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Altered serum glutathione disulfide levels in acute relapsed schizophrenia are associated with clinical symptoms and response to electroconvulsive therapy

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Abstract

Background The pathophysiological mechanisms of schizophrenia are complex and not fully elucidated. This study aimed to investigate changes to total glutathione (T-GSH), glutathione disulfide (GSSG), reduced glutathione (GSH), and the GSH/GSSG ratio before and after electroconvulsive therapy (ECT) for patients with acute relapse of schizophrenia and associations with clinical symptoms.

Methods The study cohort included 110 patients with acute relapse of schizophrenia and 55 healthy controls. All patients received 8–10 sessions of ECT. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS).

Results As compared to the healthy controls, schizophrenia patients had decreased baseline GSSG levels (t = -2.115, $p = 0.036$) and elevated GSH/GSSG ratios (t = 2.141, $p = 0.034$). Baseline GSSG levels were negatively correlated with both PANSS total scores (beta = -0.369, t = -4.108, $p < 0.001$) and positive symptom scores (beta = -0.332, t = -3.730, $p < 0.001$), while changes to GSSG levels were positively correlated with improvements in PANSS total scores (r = 0.392, $p < 0.001$) and positive symptom scores (r = 0.293, $p = 0.005$) after ECT treatment. In treatment responders, GSSG levels were significantly increased (t = -2.817, $p = 0.006$) and GSH/GSSG ratios were decreased (t = 4.474, $p < 0.001$), as compared to before ECT, with baseline T-GSH (B = 0.734, OR = 2.083, 95%CI:1.287–3.372, $p = 0.003$), GSSG (B = -2.720, OR = 0.066, 95%CI:0.011–0.390, $p = 0.003$), and GSH/GSSG ratio (B = -1.013, OR = 0.363, 95%CI:0.142–0.930, $p = 0.035$) predictive of clinical improvement.

Conclusion Patients with schizophrenia exhibit significant redox imbalance, and GSSG levels may serve as a potential biomarker to evaluate and predict ECT outcomes.

Keywords Schizophrenia, Electroconvulsive therapy, Glutathione disulfide, Redox state, Oxidative stress

†Li Xu, Ping Yu and Haidong Yang contributed equally to this study. They should be regarded as joint first authors.

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Introduction

Schizophrenia is a severe mental disorder with a global prevalence of approximately 1%, characterized by positive symptoms, negative symptoms, and cognitive impairment [1]. This disorder significantly diminishes the quality of life of patients, while imposing substantial disease burdens on families and society [2, 3]. Despite decades of intensive research, the exact pathophysiological mechanisms of schizophrenia remain incompletely understood, particularly regarding the biological basis of acute relapse [4]. Accumulating evidence suggests that multiple pathological processes, including oxidative stress (OS), may be involved in the development and progression of this disorder [5, 6].

Of the various markers of OS, the glutathione system is among the most important antioxidant defense mechanisms in organisms, and dysregulation may contribute to the onset and progression of schizophrenia [7, 8]. This system comprises total glutathione (T-GSH), glutathione disulfide (GSSG), and reduced glutathione (GSH), with the GSH/GSSG ratio serving as a critical indicator of cellular redox status [9, 10]. During OS, GSH is converted to GSSG through oxidation reactions, resulting in an accumulation of GSSG and a decrease in GSH levels [11]. The GSH/GSSG ratio is widely used as a critical indicator of cellular redox status, with a decreased ratio indicating increased OS [12]. Previous studies have revealed significantly lower glutathione levels in both peripheral blood and cerebrospinal fluid samples of schizophrenia patients as compared to healthy controls, with glutathione levels correlating with disease severity [13, 14]. Stress studies have demonstrated that serum GSH and GSSG levels in male Sprague Dawley rats are negatively correlated with social ability [15]. The glutathione peroxidase/glutathione-dependent antioxidant system may play a protective role in methamphetamine-treated mice, particularly through glutathione peroxidase expression against OS [16]. While these findings demonstrate the importance of glutathione system in schizophrenia, recent studies have focused more on characterizing altered glutathione levels in different contexts rather than their direct associations with clinical symptom severity [17–19]. The diagram of the glucose-6-phosphate dehydrogenase (G6PD)-GSH antioxidant pathway in schizophrenia is shown in Fig. 1.

Electroconvulsive therapy (ECT) is reportedly effective for acute schizophrenia, particularly in treatment-resistant cases and those with severe symptoms such as

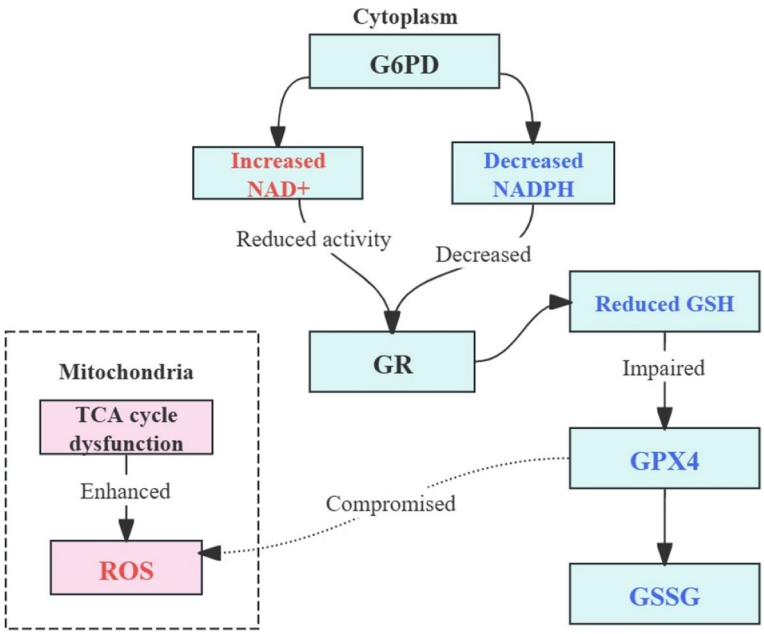

Fig. 1 Diagram of glucose-6-phosphate dehydrogenase (G6PD)-reduced glutathione (GSH) antioxidant pathway in schizophrenia. In the pathophysiological mechanism of schizophrenia, the G6PD-NADPH (nicotinamide adenine dinucleotide phosphate)-GSH system shows significant impairments in maintaining cellular redox balance. The pathway demonstrates decreased GSH levels and increased oxidized glutathione (GSSG), along with compromised glutathione peroxidase 4 (GPX4)-mediated antioxidant defense, leading to elevated reactive oxygen species (ROS) levels. Mitochondrial dysfunction, particularly in the tricarboxylic acid (TCA) cycle, further exacerbates the oxidative stress state. These alterations in both cytoplasmic and mitochondrial compartments contribute to the complex pathophysiological processes of schizophrenia. Solid arrows indicate direct metabolic conversions, while dashed arrows represent regulatory effects. Red and blue text indicates increased and decreased levels, respectively. NAD + : nicotinamide adenine dinucleotide; GR: glutathione reductase

catatonia or life-threatening conditions [20]. While not a first-line treatment, ECT is included in major treatment guidelines as an important therapeutic option for specific clinical scenarios [21, 22], although the underlying mechanisms remain incompletely understood. Evidence suggests that the effects of ECT may be exerted through modulation of OS levels [23]. Animal studies have demonstrated that ECT significantly reduces malondialdehyde levels, while increasing superoxide dismutase, GSH, and brain-derived neurotrophic factor levels in the rat hippocampus [24], indicating that ECT might improve symptoms by enhancing antioxidant capacity and reducing lipid peroxidation. Additionally, chronic electroconvulsive stimulation increased mitochondrial RNA oxidation by 58%, as measured by 8-oxo-7,8-dihydroguanosine in the rat piriform cortex, while mitochondrial hydrogen peroxide production remained unchanged [25]. Clinical studies have shown that ECT reduces serum levels of reactive oxygen species, including nitric oxide [26]. While studies have examined various OS markers in ECT, research specifically investigating changes to the glutathione system during ECT and its potential associations with clinical symptoms remains limited [27].

Given the crucial role of the glutathione system in responses to OS and the documented effects of ECT on various OS markers, we hypothesized that the components of the glutathione system might play significant roles in both the pathogenesis and treatment response of schizophrenia. We postulated that patients with acute relapse of schizophrenia might exhibit alterations to the glutathione system (including T-GSH, GSSG, GSH levels, and the GSH/GSSG ratio), which could potentially correlate with clinical symptoms and ECT outcomes. Therefore, this study aimed to investigate: 1) differences in serum glutathione system parameters between patients with acute relapse of schizophrenia and healthy controls; 2) correlations between these parameters and clinical symptoms; 3) changes to glutathione system parameters following ECT; 4) differential changes to these parameters between ECT responders and non-responders; and 5) the potential value of glutathione system parameters to predict responses to ECT.

Methods

Subjects

The study cohort included 110 patients with acute relapse of schizophrenia who were recruited from the Fourth People's Hospital of Lianyungang (Lianyungang City, China). All patients met the diagnostic criteria for schizophrenia described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and each diagnosis was confirmed by psychiatrists using the Structured Clinical Interview for DSM. All patients had a previous history of schizophrenia and experienced acute relapse due to medication discontinuation for at least 4 weeks prior to enrollment. These patients were of Han Chinese ethnicity, aged between 18 and 65 years, had completed primary school or above, and had not received any anti-inflammatory or antibiotic treatment in the 4 weeks before enrollment.

Additionally, 55 healthy subjects matched for age and sex were recruited as controls through community advertisements. The healthy controls did not meet the diagnostic criteria for any DSM-IV Axis I disorder and had no family history of psychiatric disorders. Both groups excluded individuals with epilepsy, neurodegenerative diseases, history of brain trauma, alcohol or substance dependence, endocrine system diseases (such as thyroid dysfunction or diabetes), and current use of anti-inflammatory medications.

The study protocol was approved by the Ethics Committee of the Fourth People's Hospital of Lianyungang, and written informed consent was obtained from all participants or their legal guardians.

ECT

Each participant received a series of 8–10 bilateral ECT sessions on alternate days. Following comprehensive pre-treatment evaluation and overnight fasting, each session was scheduled between 07:00 and 09:00. The standardized pre-treatment protocol included intravenous administration of atropine sulfate (0.05 mg), propofol (0.8–1.2 mg/kg), and succinylcholine (1.0 mg/kg). ECT was performed using a Thymatron TMDG device (Somatics LLC, Lake Bluff, IL, USA) with stimulus electrodes positioned bilaterally on the frontotemporal regions. Treatment parameters were standardized across all sessions, with specifications including maximum charge delivery (504 mC), current output (0.9 A), frequency range (10–70 Hz), pulse duration (0.5 ms), and maximum stimulus interval (8 s). Throughout each session, healthcare professionals monitored motor seizures and cardiac responses while recording electroencephalographic activity.

Symptom rating

Two senior psychiatrists evaluated the severity of psychiatric symptoms using the Positive and Negative Syndrome Scale (PANSS), with an interrater correlation coefficient greater than 0.8. Based on the reduction rate of the total PANSS score after 4 weeks of treatment, the patients were classified as responders (reduction rate > 25%) or non-responders (reduction rate ≤ 25%) [28]. All antipsychotic medication doses were converted to chlorpromazine equivalents [29].

T-GSH, GSSG, and GSH assessment

Blood samples were collected at two time points: within 24 h before the first ECT session (baseline) and within 2 h after the completion of the last ECT session in the course. The 2-h post-last-ECT timing was specifically chosen as it allows for the assessment of cumulative effects of the complete ECT course on OS parameters, while minimizing potential confounding effects from other factors. Peripheral venous blood samples were collected from all subjects under fasting conditions, between 07:00 and 09:00 for baseline samples and between 07:00 and 11:00 for post-ECT samples. The samples were collected into procoagulant tubes, allowed to clot for 30 min at room temperature, and then centrifuged at 3000 rpm for 15 min. The separated serum was immediately aliquoted and stored at −80 °C until analysis by professional technicians who were blinded to the clinical status of the subjects. Serum levels of T-GSH, GSSG, and GSH were measured using the microplate method with commercial kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) in accordance with the manufacturer's instructions. All samples were analyzed in duplicate, with intra- and inter-assay coefficients of variation ranging from 1.2% to 6.7%. The results are expressed in μmol/L.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Continuous variables are presented as mean ± standard deviation or median (interquartile range) based on distribution, while categorical variables are expressed as frequencies (percentages). The independent samples *t*-test was used for between-group comparisons of normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and the chi-square test for categorical variables. The non-normally distributed data of T-GSH, GSSG, and GSH were natural logarithm-transformed to achieve normal distributions. Changes to PANSS scores and T-GSH, GSSG, and GSH levels before and after treatment were analyzed using the paired samples *t*-test. Analysis of covariance was performed to control for potential confounding factors, such as age, education, sex, age of onset, and duration of illness. Pearson's correlation coefficient or Spearman's rank correlation coefficient was used, as appropriate, to analyze the associations of T-GSH, GSSG, and GSH levels with psychopathological symptoms. Multiple linear regression analysis was performed to assess the associations of T-GSH, GSSG, and GSH levels with psychopathological symptoms after controlling for confounding factors. Effect size calculations (Cohen's d) and power analysis were conducted using G*Power 3.1 software (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower), with statistical significance set at $p < 0.05$ (two-tailed).

Results

Demographic data

The demographic and clinical characteristics of the schizophrenia patients and healthy controls are summarized in Table 1. There were no significant differences in age, sex, education, smoking status, and body mass index (BMI) between the groups (all, $p > 0.05$). In the patient group, the mean age of onset was 24.90 ± 5.56 years and the duration of illness was 11.15 ± 9.11 years. Of the 110 schizophrenia patients, 26 (23.6%) had a family history of mental disorders. Upon admission, all patients were prescribed antipsychotic medications concurrent with ECT treatment, with a mean chlorpromazine equivalent of 669.89 ± 295.02 mg/day during the ECT course.

Measurement of serum T-GSH, GSSG, and GSH

Serum GSSG levels (t = −2.115, $p = 0.036$, Cohen's d = −0.34, Fig. 2A) and the GSH/GSSG ratio (t = 2.141, $p = 0.034$, Cohen's d = 0.31, Fig. 2B) were significantly lower in patients with acute relapse schizophrenia as compared to the healthy controls, while there were no significant differences in T-GSH and GSH levels (both, $p > 0.05$).

Association of T-GSH, GSSG and GSH serum levels with psychopathological symptoms

GSSG levels were negatively correlated to the PANSS positive subscale score (r = −0.332, df = 110, $p < 0.001$) and PANSS total score (r = −0.386, df = 110, $p < 0.001$) in acute relapse schizophrenia patients. However, there were no significant associations of the T-GSH and GSH levels, GSH/GSSG ratio, and PANSS total score with other subscales scores (all $p > 0.05$).

Further, multiple regression analyses were performed with the PANSS total score and PANSS positive subscale score as dependent variables and serum GSSG level as the independent variable, while controlling for covariates of age, sex, smoking status, education level, chlorpromazine equivalent dose, age of onset, and duration of illness. The results revealed significant negative associations between serum GSSG levels and both PANSS total score (beta = −0.369, t = −4.108, $p < 0.001$, Fig. 3A) and PANSS positive subscale score (beta = −0.332, t = −3.730, $p < 0.001$, Fig. 3B). Age of onset (beta = 0.255, t = 2.753, $p = 0.007$) was identified as a confounding factor in the relationship between GSSG levels and PANSS positive subscale scores.

Table 1 Demographic and clinical characteristics of patients with acute relapse schizophrenia and healthy controls

	Patients (n = 110)	Healthy Controls (n = 55)	t/Z/χ2	*p*
Age (years)	36.05 ± 11.49	38.69 ± 11.72	−1.379[a]	0.170
Sex (M/F)	57/53	27/28	0.109[b]	0.741
Education (years)	12.0 (11.0, 14.0)	15.0 (8.0, 16.0)	−1.782[c]	0.075
Smoking (yes/no)	32/78	15/40	0.060[b]	0.807
BMI (kg/m2)	25.36 ± 4.56	24.49 ± 3.92	0.643[a]	0.521
Age of onset (years)	24.90 ± 5.56[d]	-	-	-
Duration of illness (years)	11.15 ± 9.11[d]	-	-	-
Family history of mental disorders (yes/no)	26/84	-	-	-
Chlorpromazine equivalents (mg/d)	669.89 ± 295.02[d]	-	-	-
PANSS positive subscale	32.52 ± 10.85[d]	-	-	-
PANSS negative subscale	22.39 ± 11.24[d]	-	-	-
PANSS general subscale	44.27 ± 12.14[d]	-	-	-
PANSS total score	98.57 ± 15.37[d]	-	-	-
T-GSH (μmol/L)	13.91 ± 2.86	14.19 ± 1.79	−0.678[a]	0.499
GSSG (μmol/L)	3.25 ± 0.85	3.56 ± 0.95	−2.115[a]	0.036
GSH (μmol/L)	7.42 ± 3.60	7.08 ± 1.87	0.644[a]	0.520
GSH/GSSG ratio	2.70 ± 2.03	2.20 ± 0.97	2.141	0.034

Abbreviations: *BMI* body mass index, *T-GSH* total glutathione, *GSH* reduced glutathione, *GSSG* glutathione disulfide, *PANSS* positive and negative syndrome scale

[a] Independent samples *t*-test

[b] χ2 test

[c] Mann–Whitney U test

[d] Student's *t*-test

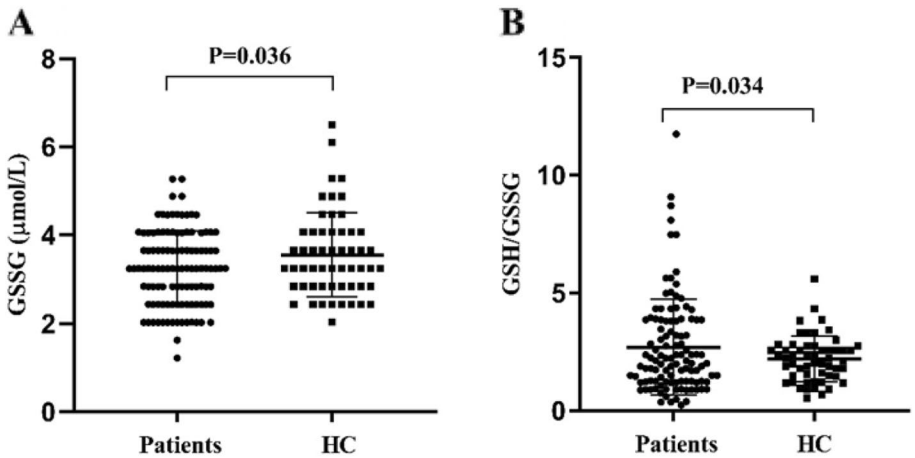

Fig. 2 Serum GSSG levels and the GSH/GSSG ratio in patients with acute relapse schizophrenia and healthy controls (HC)

Comparison of serum T-GSH, GSSG, and GSH levels and psychopathological symptoms before and after ECT

As shown in Table 2, the paired-samples *t*-test revealed that after ECT, the psychopathological symptom score and GSH/GSSG ratio (t = 3.405, $p = 0.001$,) were significantly decreased, while serum GSSG levels were significantly elevated (t = −2.252, $p = 0.026$), whereas there were no significant changes to serum T-GSH and GSH levels (both, $p > 0.05$).

Associations of serum T-GSH, GSSG, and GSH levels with clinical outcomes of treatment responders

Based on a reduction rate of ≥ 25% in the PANSS total score after ECT as the criterion for clinical improvement,

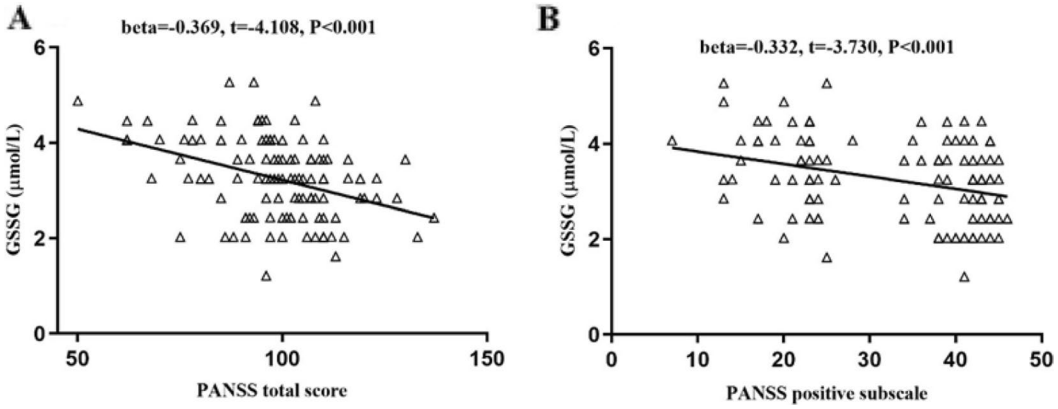

Fig. 3 Correlation of serum GSSG levels with PANSS total score and PANSS positive subscale score of acute relapse schizophrenia patients

Table 2 Changes to psychopathological symptoms and serum T-GSH, GSSG, and GSH levels following ECT

	Before ECT	After ECT	t	*p*
PANSS positive subscale	32.52 ± 10.85	17.17 ± 6.83	12.557	< 0.001
PANSS negative subscale	22.39 ± 11.24	14.57 ± 6.20	6.390	< 0.001
PANSS general subscale	44.27 ± 12.14	31.35 ± 9.40	8.822	< 0.001
PANSS total scores	98.57 ± 15.37	63.10 ± 17.02	16.221	< 0.001
T-GSH (μmol/L)	13.91 ± 2.86	13.49 ± 3.08	0.971	0.334
GSSG (μmol/L)	3.25 ± 0.85	3.46 ± 0.53	−2.252	0.026
GSH (μmol/L)	7.42 ± 3.60	6.56 ± 2.96	1.779	0.078
GSH/GSSG ratio	2.70 ± 2.03	1.95 ± 0.94	3.405	0.001

patients were classified as responders or non-responders. Overall, 91 patients (82.7%) met the improvement criterion, while 19 (17.3%) did not. In the responder group, serum GSSG levels were significantly increased (3.14 ± 0.83 vs. 3.44 ± 0.55 μmol/L, t = −2.817, $p = 0.006$, Cohen's d = −0.30, Fig. 4A), while the GSH/GSSG ratio was significantly decreased (2.95 ± 2.01 vs. 1.89 ± 0.95, t = 4.474, $p < 0.001$, Cohen's d = 0.47, Fig. 4B) after ECT, while there were no significant differences in GSSG levels (3.75 ± 0.79 vs. 3.56 ± 0.44 μmol/L, t = 0.962, $p = 0.349$) or the GSH/GSSG ratio (1.48 ± 1.66 vs. 2.24 ± 0.81, t = −1.826, $p = 0.085$) in the non-responder group.

One-way analysis of variance revealed significant differences in serum GSSG levels (F = 6.034, $p = 0.003$) and the GSH/GSSG ratio (F = 12.620, $p < 0.001$) before and after ECT as compared to the healthy controls. Subsequent Bonferroni post-hoc analysis demonstrated significant differences in GSSG levels after ECT treatment ($p = 0.025$), as well as before treatment and the healthy control group ($p = 0.005$). However, there were no significant differences after ECT as compared to the healthy controls ($p > 0.05$). There was a significant difference in the GSH/GSSG ratio before and after ECT ($p < 0.001$), and before ECT and the healthy controls ($p = 0.008$), but not after ECT and the healthy controls ($p = 0.648$).

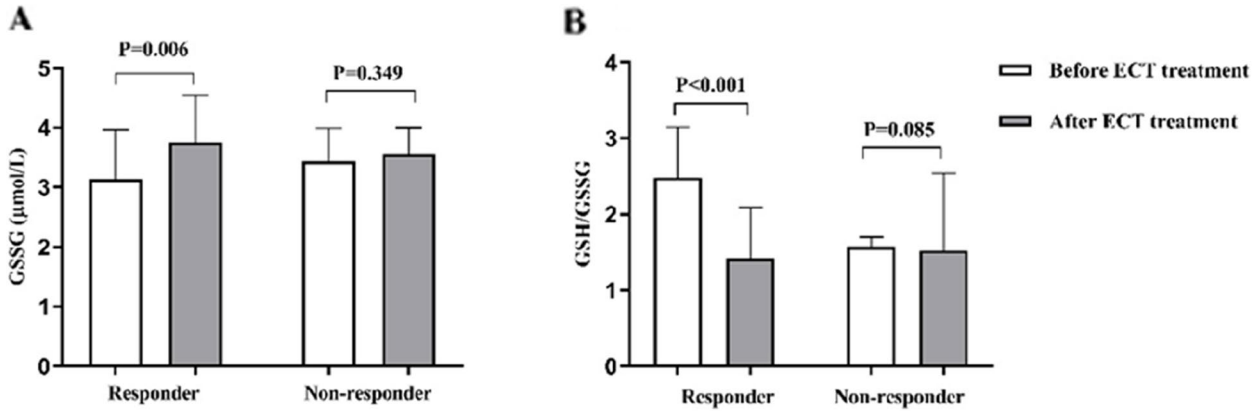

Fig. 4 GSSG levels and the GSH/GSSG ratio in the responder and non-responder groups before and after ECT

Further, in the responder group, Pearson's correlation analysis revealed significant positive correlations of changes to serum GSSG levels with the PANSS total score (r = 0.392, $p < 0.001$, Fig. 5A) and PANSS positive subscale score (r = 0.293, $p = 0.005$, Fig. 5B) following ECT.

Clinical predictors of symptom improvement

Binary logistic regression analysis to predict clinical outcomes (with the symptom improvement group coded as 1 and the non-improvement group as 0) included demographic characteristics (age, sex, education), clinical features (BMI, chlorpromazine equivalent dose, duration of illness, age of onset), baseline PANSS total scores, and OS indicators (TGSH, GSSG, GSH, and GSH/GSSG ratio) before and after ECT. Correlation analysis revealed that baseline PANSS total scores were positively correlated with PANSS score reduction (r = 0.570, $p < 0.001$). Multivariate logistic analysis revealed that a lower baseline GSSG level was a favorable predictor of clinical symptom improvement (B = −2.720, OR = 0.066, 95%CI: 0.011–0.390, $p = 0.003$), while baseline T-GSH level was positively associated with clinical improvement (B = 0.734, OR = 2.083, 95% CI: 1.287–3.372, $p = 0.003$). Additionally, baseline GSH/GSSG ratio (B = −1.013, OR = 0.363, 95%CI: 0.142–0.930, $p = 0.035$) and baseline PANSS total scores (B = −0.054, OR = 0.947, 95%CI: 0.901–0.996, $p = 0.034$) were also significant predictors of symptom improvement.

Discussion

The present study revealed several key findings: 1) acute relapse of schizophrenia was associated with significantly decreased serum GSSG levels and increased GSH/GSSG ratios compared to healthy controls; 2) reduced serum GSSG levels were significantly negatively correlated with both the PANSS total score and positive symptom score; 3) after ECT, serum GSSG levels were significantly increased and GSH/GSSG ratios were significantly decreased, with no significant difference after ECT treatment with the healthy control group; 4) in treatment responders, changes to serum GSSG levels were positively correlated with reductions in both the PANSS total score and positive symptom score, and 5) GSSG may be a predictor for clinical symptom improvement. While previous studies have investigated various OS markers in ECT-treated patients with schizophrenia [27, 30], the present study is the first to specifically examine GSSG levels and GSH/GSSG ratio changes following ECT in a Chinese schizophrenia population.

Our study demonstrated that acute relapse of schizophrenia was associated with significantly decreased serum GSSG levels and increased GSH/GSSG ratios, in contrast to the findings of previous research. Ballesteros et al. reported elevated whole blood GSSG levels in clinically stable medicated schizophrenia patients [18, 31], while Raffa et al. observed increased plasma GSSG levels in drug-naive first-episode schizophrenia patients [19]. Similarly, a study of stress with an adolescent animal model reported elevated GSSG levels in both serum and the ventral hippocampus [15]. These discrepancies might be attributed to several factors, including differences in blood sample sources, medication status, disease state, sample processing methods, sample size, and the heterogeneity of OS responses across different stages of schizophrenia. In our study, the decreased serum GSSG levels and elevated GSH/GSSG ratios observed in acute relapse schizophrenia patients may indicate alterations to GSH

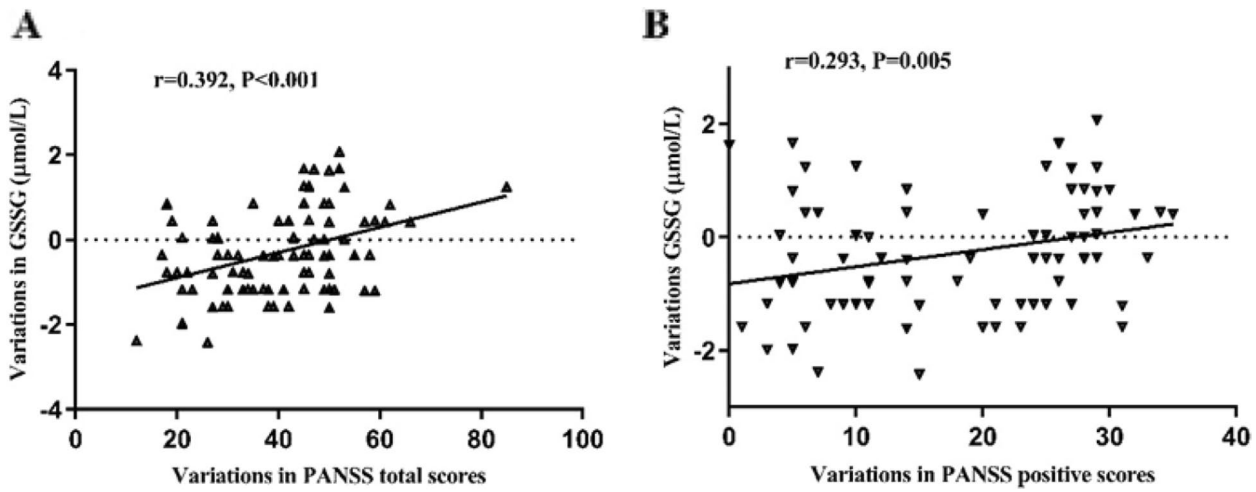

Fig. 5 Association of GSSG levels with improvement in PANSS total scores and positive scores following ECT

metabolism. This pattern could reflect either a disruption to GSSG-mediated redox homeostasis or compensatory enhancement of the antioxidant defense system under OS conditions. The reduction in GSSG levels might represent a distinct pathophysiological state in acute relapse, possibly involving different mechanisms from those in first-episode or stable phases of the illness [32]. However, the precise molecular mechanisms underlying these alterations, particularly the relationship between GSSG reduction and the acute exacerbation of psychotic symptoms, require further investigation.

Our study revealed a significant negative correlation between serum GSSG levels and both the PANSS total score and positive symptom score, suggesting a potential association between alterations to the redox system and disease severity. This finding aligns with previous studies that have documented associations between various OS markers and psychiatric symptoms. For instance, Piatoikina et al. reported correlations between lipid peroxidation levels and psychotic symptoms [33], while Yang et al. observed a positive correlation between catalase levels and PANSS total scores [34]. N-acetylcysteine, as a key modulator of the balance between GSH and GSSG, has demonstrated significant associations with psychiatric symptoms [35]. However, the relationship between GSSG levels and psychiatric symptoms warrants careful interpretation because this association may involve multiple aspects, including alterations to antioxidant defense systems, regulation of GSH metabolism, and stress responses to acute disease exacerbation.

Previous studies have demonstrated that schizophrenia patients exhibit significant OS imbalance, characterized by decreased antioxidant defense capacity and altered free radical metabolism, which is closely associated with disease pathogenesis and progression [36, 37]. After ECT treatment, the total oxidant status and calculated OS index values were significantly decreased in schizophrenia patients as compared to baseline measurements [30]. In this study, following ECT treatment in patients with acute relapsed schizophrenia, serum GSSG levels were significantly increased and the GSH/GSSG ratio was significantly decreased, with these indicators approaching levels comparable to those of healthy controls. These findings may reflect an immediate stress response following ECT [38], as electrophysiological intervention might temporarily promote the conversion of GSH to GSSG [39]. This conversion likely represents a compensatory mechanism to maintain redox balance rather than a pathological change [40]. Notably, the decrease in the GSH/GSSG ratio may be a time-dependent phenomenon, and the convergence of OS indicators with those of healthy controls suggests that ECT may play a role in regulating redox balance, potentially helping to correct the pre-existing OS imbalance in schizophrenia patients [41]. Although the decrease in the GSH/GSSG ratio was contrary to expectations, the achievement of near-normal levels may indicate gradual functional restoration of the redox system.

In this study, we observed a positive correlation between changes in serum GSSG levels and reductions in both the total PANSS scores and positive symptom scores among ECT responders, suggesting that the redox state changes correspondingly with the improvement to clinical symptoms. The relationship between peripheral and central OS markers is supported by evidence that glutathione and GSSG can cross the blood–brain barrier through specific transporters [42]. Studies have shown that OS markers in the peripheral circulation can reflect central nervous system pathology, as systemic OS may influence brain redox status through altered blood–brain barrier permeability [43, 44]. Previous studies have demonstrated that electroconvulsive shock can activate microglia, upregulate proinflammatory cytokines, and enhance OS responses [38]. Upon activation, microglia generate reactive oxygen and nitrogen species, which may either cause neuronal damage or promote neuroplasticity through activation of specific signaling pathways [45]. Moreover, moderate OS may exert compensatory protective effects by inducing upregulation of antioxidant defense systems and enhancing cellular tolerance to injury. These findings from preclinical studies, combined with our observed peripheral GSSG changes during ECT, suggest a possible link between ECT-induced oxidative responses and therapeutic effects. However, further research is needed.

In this study, changes to serum GSSG levels were positively correlated with reductions in both PANSS total scores and positive symptom scores among ECT responders, indicating that changes to the redox state occurred in parallel with clinical symptom improvement. Previous studies have demonstrated that electroconvulsive shock can activate microglia, upregulate neuroinflammatory cytokines, and enhance OS responses [46, 47]. These findings suggested that the observed changes to GSSG levels during ECT treatment might be associated with microglial activation and subsequent OS responses, which might constitute part of the therapeutic mechanism.

An interesting finding of this study is that lower GSSG levels may serve as a predictor of clinical improvement in schizophrenia patients. This predictive value remained significant after controlling for baseline symptom severity, indicating GSSG as an independent biological marker for treatment response. The observed reduction in GSSG levels reflects a compensatory regulation of redox balance, suggesting a potential

self-protective mechanism that may play a crucial role in maintaining neurological homeostasis [48, 49]. As a pivotal molecule in the GSH redox system, GSSG levels directly indicate cellular OS status [50, 51]. Lower GSSG levels suggest enhanced antioxidant capacity and improved cellular metabolic function, which may contribute to neuronal protection and functional recovery [52]. Interestingly, the GSH/GSSG ratio emerged as another significant predictor in our study, with lower ratios associated with better clinical outcomes. The combination of both GSSG levels and GSH/GSSG ratio as predictive markers may help clinicians identify patients who are more likely to respond favorably to ECT treatment. However, the specific regulatory mechanisms of GSSG in the pathophysiological process of schizophrenia warrant further investigation.

There were several limitations to this study that should be addressed. First, although we observed temporal changes in both GSSG levels and clinical symptoms during ECT treatment, a definitive causal relationship between these changes could not be established due to the observational nature of our study. Second, GSSG levels were only measured at two time points (before and after ECT), which may not fully capture the dynamic changes to the redox state throughout the treatment process. Third, this was a single-center study with a relatively small sample size, thus, requiring validation through larger-scale multicenter studies in the future. Fourth, we only measured peripheral OS markers. Although evidence supports peripheral-central correlation, future studies with cerebrospinal fluid analysis would provide more direct evidence of brain OS changes during ECT. Fifth, as antipsychotic medications were administered concurrently with ECT following standard clinical practice, it was not possible to distinguish the individual effects of ECT from those of antipsychotic medications on oxidative stress markers. However, this limitation reflects real-world clinical practice where combined treatment is typically necessary for patients with acute relapse schizophrenia.

In conclusion, this study revealed a significant redox imbalance in patients with acute relapse of schizophrenia, characterized by decreased serum GSSG levels and elevated GSH/GSSG ratios. ECT normalized the redox state, with increases in GSSG levels and decreases in the GSH/GSSG ratio significantly correlated with clinical improvement in treatment responders, while no notable changes in redox indicators were observed in non-responders. These findings not only suggest the crucial role of redox imbalance in the pathogenesis of schizophrenia, but also indicate that GSSG levels may serve as a potential biomarker to predict and evaluate ECT outcomes.

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Clinical trial
Not applicable.

Authors' contributions
Li Xu, Ping Yu and Haidong Yang wrote the manuscript; Xiaobin Zhang and Xiaowei Tang was responsible for study design; Haidong Yang and Chengbing Huang performed the statistical analysis; Li Xu, Ping Yu, Haidong Yang, and Wenxi Sun were responsible for performing the clinical rating, recruiting the patients, and collecting the samples. All authors have contributed to and have approved the final manuscript.

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Data availability
The data supporting the results of this study are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate
We declare that all experiments on human subjects were conducted in accordance with the Declaration of Helsinki and that all procedures were carried out with the adequate understanding and written consent of the subjects. All experimental protocols were approved by the Ethics Committee of Lian Yun Gang Fourth People's Hospital. Informed consent was obtained from all the participants and/or their legal guardians. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

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