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ORIGINAL ARTICLE

PSPH and CXCL2 Predict Treatment Response in First-Episode Schizophrenia: a Retrospective Study

Jingjing Zheng

Department of Psychiatry, Hengshui Seventh People's Hospital, Hebei Hengshui, China

SUMMARY

Background: **The aim was to evaluate serum levels of Phosphoserine Phosphatase (PSPH) and Chemokine C-X-C Motif Ligand 2 (CXCL2) as biomarkers for predicting antipsychotic treatment response in male first-episode schizophrenia patients.**

Methods: **Bioinformatics analysis identified upregulated PSPH and CXCL2 expression in PBMCs of schizophrenia patients. Clinical data from 297 male patients (treated with olanzapine from 2019 to 2024) were retrospectively analyzed. After 4 weeks, patients were categorized into improvement (n = 118) and non-improvement (n = 179) groups. Serum PSPH and CXCL2 levels were measured by ELISA. Predictive value was assessed via ROC and multivariate logistic regression.**

Results: **The non-improvement group had higher PSPH/CXCL2 levels. Both biomarkers correlated positively with PANSS scores (r = 0.249, 0.335; p < 0.001). Logistic regression confirmed PSPH/CXCL2 levels, pre-treatment PANSS, shorter disease duration, and younger age as independent predictors (p < 0.05). Combined PSPH/CXCL2 showed superior predictive performance (AUC = 0.823, p < 0.05).**

Conclusions: **Serum levels of PSPH and CXCL2 can be considered as potential biomarkers for predicting the efficacy of antipsychotic treatment in male patients with first-episode schizophrenia.**

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Correspondence:
Jingjing Zheng
Department of Psychiatry
Hengshui Seventh People's Hospital
Hengshui, Hebei
China
Email: Jingjing_Zheng26@163.com

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KEYWORDS

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INTRODUCTION

Schizophrenia is a prominent mental disorder characterized by the occurrence of positive symptoms, encompassing phenomena such as hallucinations and delusions, along with negative symptoms, which manifest as emotional blunting and a tendency toward social withdrawal. It affects approximately 1% of the global population and ranks among the top ten causes of disability worldwide [1,2]. Despite the availability of various antipsychotic medications, many patients exhibit poor treatment responses, experience adverse effects, and face a risk of relapse [3-5]. Therefore, exploring more effective treatment approaches and biomarkers holds significant importance for improving patient outcomes.

Inflammatory responses are considered a crucial aspect in the pathogenesis of schizophrenia [6,7]. Phosphoserine phosphatase (PSPH), a key enzyme involved in the phosphorylation process, plays a vital role in cellular metabolism and signal transduction. It is essential for the targeted regulation of immune responses, cell proliferation, and lipid/protein metabolism [8,9]. In neural cells, alterations in PSPH activity may affect the synthesis and metabolism of neurotransmitters, thereby interfering with the normal transmission of neural signals [10]. Additionally, cellular experimental studies have revealed changes in the gene expression profile of PSPH in CNON cells between schizophrenia patients and healthy controls, suggesting that PSPH may influence the function of the serine biosynthesis pathway and subsequently impact neurodevelopment and the onset of schizophrenia [11]. Chemokine C-X-C Motif Ligand 2 (CXCL2), a member of the C-X-C chemokine subfamily, serves as a potent neutrophil chemoattractant. Its primary biological function is to recruit and activate neutrophils at sites of inflammation and infection, extensively participating in the development of various acute and chronic inflammatory diseases as well as cancers [12]. Bioinformatics studies have indicated that CXCL2 is one of the core genes influencing schizophrenia [13]. However, evidence regarding whether serum levels of PSPH and CXCL2 are associated with the efficacy of drug treatment in schizophrenia patients remains lacking.

The objective of this research is to explore the significance of serum concentrations of PSPH and CXCL2 as potential biomarkers for forecasting the effectiveness of pharmacological interventions in male individuals experiencing their first episode of schizophrenia. Through bioinformatics analysis and clinical sample testing, we aim to elucidate the roles of PSPH and CXCL2 in treatment response to schizophrenia and provide new references for clinical practice.

MATERIALS AND METHODS

Bioinformatics analysis

The schizophrenia-related microarray dataset GSE273 83 was selected from the GEO database (https://www.ncbi.nlm.nih.gov) for analysis. This dataset documented the differentially expressed genes in the peripheral blood of male schizophrenia patients and healthy controls. The limma package was employed for differential expression analysis, with a fold-change threshold set at 1.2. During the data preprocessing stage, the normalizeBetweenArrays function was utilized to standardize the expression values across samples. To facilitate visualization, the ggplot2 package was employed to create both volcano plots and boxplots. The statistical test method employed for the boxplots was the *t*-test.

Study subjects

Based on previous research findings indicating a response rate of 40.00% for olanzapine in the treatment of first-episode schizophrenia [14] and setting an error margin not exceeding 5% (i.e., the difference between the upper and lower limits of the confidence interval being 10%), a sample size of at least 278 was calculated using PASS15.0 software with a significance level of $1-\alpha = 0.9$ (two-tailed test) to ensure the scientific rigor of the study design.

A retrospective analysis was performed on the clinical records of 297 male individuals diagnosed with first-episode schizophrenia, all of whom underwent treatment at our facility from June 2019 to June 2024.

Inclusion Criteria: 1) Meeting the diagnostic criteria for schizophrenia as outlined in the 11th edition of the International Classification of Diseases [15]; 2) Having a disease duration $\leq$ 40 months; 3) Being first-episode and having never received any form of antipsychotic medication previously; 4) Scoring $\geq$ 60 on the Positive and Negative Syndrome Scale (PANSS) [16]; 5) Aged between 18 and 35 years, and male in gender; 6) Having complete medical records and being available for follow-up.

Exclusion criteria: 1) Having a comorbid immune disease; 2) Having a severe somatic disease; 3) Having an acute or chronic infection; 4) Having a substance (alcohol, tobacco, or drugs) dependence; 5) Being a chronic, multiple-relapse patient; 6) Having a clear neurodevelopmental disorder such as intellectual disability, autism spectrum disorder, or mental retardation; 7) Having another psychiatric disorder and being on other antipsychotic medications; 8) Being allergic to the medications used in this study; 9) Using other medications during treatment that could potentially affect psychiatric symptoms (e.g., antidepressants, mood stabilizers); 10) Having a disease that affects drug metabolism (e.g., thyroid dysfunction); 11) Having poor compliance or being unable to complete all pre- and post-treatment evaluation procedures.

Treatment methods

All patients received antipsychotic treatment with olanzapine (H20183500, 5 mg, manufactured by Qilu Pharmaceutical, China). The initial oral dose of olanzapine was 5 mg once daily, which was adjusted to 15 - 20 mg/day within 2 weeks. Treatment was continued for 4 weeks to observe the short-term therapeutic effect.

During the treatment period, if patients experienced adverse drug reactions, symptomatic adjustments were made. For instance, benzhexol hydrochloride tablets (produced by Shanghai Changcheng Pharmaceutical Co., Ltd., specification: 2 mg/tablet, approval number: H31020300, dosage range: 2 - 6 mg/day) were used to alleviate extrapyramidal symptoms induced by olanzapine; propranolol tablets (produced by Tianjin Lisheng Pharmaceutical Co., Ltd., specification: 10 mg/tablet, approval number: H12020151, dosage range: 10 - 30

mg/day) were used to relieve akathisia caused by olanzapine.

Detection of serum PSPH and CXCL2 levels

Serum samples stored at -80°C were collected, all of which were obtained from patients upon admission and stored. Following thawing, the samples underwent centrifugation at 2,000 × g for a duration of 10 minutes at a temperature of 4°C, after which the supernatant was carefully extracted.

The concentrations of PSPH and CXCL2 in the serum of all patients were quantified utilizing the enzyme-linked immunosorbent assay (ELISA). The ELISA kits were purchased from ABCAM, with catalog numbers ab283989 and ab184862, respectively. The operations were strictly carried out according to the kit instructions.

Efficacy evaluation and grouping

All patients underwent PANSS scale assessments on the day of admission and on the day of completing 4 weeks of treatment. The PANSS scale includes the positive scale (evaluating symptoms additional to the normal mental state, with 7 items and a score range of 7 - 49), the negative scale (evaluating characteristics missing from the normal mental state, with 7 items and a score range of 7 - 49), and the General Psychopathology Scale (estimating the overall severity of schizophrenic disorders, with 16 items and a score range of 16 - 112). The total score ranges from 30 to 210, with higher scores indicating more severe illness. The therapeutic effect was evaluated based on the reduction rate of the PANSS score. A reduction rate ≤ 30% was considered as no improvement, while a reduction rate ≥ 30% was considered as improvement [14]. The reduction rate was calculated as follows: Reduction rate = (PANSS score before treatment - PANSS score after treatment)/PANSS score before treatment × 100%.

Statistical analysis

Data analysis was performed using SPSS 26.0 software. Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), and intergroup comparisons were conducted using the *t*-test. Continuous variables with a non-normal distribution were described using the median and interquartile range [M (P_{25}, P_{75})], and intergroup differences were analyzed using the Mann-Whitney U test. Categorical variables were expressed as frequencies (n) and percentages (%), and intergroup comparisons were performed using the chi-squared (χ^2) test. Pearson's correlation analysis was used to assess the correlation between serum PSPH and CXCL2 levels and the PANSS score. Receiver Operating Characteristic (ROC) curve analysis was employed to evaluate the diagnostic value of serum PSPH and CXCL2 levels in predicting the therapeutic effect of first-episode schizophrenia. Logistic regression analysis was used to screen for risk factors affecting the therapeutic effect of first-episode schizophrenia. In this study, a p-value < 0.05 was considered statistically significant.

RESULTS

Bioinformatics analysis results

The analysis of the GSE27383 microarray dataset revealed that, compared to healthy controls, the top three most significantly upregulated indicators in the peripheral blood of male schizophrenia patients were PSPH, CXCL8, and CXCL2. Given that the dysregulation of CXCL8 expression in the serum of schizophrenia patients and its potential association with drug treatment efficacy have been extensively documented in previous studies [17,18], PSPH and CXCL2 were selected for further investigation in this study. The bioinformatics analysis demonstrated that, relative to the healthy control group, serum levels of PSPH and CXCL2 were significantly elevated in male schizophrenia patients (Figure 1). These findings suggest the potential of PSPH and CXCL2 as diagnostic indicators for schizophrenia and provide a basis for exploring their utility as predictors of drug treatment efficacy.

Comparison of general information between the improvement group and the non-improvement group

After 4 weeks of treatment, the 297 patients were divided into an improvement group (118 cases) and a non-improvement group (179 cases) based on their treatment outcomes, yielding a response rate of 39.73%. Compared to the improvement group, the non-improvement group exhibited significantly higher values for disease duration, the proportion of patients with a family history of schizophrenia, and PANSS scores, while being significantly younger ($p < 0.05$). No statistically significant differences were observed between the two groups in terms of BMI, history of alcohol consumption, history of smoking, or educational level ($p > 0.05$) (Table 1).

Comparison of pre-treatment serum PSPH and CXCL2 levels between the improvement group and the non-improvement group

Compared with the serum PSPH level (4.70 ± 1.89 ng/mL) and CXCL2 level (43.94 ± 5.00 pg/mL) in the improvement group, the serum PSPH level (6.48 ± 1.80 ng/mL) and CXCL2 level (50.46 ± 6.91 pg/mL) in the non-improvement group were both elevated, and the differences were statistically significant ($p < 0.05$) (Figure 2).

Correlation between serum PSPH and CXCL2 levels and PANSS scores

Pearson's correlation analysis revealed that both pre-treatment serum PSPH and CXCL2 levels were positively correlated with PANSS scores in both groups ($r = 0.249$ for PSPH, $r = 0.335$ for CXCL2, $p < 0.001$) (Figure 3).

Table 1. Comparison results of general information.

Variable	Improved (n = 118)	Non-Improved (n = 179)	*t*/*Z*	p
Age [*M* (P_{25}, P_{75}), age]	23.00 (21.00, 25.00)	22.00 (21.00, 24.00)	-3.405	0.001
BMI ($\bar{x}\pm s$, kg/m^2)	23.55 ± 3.15	24.12 ± 3.31	-1.480	0.140
Disease duration [*M* (P_{25}, P_{75}), month]	12.00 (9.00, 15.00)	14.00 (10.00, 17.00)	-2.881	0.004
Family history (n/%)				
Yes	53 (44.92)	120 (67.04)	14.313	0.000
No	65 (55.08)	59 (32.96)		
Alcohol consumption history (n/%)				
No alcohol	72 (61.02)	89 (49.72)	4.647	0.098
Occasional alcohol	26 (22.03)	59 (32.96)		
Mild alcohol	20 (16.95)	31 (17.32)		
Smoking history (n/%)				
Non-smoking	80 (67.80)	97 (54.19)	5.607	0.061
Occasional smoking	18 (15.25)	42 (23.46)		
Mild smoking	20 (16.95)	40 (22.35)		
Educational level [*M* (P_{25}, P_{75}), year]	12.00 (11.00, 14.00)	12.00 (10.00, 14.00)	-1.917	0.055
PANSS score ($\bar{x}\pm s$)	84.42 ± 9.32	91.65 ± 9.66	-6.407	0.000

Table 2. Results of logistic regression analysis on factors influencing treatment efficacy in first-episode schizophrenia patients.

Variable	*β*	*S.E*	*Walds*	p	*OR*	95% CI
PSPH	0.460	0.093	24.574	0.000	1.584	1.320 - 1.899
CXCL2	0.160	0.029	30.824	0.000	1.173	1.109 - 1.241
PANSS	0.043	0.017	6.185	0.013	1.044	1.009 - 1.081
Age	-0.181	0.077	5.576	0.018	0.834	0.718 - 0.970
Disease course	0.079	0.034	5.372	0.020	1.082	1.012 - 1.157
Family history	0.779	0.316	6.070	0.014	2.180	1.173 - 4.052

Table 3. Diagnostic value of serum PSPH and CXCL2 levels in predicting treatment efficacy in first-episode schizophrenia patients.

Variable	Cutoff	Sensitivity %	Specificity %	AUC	95% CI	p
PSPH	49.17	58.66	86.44	0.761	0.704 - 0.818	< 0.001
CXCL2	5.035	80.45	64.41	0.778	0.727 - 0.830	< 0.001
PSPH + CXCL2	-	64.25	89.83	0.822	0.776 - 0.869	< 0.001

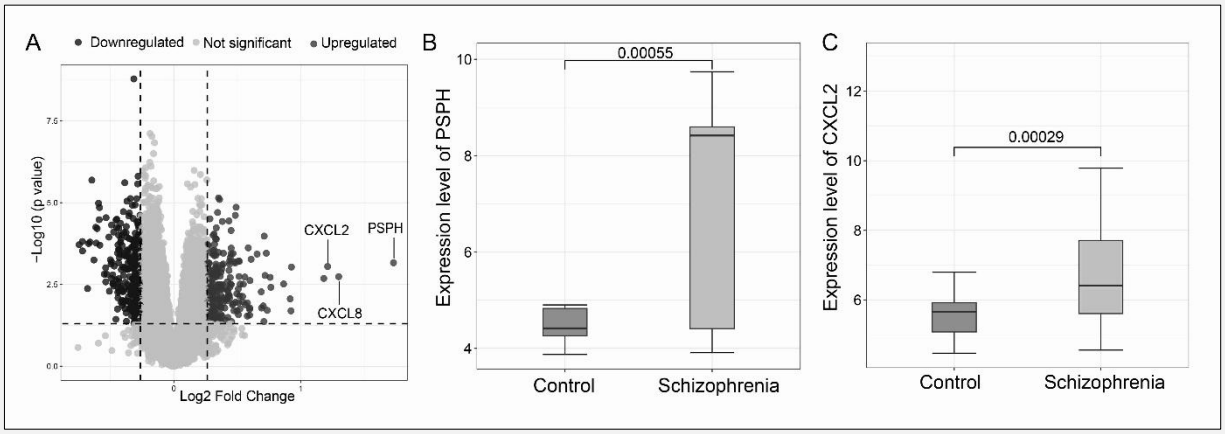

Figure 1. Analysis results of schizophrenia-related microarray GSE27383.

A) Volcanic map of GSE27383 analysis results, B - C) Expression of PSPH and CXCL2 in GSE27383 chip.

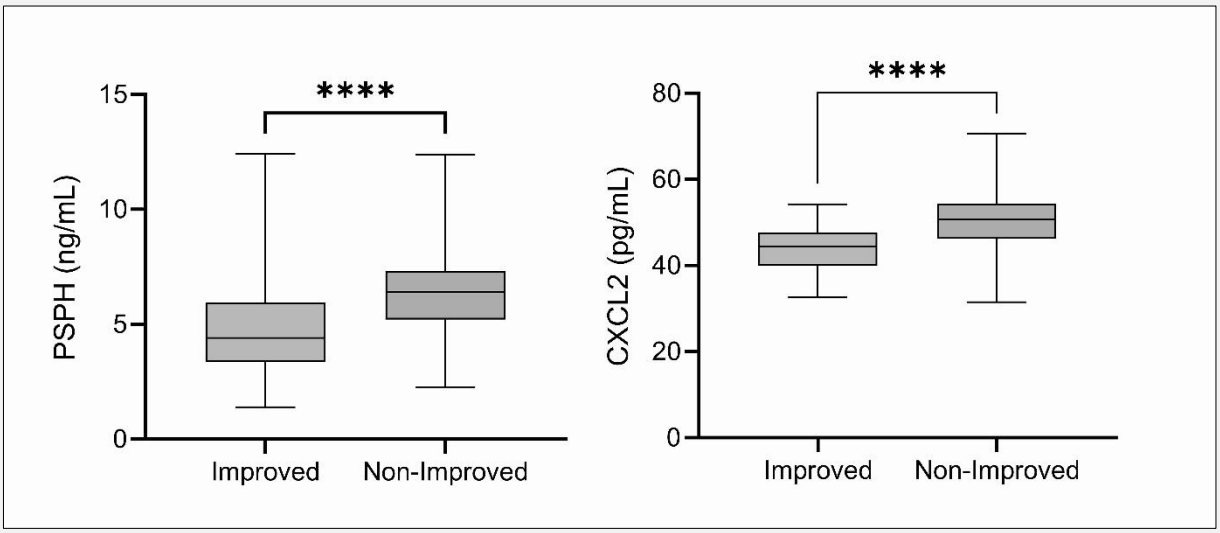

Figure 2. Comparison of pre-treatment serum PSPH and CXCL2 levels between the two groups.

Results of multivariate logistic regression analysis on factors influencing treatment efficacy in first-episode schizophrenia patients

Logistic regression analysis was performed with the patients' treatment outcomes as the dependent variable (non-improvement = 1, improvement = 0) and serum PSPH and CXCL2 levels, pre-treatment PANSS scores, age, disease duration, and family history as independent variables (Table 2, Figure 4). The results indicated that elevated serum PSPH and CXCL2 levels, high pre-treatment PANSS scores, younger age, longer disease duration, and the presence of a family history of schizophrenia were all risk factors affecting the treatment efficacy in first-episode schizophrenia patients ($p < 0.05$).

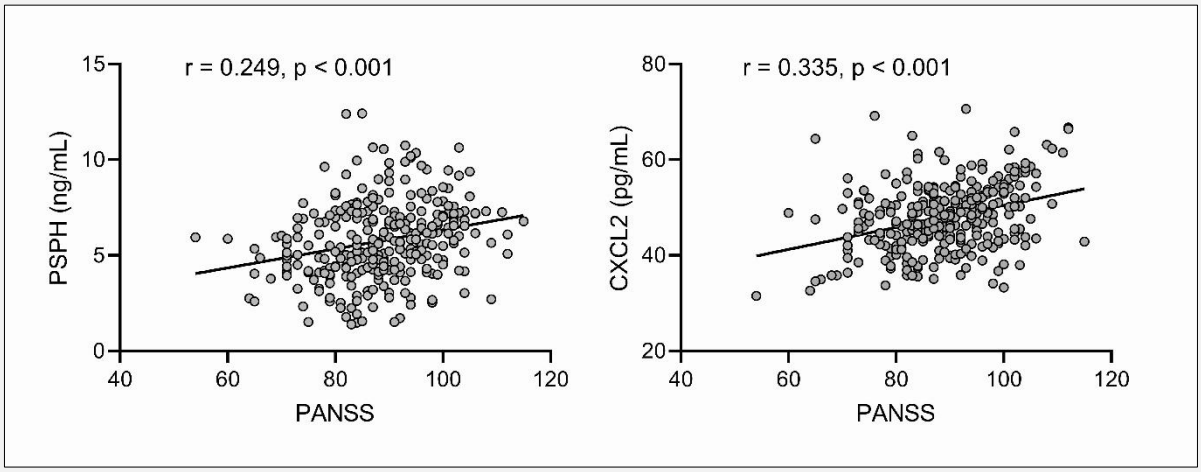

Figure 3. Correlation between serum PSPH and CXCL2 levels and PANSS scores in both groups.

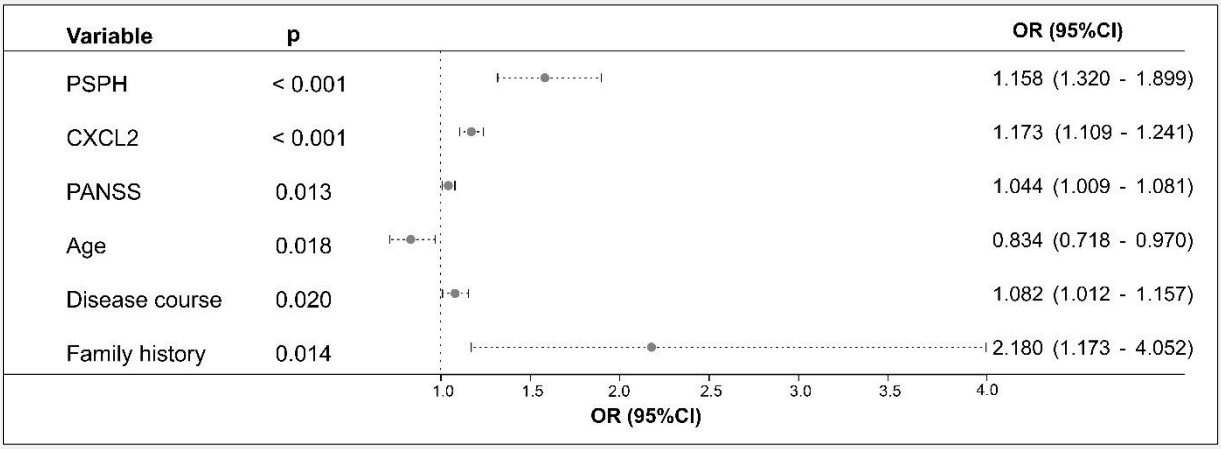

Figure 4. Forest plot of logistic regression analysis on factors influencing treatment efficacy in first-episode schizophrenia patients.

Diagnostic value of serum PSPH and CXCL2 levels in predicting treatment efficacy in first-episode schizophrenia patients

ROC curve analysis was employed to evaluate the diagnostic value of serum PSPH and CXCL2 levels in predicting the treatment efficacy in first-episode schizophrenia patients. The results indicated that the area under the curve (AUC) for the combined diagnosis using both serum PSPH and CXCL2 levels was 0.823, which was higher than the AUCs for PSPH alone (0.761) and CXCL2 alone (0.778). This suggests that serum PSPH and CXCL2 levels can serve as indicators for predicting treatment efficacy in first-episode schizophrenia patients, and their combined use provides better diagnostic performance (Table 3, Figure 5).

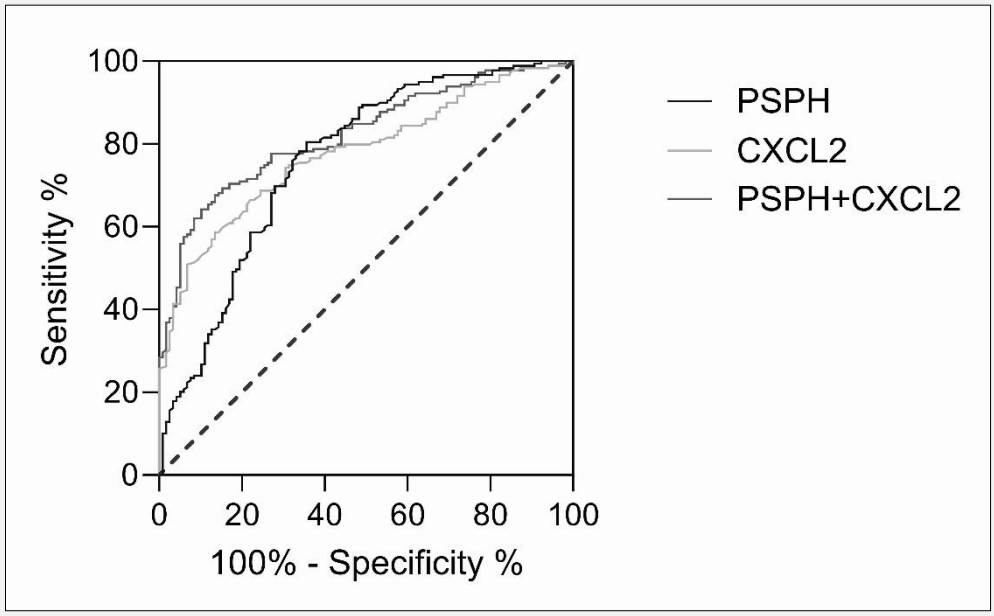

Figure 5. ROC curves for serum PSPH and CXCL2 levels in predicting treatment efficacy in first-episode schizophrenia patients.

DISCUSSION

Schizophrenia is one of the most challenging major psychiatric disorders to treat. With the deepening of research on schizophrenia, an increasing body of evidence suggests that abnormalities in the immune system and neuroinflammation play crucial roles in its pathogenesis. Maternal infection during pregnancy and the subsequent immune response may lead to inflammation during fetal brain development, affecting the normal development of the nervous system and increasing the risk of schizophrenia in offspring during adulthood [19,20]. In patients with schizophrenia, there is abnormal activation of the immune system, with significant elevations in neuroinflammatory markers observed in approximately 37% - 40% of cases [21].

Olanzapine is classified as an atypical antipsychotic medication, predominantly employed in the management of psychiatric conditions, including schizophrenia and the manic phases associated with bipolar disorder. It acts by antagonizing dopamine and serotonin receptors, effectively improving both positive and negative symptoms of patients while reducing adverse reactions such as extrapyramidal symptoms [22,23]. In this research, the administration of olanzapine led to a notable enhancement in the condition of 118 patients, achieving a response rate of 39.73%.

Through bioinformatics analysis and clinical sample testing in this study, it was found that serum levels of PSPH and CXCL2 were significantly higher in the non-improved group before treatment compared to the improved group. Moreover, pre-treatment serum levels of PSPH and CXCL2 were positively correlated with PANSS scores, suggesting that high levels of PSPH and CXCL2 may be closely associated with the severity of schizophrenia and poor treatment response.

Previous studies have identified oxidative stress as a significant factor in the pathogenesis of schizophrenia, with changes in oxidative stress indicators closely related to the severity of symptoms in patients [24]. Serine is involved in various biosynthetic pathways and signal transduction processes, and its metabolic imbalance has been linked to neurodegenerative diseases, including neuroinflammation, oxidative stress, and apoptosis [25]. As a key enzyme in serine synthesis, decreased PSPH expression levels may lead to reduced serine synthesis. [26]. Animal experiments have shown that a decrease in serine affects antioxidant-related signaling pathways, indirectly influencing the activity of antioxidant enzymes [27]. This indicates that disturbances in the serine metabolic pathway may participate in the pathogenesis of schizophrenia by affecting oxidative stress levels. Specifically, abnormal expression of PSPH leads to reduced serine synthesis, which in turn affects antioxidant signaling pathways, decreases antioxidant enzyme activity, and fails to effectively eliminate excessive reactive oxygen species in the body, thereby exacerbating oxidative stress. This enhanced

oxidative stress may damage nerve cells, affect the normal function of the nervous system, and further aggravate the severity of symptoms in patients with schizophrenia. Therefore, PSPH and its regulated serine metabolic pathway may become important targets for future research on the pathogenesis of schizophrenia and the development of potential therapeutic strategies. By regulating the expression of PSPH or the metabolic level of serine, it is expected to improve oxidative stress status, reduce nerve damage, and consequently offering novel strategies and approaches for the management of schizophrenia.

In patients with schizophrenia, inflammatory factors affect the metabolic processes of nerve cells through intracellular signaling pathways, leading to neuronal dysfunction and neurotransmitter imbalance, which are associated with the symptoms of schizophrenia [28]. CXCL2 is a chemokine involved in immune cell chemotaxis and inflammatory regulation, which can be promoted by cathepsin C in a hypothermic brain injury model, exacerbating neuroinflammation [29].

CXCL2 can activate the PI3K-Akt and MAPK pathways through its receptor CXCR2, thereby influencing cell survival, proliferation, and the release of inflammatory factors [12]. In nerve cells, this signaling may inhibit mitochondrial function, disrupt normal neural metabolic processes, and lead to neuronal dysfunction and neurotransmitter imbalance [30], potentially correlating with the cognitive dysfunction and neurodegenerative changes observed in patients with schizophrenia. Additionally, CXCL2-induced inflammatory responses may further exacerbate neuroinflammation by disrupting the integrity of the blood-brain barrier, promoting the infiltration of inflammatory factors, and forming a vicious cycle [31]. This vicious cycle exacerbates neuroinflammation, leading to chronic nerve cell damage and apoptosis, severely affecting brain function, and triggering psychiatric symptoms such as hallucinations, delusions, and cognitive impairment. Meanwhile, chronic inflammation also impairs neuroplasticity, reducing brain adaptability and repair capacity, making it difficult for patients to effectively regulate neural function and further increasing treatment difficulty. Therefore, in-depth research on the mechanism of CXCL2 and its related signaling pathways in neuroinflammation holds significant clinical importance for developing novel therapeutic strategies for schizophrenia.

ROC curve analysis revealed that the AUC value for the combined application of serum PSPH and CXCL2 was 0.823, significantly higher than that of single indicators, indicating high accuracy in predicting the treatment efficacy of first-episode schizophrenia using these two molecules in combination. Logistic regression analysis further confirmed that serum levels of PSPH and CXCL2, pre-treatment PANSS scores, younger age, longer disease duration, and a family history of schizophrenia were all independent risk factors affecting the treatment efficacy of first-episode schizophrenia. This suggests that higher serum levels of PSPH and CXCL2 may be associated with more severe neurometabolic disorders and inflammatory responses; higher pre-treatment PANSS scores typically reflect a greater symptom burden, potentially requiring more aggressive interventions [32]; younger age is associated with increased symptom severity [33], possibly related to incomplete neurodevelopment, as neurotransmitters and plasticity are in an unstable state, and the onset of schizophrenia may cause greater interference to these immature neural mechanisms, leading to poor treatment response; longer disease duration also significantly affects treatment efficacy, as long-term pathological states lead to chronic changes in brain structure and function, which are difficult to recover in the short term [34]; individuals with a family history have high genetic susceptibility, possibly carrying susceptibility genes that affect drug metabolism and treatment response [35]. Therefore, when formulating treatment plans, clinicians should fully consider the combined impact of these factors to achieve more precise and individualized treatment strategies.

In summary, the findings of this investigation indicate that serum levels of PSPH and CXCL2 can serve as potential biomarkers for predicting the efficacy of drug treatment in male patients with first-episode schizophrenia. However, this investigation possesses certain limitations. For example, the single-center sample size is limited, and the study population is restricted to male patients, which could hinder the broader applicability of the results. Subsequent research should aim to increase the sample size and incorporate more diverse populations to verify the widespread applicability of these findings. Additionally, combining other biomarkers and clinical indicators to construct a more comprehensive predictive model can provide stronger support for the precise treatment of schizophrenia.

CONCLUSION

This study demonstrates that serum levels of PSPH and CXCL2 have the potential to act as biomarkers for predicting the treatment efficacy of drug therapy in male patients with first-episode schizophrenia. High levels of these molecules are associated with more severe neuroinflammatory and neurometabolic disturbances, which may contribute to poor treatment response. Furthermore, factors such as higher pre-treatment PANSS scores, younger age, longer disease duration, and a family history of schizophrenia also independently influence treatment outcomes. However, the study's limitations, including a single-center design and a male-only sample, necessitate future research with larger, more diverse populations to validate these findings. By integrating additional biomarkers and clinical indicators, more comprehensive predictive models can be developed, offering stronger support for the implementation of precise and personalized treatment strategies in schizophrenia.

Data Availability:
The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Ethical statement:
This study was approved by the Ethics Committee of Hengshui Seventh People's Hospital (Approval No. 2022-02) and adheres to the principles outlined in the Declaration of Helsinki. Given that this research involves the analysis of stored samples, it qualifies as a retrospective study and is therefore exempt from the requirement for informed consent. All data collected were handled with strict confidentiality to ensure the anonymity of the participants.

Declaration of Interest:
The authors have no potential conflicts of interest to disclose.

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