, and the plasma was frozen at − 80 °C until detection. Plasma

concentrations of S100B, NGAL, and IFN-γ were detected by enzyme-linked immunosorbent assay (all kits were purchased from MEIMIAN Biotechnology, Jiangsu, China) according to the manufacturer's instructions. The intra- and inter-assay coefficients of variation were less than 5%.

Statistical analysis

All statistical analyses were conducted using IBM SPSS 25.0. The data were examined for normal distribution with the Kolmogorov–Smirnov test. The levels of S100B, NGAL, and IFN-γ showed approximately normal distribution. Comparison of differences between groups in demographic characteristics, clinical symptoms, and cognitive function was performed using the Chi-square (χ^2) test for categorical variables and *t* test for continuous data. Because BMI has an effect on all inflammatory indicators, we further used analysis of covariance (ANCOVA) to explore the differences in biomarkers between the two groups. Pearson correlation analysis was used to assess the correlations between the inflammatory biomarkers, PANSS scales, and the nine domains of MCCB. Due to multiple tests, Bonferroni corrections were applied to prevent possible Type I errors.

Further, the influences of general profiles and clinical variables on cognitive function were evaluated using multiple linear regression analyses. Taking the MCCB total score as the dependent variable, the multiple linear regression model was selected for the following variables: PANSS negative symptoms subscale scores, PANSS general psychopathological subscale scores, NGAL, and IFN-γ as independent variables that showed significance after correlation analysis. Then binary logistic regression was used to identify the independent factors (education, BMI, NGAL, and IFN-γ) associated with the diagnosis of schizophrenia. All *P* values were set at a two-tailed significance level of < 0.05.

Results

Demographic, clinical characteristics, and cognitive function of patients with schizophrenia and healthy control

As shown in Table 1, patients with schizophrenia had significantly lower education levels and BMI than healthy control (all $P < 0.01$). Moreover, there were significant differences in all MCCB domain scores and total scores between patients with schizophrenia and the healthy control group (all $P < 0.001$).

Inflammatory factors of patients with schizophrenia and healthy control

Plasma S100B, NGAL, and IFN-γ levels in schizophrenia patients and the healthy controls are shown in Fig. 1. S100B levels in patients with schizophrenia were not significantly different from those in healthy controls (Fig. 1A). We found that NGAL and IFN-γ levels were significantly lower in patients with schizophrenia than in the healthy controls (Fig. 1B, C). After controlling for BMI, these significances were still found in NGAL and IFN-γ (all $P < 0.01$). Moreover, these differences remained significant after the Bonferroni correction (all $P < 0.01$).

Correlation between inflammatory biomarkers, clinical symptoms, and cognitive function

As shown in Table 2, Pearson correlation analysis showed that NGAL was negatively correlated with the positive symptoms score, general psychopathological symptoms score, and total score of PANSS in schizophrenia. Additionally, the IFN-γ has a negative relationship with positive symptoms score and general psychopathological symptoms score.

Furthermore, there were significant positive correlations between NGAL and working memory, visual learning, neurocognition, and MCCB total scores. The IFN-γ has a significant positive correlation with the following parameters: visual learning, neurocognition, and MCCB total score.

Multiple linear regression further analyzed the factors influencing cognitive function in schizophrenia (Table 3). We found that NGAL levels ($\beta = 0.352$, $t = 5.553$, 95% CI 0.228–0.477, $P < 0.001$) and negative symptoms subscale scores ($\beta = -0.321$, $t = -5.633$, 95% CI −0.433 to −0.209, $P < 0.001$) were independently associated with the MCCB total score.

Binary logistics regression in subjects with or without schizophrenia

The stepwise binary logistic regression was performed to analyze the risk factors for schizophrenia. The diagnosis (with or without schizophrenia) was a dependent variable, and independent variables included education, BMI, and the concentrations of NGAL and IFN-γ. The results in Table 4 showed that the NGAL ($\beta = -0.246$, OR = 0.782, 95% CI 0.651–0.939, $P = 0.008$) and IFN-γ ($\beta = 0.007$, OR = 1.007, 95% CI 1.004–1.011, $P < 0.001$) were independently associated with the diagnosis.

Diagnostic accuracy of the plasma NGAL was assessed by receiver operating characteristic (ROC) curve analysis. The ROC curve analysis revealed that the area under the curve (AUC) was 0.755 (95% CI 0.688–0.822; $P < 0.0001$)

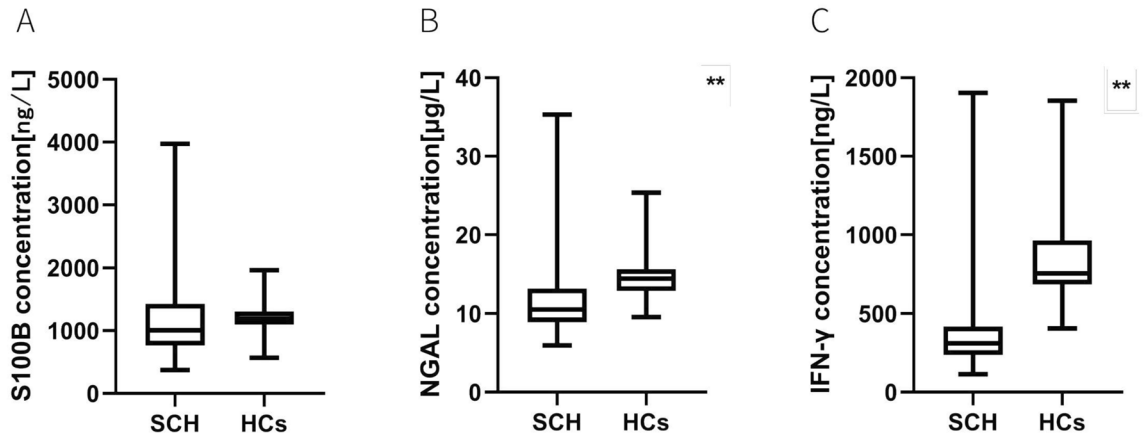
Table 1 Demographics, clinical characteristics, and cognitive function

	Schizophrenia ($n=140$)	Healthy control ($n=69$)	$t/\chi^2/Z$	P value
Gender, M/F	51/89	31/38	0.961	0.327
Age (years)	36.09 ± 10.24	36.19 ± 8.92	− 0.218	0.828
Education (years)	12.41 ± 3.38	13.54 ± 4.01	− 3.067	**0.002**
Smoking	29(20.71%)	17(24.64%)	0.420	0.810
BMI (kg/m^2)	22.48 ± 3.76	24.43 ± 4.14	− 3.203	**0.001**
Age of onset (years)	32.31 ± 9.73	NA	NA	NA
Duration of untreated illness (months)	47.28 ± 63.51	NA	NA	NA
PANSS score				
P subscale scores	26.77 ± 5.27	NA	NA	NA
N subscale scores	20.34 ± 6.24	NA	NA	NA
G subscale scores	43.02 ± 7.59	NA	NA	NA
Total scores	90.55 ± 14.80	NA	NA	NA
MCCB score				
Speed of processing	31.81 ± 12.48	51.03 ± 10.32	− 11.06	**< 0.001**
Attention/vigilance	35.07 ± 11.46	48.43 ± 10.72	− 8.10	**< 0.001**
Working memory	37.31 ± 10.35	45.03 ± 10.97	− 4.97	**< 0.001**
Verbal learning	35.85 ± 11.81	44.28 ± 8.85	− 5.24	**< 0.001**
Visual learning	38.64 ± 12.41	48.32 ± 11.31	− 5.46	**< 0.001**
Reason and problem-solving	38.61 ± 10.41	54.16 ± 10.48	− 10.13	**< 0.001**
Social cognition	30.25 ± 7.85	35.42 ± 8.01	− 4.45	**< 0.001**
Neurocognition	29.41 ± 11.34	47.81 ± 10.95	− 11.16	**< 0.001**
MCCB total score	26.41 ± 11.04	44.61 ± 10.45	− 11.4	**< 0.001**

Data are given as mean ± SD

BMI body mass index, BMI = kg/m^2, *PANSS* Positive and Negative Syndrome Scale, *P subscale* PANSS positive symptoms subscale, *N subscale* PANSS negative symptoms subscale, *G subscale* PANSS general psychopathological symptoms subscale, *MCCB* MATRICS Consensus Cognitive Battery

Bold values indicate statistically significant ($P<0.05$)



Abbreviations: S100B, S-100 calcium-binding protein B. NGAL, neutrophil gelatinase-associated lipocalin. IFN-γ, interferon-γ. SCH, Schizophrenia. HCs, healthy controls.

Fig. 1 Comparison of serum S100B (**A**), NGAL (**B**), and IFN-γ (**C**) concentration between drug-naïve patients with schizophrenia and healthy controls. *S100B* S-100 calcium-binding protein B, *NGAL* neutrophil gelatinase-associated lipocalin, *IFN-γ* interferon-γ, *SCH* schizophrenia, *HCs* healthy controls

Table 2 Correlation analysis between serum levels of protein factors and clinical characteristics in subjects

	Schizophrenia ($n=140$)						Healthy control ($n=69$)					
	S100B		NGAL		IFN-γ		S100B		NGAL		IFN-γ	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
PANSS score												
P subscale scores	−0.151	0.079	−0.199	**0.017**	−0.187	**0.026**	NA	NA	NA	NA	NA	NA
N subscale scores	0.067	0.437	0.016	0.852	0.014	0.871	NA	NA	NA	NA	NA	NA
G subscale scores	−0.135	0.118	−0.210	**0.012**	−0.184	**0.028**	NA	NA	NA	NA	NA	NA
Total scores	−0.103	0.235	−0.177	**0.034**	−0.160	0.056	NA	NA	NA	NA	NA	NA
MCCB score												
Speed of processing	−0.010	0.906	0.127	0.132	0.065	0.442	−0.111	0.479	−0.019	0.905	0.064	0.684
Attention/vigilance	0.024	0.792	0.162	0.062	0.067	0.440	0.116	0.458	0.132	0.397	0.065	0.679
Working memory	0.047	0.590	0.214	**0.011**	0.134	0.113	−0.216	0.164	−0.137	0.381	0.211	0.175
Verbal learning	0.025	0.769	0.152	0.071	0.138	0.101	−0.264	0.087	−0.150	0.337	0.041	0.793
Visual learning	0.122	0.160	0.236	**0.005**	0.170	**0.044**	−0.011	0.943	0.045	0.772	0.045	0.777
Reason and problem-solving	−0.029	0.740	0.103	0.220	0.033	0.699	−0.107	0.493	0.080	0.610	0.285	0.064
Social cognition	−0.037	0.671	0.050	0.556	0.093	0.274	−2.04	0.120	−0.119	0.447	0.258	0.095
Neurocognition	0.049	0.588	0.246	**0.004**	0.189	**0.030**	−0.18	0.249	−0.031	0.841	0.217	0.162
MCCB total score	0.048	0.594	0.245	**0.004**	0.175	**0.043**	−1.34	0.393	0.001	0.994	0.180	0.249

S100B S-100 calcium-binding protein B, *NGAL* neutrophil gelatinase-associated lipocalin, *IFN-γ* interferon-γ, *PANSS* Positive and Negative Syndrome Scale, *P subscale* PANSS positive symptoms subscale, *N subscale* PANSS negative symptoms subscale, *G subscale* PANSS general psychopathological symptoms subscale, *MCCB* MATRICS Consensus Cognitive Battery, *NA* not appliances

Bold values indicate statistically significant ($P<0.05$)

Table 3 Multiple linear regression analysis of influencing factors of cognitive function in patients with drug-naïve schizophrenia

Model		Unstandardized coefficient		Standardized coefficient	*t*	*P*	95% confidence interval for *B*	
		B	Standard Error	Beta			Lower	Upper
MCCB total score	Constant	35.717	2.151		16.608	**< 0.001**	31.496	39.938
	NGAL	0.352	0.063	0.280	5.553	**< 0.001**	0.228	0.477
	IFN-γ	0.000	0.001	−0.014	−0.274	0.784	−0.001	0.001
	N scores	−0.321	0.057	−0.199	−5.633	**< 0.001**	−0.433	−0.209
	G scores	0.079	0.048	0.060	1.644	0.101	−0.015	0.172

NGAL neutrophil gelatinase-associated lipocalin, *IFN-γ* interferon-γ, *MCCB* MATRICS Consensus Cognitive Battery, *N scores* PANSS negative symptoms subscale scores, *G scores* PANSS general psychopathological symptoms subscale scores

Bold values indicate statistically significant ($P<0.05$)

Table 4 Binary logistic regression analysis for variables related to the diagnosis of schizophrenia

Variables	*B*	Standard error	Wald	*P*	Exp (*B*)	95% confidence interval for Exp (*B*)	
						Lower	Upper
Constant	−5.668	1.850	9.383	0.002			
NGAL	−0.246	0.093	6.942	**0.008**	0.782	0.651	0.939
IFN-γ	0.007	0.002	21.575	**< 0.001**	1.007	1.004	1.011
BMI	0.100	0.058	2.972	0.085	1.106	0.986	1.239
Education (years)	0.095	0.066	2.060	0.151	1.100	0.966	1.253

NGAL neutrophil gelatinase-associated lipocalin, *IFN-γ* interferon-γ, *BMI* body mass index

Bold values indicate statistically significant ($P<0.05$)

(Fig. 2) when assessing the diagnostic accuracy of the plasma NGAL concentration of comparison between patients with schizophrenia and healthy controls. The sensitivity and specificity of NGAL for the diagnosis of schizophrenia were 98.6% and 36.2%, respectively, when using 24.83 μg/ml as the cutoff value for the plasma NGAL concentration (Fig. 2).

Discussion

To our knowledge, this is the first study to investigate the relationship between the inflammatory markers S100B, NGAL, and IFN-γ and clinical symptoms and cognitive function in drug-naïve schizophrenia. The main findings of our study were as follows. (1) Patients with schizophrenia had significantly lower cognitive function, NGAL, and IFN-γ levels compared to the healthy controls. (2) In schizophrenia patients, the NGAL and IFN-γ levels were negatively correlated with the positive symptoms and general psychopathological symptoms. Besides, the plasma level of NGAL negatively correlated with PANSS total scores. The plasma level of NGAL and IFN-γ significantly positively correlated with visual learning, neurocognition, and MCCB total score. There was a significant positive relationship between plasma NGAL and working memory. (3) The NGAL level was an independent protective factor for cognitive function, whereas the negative symptom score was an independent risk factor for cognitive function in schizophrenia. (4) The NGAL level and IFN-γ were independent risks for the diagnosis of schizophrenia.

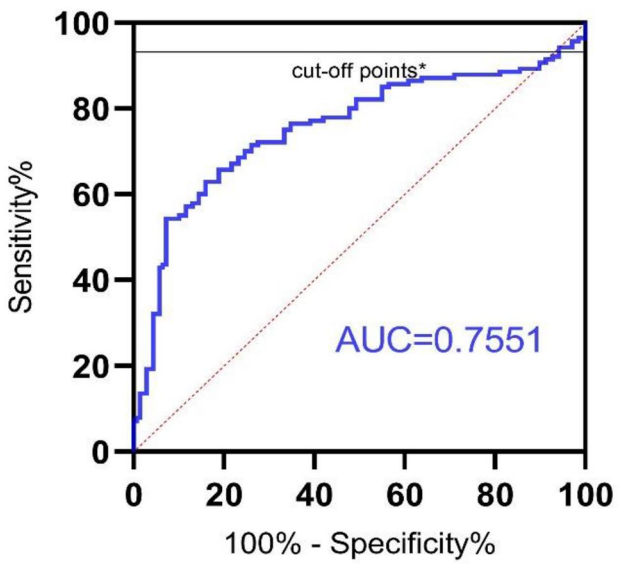


Fig. 2 The receiver-operator characteristic (ROC) curve for level of plasma NGAL in schizophrenia patients and healthy controls (AUC, area under the curve). The area under the curve (AUC) was 0.755 (95% confidence interval, 0.688–0.822; $P<0.0001$). When using 24.84 μg/L as the cutoff value for the plasma NGAL concentration, the sensitivity and specificity of NGAL for the diagnosis of schizophrenia were 98.6% and 43.2%, respectively

The changes of inflammatory factors in schizophrenia

We found the plasma levels of S100B in patients with schizophrenia were higher than those in the healthy controls, but it was not statistically significant. The result trend is consistent with previous studies that reported higher S100B levels in patients with schizophrenia compared with healthy controls [25, 32–35]. For instance, in a review article on S100B and schizophrenia, higher serum S100B concentrations were found in schizophrenia patients than in healthy controls [25], and most showed an increase in S100B during the acute stages of the disease. This negative finding may be explained by the fact that the age of onset or duration of untreated illness of the samples recruited in our study differed from previous studies [25, 32–35]. What is more, Liu et al. had put forward that looking for biomarkers in blood may be greatly influenced by the choice of sample material [36]. Therefore, it is possible that differences in the test specimens may also account for the inconsistency of our results with previous ones.

The role of NGAL in kidney injury has been repeatedly confirmed [37–39], and the researchers focused on animals and humans additionally pointed out that the level of NGAL can reflect brain injury [40]. Previous studies have focused on the effects of NGAL on psychiatric disorders, including late-life depression, Alzheimer's disease, and OCD [41–43]. Our study found that NGAL levels were significantly lower in schizophrenia patients than in healthy controls, which was inconsistent with previous studies [44, 45]. This inconsistency may be related to the different characteristics of the enrolled subjects. In our study, only patients with drug-naive schizophrenia were selected. In addition, previous studies measured serum [45], whereas we measured plasma NGAL levels. Finally, differences in ethnicity may play an important role in this inconsistent outcome [45].

After controlling for confounding factors, we found that IFN-γ levels were lower in schizophrenia patients compared with healthy controls. Although there is still some uncertainty about the trend of interferon levels in patients with schizophrenia [18, 19, 46], our findings are still supported by some evidence [16]. A meta-analysis of 21 studies published in 2015 found that patients with schizophrenia had lower IFN- γ than healthy controls [47]. However, a meta-analysis study conducted in the UK on the inflammatory characteristics of schizophrenia pointed out that there was no significant difference in IFN-γ between schizophrenic patients and healthy controls [21]. Moreover, other meta-analysis results show no significant

difference between the two groups [20]. These inconsistencies suggest that changes in IFN-γ levels warrant further study.

Inflammatory factors and clinical symptoms in schizophrenia

Our study was the first to report that NGAL and IFN-γ concentrations were negatively associated with psychotic symptoms. However, studies of other biological indicators (CRP, TNF-α, and IL-6) have shown a modest correlation between inflammatory factors and symptom severity in schizophrenia [48–50]. The relationship between NGAL and IFN-γ and schizophrenia has remained unclear. The homolog of NGAL in mice is known as lipocalin 2 (Lcn2). An animal study found that Lcn2-deficient mice exhibited increased anxiety and depression-like behaviors [51]. In addition, previous studies explored the correlation between NGAL and symptom severity in patients with depression and OCD [52, 53]. These findings suggest that psychiatric disorders are associated with NGAL [54]. Furthermore, the main finding of our study was that low levels of NGAL were an independent risk factor for schizophrenia. This finding demonstrates that NGAL may be a potential biomarker for schizophrenia.

A systematic review with meta-analysis found elevated levels of IFN-γ in patients with first-episode unmedicated schizophrenia compared to healthy controls [55]. However, some studies have also found that IFN-γ levels were not higher in patients with schizophrenia than in healthy controls [16]. Our current study firstly found that IFN-γ was independently associated with the diagnosis of schizophrenia. Chronic subclinical inflammation is thought to be one of the factors involved in the pathogenesis of the disease [56]. IFN-γ has been found to be associated with disruption of the integrity of white matter microstructures in various brain regions, particularly corpus callosum region 2 [57].

We found no significant correlation between the plasma level of S100B and clinical symptoms in schizophrenia. The results are consistent with prior studies' findings [35, 58]. However, Hong et al. found that S100B concentrations were higher in patients with schizophrenia than in healthy controls and negatively correlated with symptom severity [23]. In addition, one study found that negative symptoms were positively associated with S100B in patients with schizophrenia [59]. There are several reasons for this inconsistency. First, the sample size of the study by Hong et al. was too small; it recruited only 41 patients with schizophrenia and 33 healthy controls [23]. Second, the ethnicity and stage of the disease also lead to different results [59]. Finally, the heterogeneity of S100B is greater than 70%, which can bring inconsistent results in the studies [60].

Inflammatory factors, clinical symptoms, and cognitive function in schizophrenia

The main finding of the current study was that plasma NGAL and IFN-γ levels were positively associated with visual learning, neurocognition, and the MCCB total scores in drug-naïve schizophrenia. Recent studies have found that cognitive function is associated with inflammatory factors in schizophrenia [61]. Unfortunately, there are fewer studies on NGAL and IFN-γ and cognitive functioning in schizophrenia. A prospective cohort study found a significant negative effect of IFN-γ on TMT-A and symbolic coding performance [62]. NGAL and cognitive function studies have only been seen in Alzheimer's disease and late-life depression [13, 63]. For example, one study found that NGAL was associated with cognitive decline in late-life depression [63]. Interestingly, we found that NGAL levels were an independent protective factor for cognitive function in schizophrenia. Further studies are still needed to explore the relationship between NGAL and IFN-γ and cognitive function in schizophrenia.

Numerous studies have examined the relationship between clinical symptoms and cognitive functioning in schizophrenia [64–66]. We found that negative symptoms can impair cognitive function in patients with schizophrenia. This result is consistent with the results of previous studies [41, 42]. For instance, a recent study found that episodic memory was negatively associated with negative symptoms of schizophrenia [41]. Studies have found that disrupted white matter microstructure in schizophrenia leads to negative symptoms and social cognitive dysfunction [43]. However, the relationship between inflammatory factors and clinical symptoms and cognitive function in schizophrenia has been studied extensively [44, 55, 67, 68]. The relationship between them has still not been elucidated. Therefore, further studies are urgently needed to analyze the relationship between inflammatory factors and clinical symptoms and the cognitive function of schizophrenia.

It is well known that cognitive impairment in schizophrenia is primary and does not arise on the basis of positive or negative symptoms [69]. Therefore, cognitive function in schizophrenia is independent of psychotic symptoms [70]. For example, some studies found no significant correlation between cognitive impairment and positive and negative symptoms in patients with schizophrenia [71]. Tamminga found that cognitive impairment in schizophrenia was independent of psychotic symptoms [72]. There are also inconsistent studies. Verbraak found that cognitive impairment was only associated with negative symptoms [73]. In addition, Addington found that improvement in cognitive impairment was only associated with improvement in positive symptoms, but not with negative symptoms [74]. We found that NGAL and IFN-γ were negatively correlated with psychotic symptoms,

while positively correlated with cognitive functions. Our findings may illustrate the independent relationship between cognition and psychotic symptoms from the perspective of inflammatory factors.

Several limitations of our study need to be noted. First, our cross-sectional study found a relationship between inflammatory markers and clinical symptoms and cognitive function in patients with schizophrenia, but could not prove a causal relationship. In addition, longitudinal studies are needed to determine the dynamic relationship. Second, the levels of inflammatory factors are influenced by many confounding factors. However, only a few factors, such as BMI, were considered in the present study. Our study did not include oxidative stress factors, glucose, and lipid metabolism. Third, patients with schizophrenia in our sample had a lower BMI than healthy controls. Possible reasons are that the patients had not used antipsychotic drugs before and were relatively young. Fourth, only 140 patients with schizophrenia and 69 healthy controls were recruited in our study. The small sample size may increase the likelihood of Type II error. Fifth, we recruited only unmedicated schizophrenic patients. Therefore, caution should be exercised when using our conclusions. Finally, we excluded substance use disorders, which have a high co-morbidity rate with schizophrenia. Therefore, it might be difficult to generalize the findings over the whole population of patients with schizophrenia.

In conclusion, our findings suggested the NGAL and IFN-γ levels were negatively correlated with positive symptoms. In addition, the NGAL and IFN-γ levels had significant positive correlations with the total MCCB score. The NGAL level was an independent protective factor for cognitive function. Finally, the NGAL levels were an independent risk for schizophrenia. These results add to the literature on the relationship between inflammatory factors and clinical symptoms and cognitive function in schizophrenia. In clinical work, these indicators can be used as potential biological indicators of psychiatric symptoms, cognitive function, and the diagnosis of schizophrenia.

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Author contributions XS, GL, and JL were responsible for the study concept and design, drafting of the manuscript, and study supervision. XS, GL, and XL collected data and prepared the initial draft of the manuscript. YQ and ML were involved in evolving the ideas and editing the manuscript. XS and JW were responsible for recruiting the patients, performing the clinical rating, and collecting the samples. All authors contributed to and approved the final manuscript.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors declare no conflict of interest.

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