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ORIGINAL RESEARCH

Abnormal Serum Biochemical Results and Mitochondrial Damage of Lymphocytes in Patients with Schizophrenia and SARS-CoV-2 Infection: A Retrospective Study

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Purpose: In this study, we investigated the differences in clinical biochemical values and mitochondrial mass between schizophrenia patients with and without COVID-19, so as to provide assistance to the treatment and management of COVID-19 positive patients with schizophrenia.

Patients and methods: We undertook an exploratory, retrospective review of patient data from Dec. 6, 2022, to Jan. 31, 2023. A total of 1696 inpatients with psychosis (921 schizophrenia patients and 775 diagnosed with other mental diseases) during this period were identified. Finally, 60 schizophrenia patients were enrolled in our study, and 20 of them were infected with syndrome coronavirus 2 (SARS-CoV-2). The serum biochemical levels and single-cell mitochondrial mass (SCMM) of the T lymphocytes of all schizophrenia patients were analyzed.

Results: The serum levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine (Cr) and lactate dehydrogenase (LDH) were significantly higher in schizophrenia patients with COVID-19 (SCZ-C) group. In addition, the SCZ-C group showed lower $CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$ cell counts and higher SCMM of T lymphocytes compared to SCZ group. Furthermore, positive correlations were found between the T-cell subpopulation counts and positive symptom scores on the Positive and Negative Syndrome Scale (PANSS).

Conclusion: Our study findings showed that schizophrenia patients with COVID-19 have a phenotype of mitochondrial damage in T lymphocytes and higher serum levels of AST, ALP, Cr and LDH, which might provide evidence for treating individuals with schizophrenia during subsequent spread of infectious disease.

Keywords: biochemical characteristics, lymphocyte, mitochondrial damage, COVID-19, schizophrenia

Introduction

COVID-19 caused by SARS-CoV-2 infection has been raging worldwide since January 2020, bringing major challenges to public health and medical communities around the world.[1] Although the pathogenicity of the Omicron variant is considered to be significantly attenuated, the COVID-19 pandemic remains a worldwide public health crisis.[2,3] Several studies revealed that the incidence of COVID-19 was higher in schizophrenia patients than in those without psychiatric diagnoses.[4,5] Schizophrenia (SCZ) is a chronic, complex and disabling psychiatric disorder that is caused by genetic and/or environmental disruption of brain development. Previous studies have concluded that the season of birth is associated with the development of schizophrenia.[6,7] About one-third of schizophrenia patients exhibit treatment resistance features

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and do not respond adequately to conventional antipsychotic medication.[8,9] Protecting the mental health of these patients is therefore important not only for their own long-term health but also for controlling the pandemic.[10,11]

Coronavirus infection itself may exacerbate symptoms in people with schizophrenia, as coronaviruses may be associated with symptoms of psychosis through an immune-related mechanism.[12] It can be said that COVID-19 can cause several changes in the human immune system that are known possible etiologies of schizophrenia.[11] Previous studies have shown that COVID-19 has various psychosocial effects on schizophrenia patients.[4,13,14] At the same time, SARS-CoV-2 infection might present as liver injury, kidney injury, cardiac failure and mitochondriopathy.[15–19] Besides, mitochondrial therapy can be used to alleviate neurological complications during the COVID-19 pandemic.[20] However, there is still a lack of clinical data on whether mitochondria are therapeutic targets for schizophrenia patients with SARS-CoV-2 infection. To effectively prioritize resources for schizophrenia patients, the identification of clinical and laboratory biochemical markers is urgently needed.

In this study, we retrospectively analyzed the differences in the serum biochemical levels and single-cell mitochondrial mass (SCMM) of T lymphocytes between schizophrenia patients with and without SARS-CoV-2 infection and evaluated the relationship between these values and symptoms of psychosis. The aim of this research is to provide an objective index for schizophrenia patients with COVID-19 to help with their treatment.

Methods

Study Population

In this retrospective observational study, schizophrenia patients in Xiamen Xianyue Hospital, Xiamen Mental Health Center in Fujian, China, between December 6, 2022, and January 31, 2023, were enrolled. A total of 1696 inpatients with psychosis (921 schizophrenia patients and 775 diagnosed with other mental diseases) during this period were identified. Patients who met the following criteria were included: i) meeting the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); ii) having complete clinical and biological data; and iii) aged 18–70 years. Patients with allergies, autoimmune disorders, a history of substance abuse, other mental illnesses, cancer, hypertension, coronary heart disease, diabetes, nervous system diseases or other infectious diseases were excluded. The flow chart of participant enrollment is shown in Figure 1. Finally, 60 schizophrenia patients were enrolled in this study. Then, 20 schizophrenia patients with laboratory-confirmed COVID-19 represented the schizophrenia-COVID-19 (SCZ-C) group. The remaining 40 schizophrenia patients represented the schizophrenia (SCZ) group. Clinical presentations of schizophrenia patients with COVID-19 were presented in Supplementary Table 1. The schizophrenia patients in this study did not receive injectable treatment and episodes of mechanical restraint, and the antiviral and concomitant medications were not used. Meanwhile, 40 age-and sex-matched healthy volunteers with no history or family history of major psychiatric disorders were selected as controls.

Data Collection and Processing

Demographic and clinical data, including sex, age, body mass index (BMI), years of education and mental disorder duration, were collected. The severity of symptoms of psychosis was evaluated using the PANSS.

The laboratory data, including flow cytometry data and biochemical test results, were collected. Flow cytometry was performed using Novocyte (Agilent Technologies, USA), and flow cytometry antibodies CD3-FITC/CD8-PE/CD4-PE-Cy7/CD45-PerCP-Cy5.5 and Mito dye were produced by UBBIO LTD (Zhejiang, China). The flow cytometry data included the percentage and absolute counts of lymphocytes, T cells ($CD3^+$), helper T cells (Th cells: $CD3^+$ $CD4^+$) and killer T cells (TS cells: $CD3^+$ $CD8^+$), as well as the SCMM (single-cell mitochondrial mass) of each subset. The SCMM of T lymphocytes was obtained by calculating the absolute count of the mitochondrial mass (MM) and cells.[21,22]

Serum biochemical tests such as tests were performed using a Beckman AU5800 automatic biochemistry analyzer (Beckmann, USA). This study was approved by the Institutional Ethics Committee of Xiamen Xianyue Hospital, Xiamen Mental Health Center (No. 2022-KY-034) and complied with the Declaration of Helsinki.

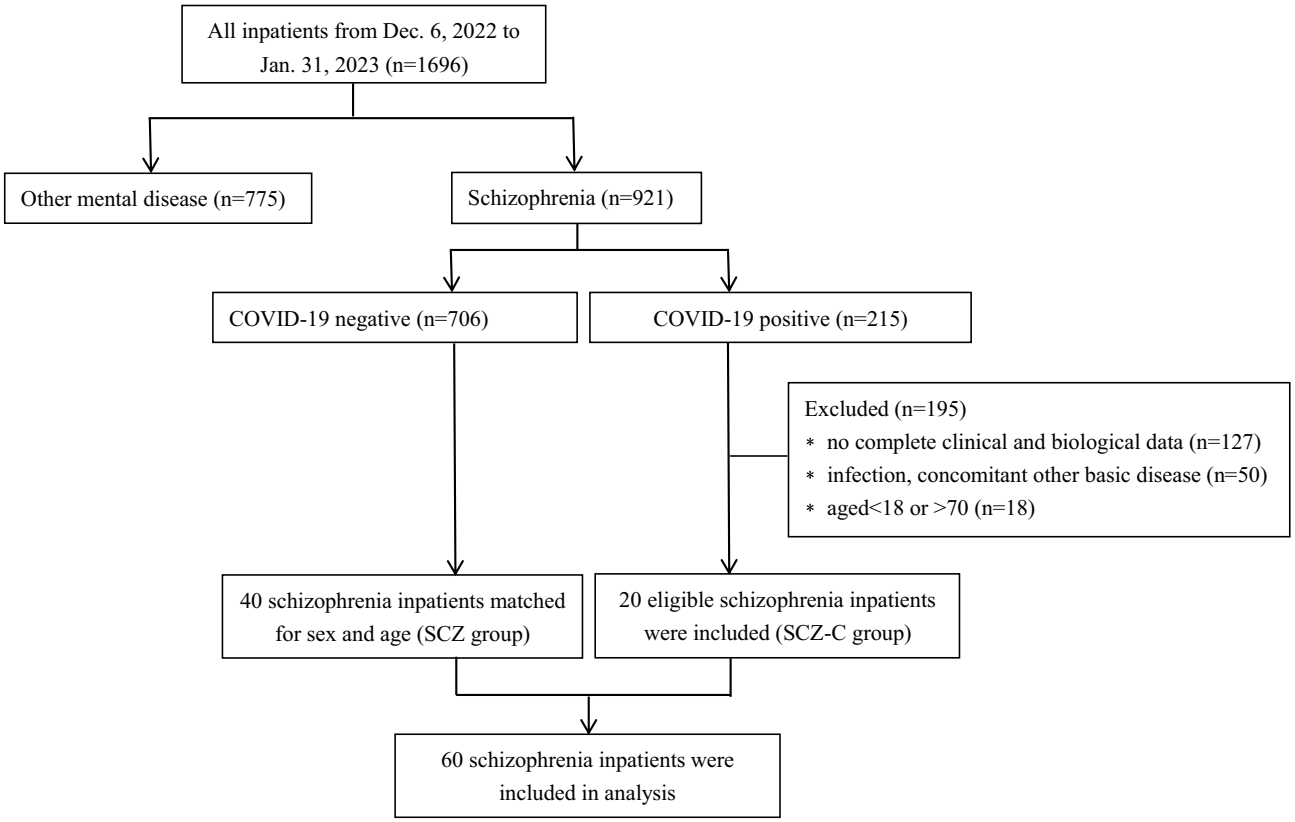

Figure 1 Flow chart of the enrolled participants.

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) Assay for SARS-CoV-2 Infection

The RT–PCR test was performed using nasopharyngeal and oropharyngeal samples taken from the patients.[23] A Daan 2019-nCoV RT–PCR Kit (Daan Gene, China) targeting open reading frame 1a or 1b (ORF1ab) and the nucleocapsid protein (N) gene was used to detect SARS-CoV-2 according to the manufacturer's instructions. All reactions were carried out with a SLAN®-96S Real-Time PCR System (Hongshi Medical Technology Co., Ltd., China).

Statistical Analysis

All statistical analyses were performed using SPSS v22.0 software (SPSS, Inc.). The results are expressed as the mean ± standard (for normally distributed data) and median with interquartile ranges (for non-normally distributed). The variables were compared using one-way ANOVA test, while non-normally distributed variables were compared using Mann–Whitney *U*-tests and Kruskal–Wallis H. Qualitative variables were analyzed using the chi-square test. Correlation analysis was performed with the Spearman's rank correlation coefficient. The correlation coefficients of these relationships were represented by a heatmap. The significance level was set at $P<0.05$.

Results

Patient Demographics and Characteristics

The present study consisted of 60 schizophrenia patients, 20 of whom were confirmed by laboratory tests to have COVID-19 and 40 healthy controls. The demographic and clinical characteristics are shown in Table 1. No significant differences were found in sex, age, BMI and years of education among the health controls, SCZ and SCZ-C groups. Besides, we did not find any significant difference between the SCZ-C and SCZ groups in mental disorder duration, treatment status and PANSS score.

Table 1 Demographic and Clinical Characteristics of the Participants

Variables	Healthy controls	SCZ group	SCZ-C group	P^a	P^b
Sex (M/F)	32/8	32/8	16/4	0.641	
Age	35.5(33.0–41.0)	41.0(36.0–54.5)	45.0(29.0–55.5)	0.493	
BMI(kg/m^2)	22.3(20.5–24.6)	21.7(19.9–25.2)	22.9(19.4–27.3)	0.341	
Education(y)	12.0(12.0–16.0)	9.0(9.0–12.0)	9.0(9.0–14.0)	0.489	
Mental disorder duration(y)	NA	18.0(12.0–25.0)	18.5(10.5–25.0)		0.858
Alcohol use(n)					1.000
Yes	NA	6(15%)	3(15%)		
No	NA	34(85%)	17(85%)		
Smoking(n)					0.402
Yes	NA	18(45%)	6(30%)		
No	NA	22(55%)	14(70%)		
Treatment status(n)					
Drug free	NA	12(30.0%)	5(25.0%)		0.769
Treated	NA	28(70.0%)	15(75.0%)		
PANSS score					
PANSS-P	NA	7.0(7.0–14.0)	7.0(7.0–11.0)		0.048
PANSS-N	NA	14.0(10.0–16.0)	11.0(11.0–14.0)		0.634
PANSS-G	NA	18.5(17.0–20.5)	18.0(17.0–20.0)		0.074
PANSS-T	NA	44.0(41.0–50.0)	42.0(38.5–47.5)		0.318

Notes: Data are presented as median (IQR). Age, BMI and education in different groups were compared using a Kruskal–Wallis *H*-test. Mental disorder duration and PANSS score in different groups were compared using a Mann–Whitney *U*-test. Categorical variables were compared using a Chi-square test. P^a: comparison between the healthy controls, SCZ and SCZ-C groups. P^b: comparison between the SCZ and SCZ-C groups.

Abbreviations: SCZ, schizophrenia; SCZ-C, schizophrenia patients infected with COVID-19; M, male; F, female; IQR, interquartile range; BMI, body mass index; SD, standard deviation; PANSS, positive and negative syndrome scale; PANSS-N, the negative symptom score of PANSS; PANSS-P, the positive symptom score of PANSS; PANSS-G, the general psychopathology score of PANSS; PANSS-T, the total PANSS score; NA, not available.

Comparison of Serum Biochemical Tests Among Different Groups

The serum levels of AST, ALP, Cr, LDH were significantly higher in the SCZ-C group compared to SCZ group (28.8 U/L [22.1–62.0] vs 22.0 U/L [18.8–27.0], p=0.009; 85.04 ± 3.80 U/L vs 72.53 ± 3.71 U/L, p=0.048; 72.3 umol/L [63.0–103.3] vs 67.7 umol/L [58.7–72.9], p=0.048; 184.7 U/L [144.5–204.4] vs 142.0 U/L [129.5–176.7], p=0.023) (Table 2). Furthermore, the patients were divided into four subgroups according to SARS-CoV-2 infection and antipsychotic medication use (Table 1). Antipsychotic medication and dosage used in schizophrenia patients were presented in Supplementary Table 2. Nevertheless, we found no statistically difference between drug-free and treated groups between SCZ and SCZ-C patients (p>0.05) (Table 3).

Table 2 Comparison of Serum Biochemical Tests Between Groups

Variables	Healthy controls	SCZ group	SCZ-C group	P^a	P^b
ALT(U/L)	18.7(12.2–27.4)	19.5(15.7–30.9)	23.1(15.6–37.6)	0.268	0.673
AST(U/L)	23.0(17.9–26.9)	22.0(18.8–27.0)	28.8(22.1–62.0)	**0.008**	**0.009**
ALP(U/L)	68.18±3.36	72.53±3.71	85.04±3.80	**0.003**	**0.048**
GGT(U/L)	24.25±3.01	22.26±2.04	22.01±3.15	0.824	0.958
ALB(g/L)	48.3(47.2–50.1)	44.7(42.6–46.5)	44.2(42.3–46.2)	**<0.001**	0.426
GLO(g/L)	27.14±3.29	25.29±4.72	25.21±3.08	0.052	0.932
TP(g/L)	75.67±4.32	69.96±6.72	68.07±7.68	**<0.001**	0.585
TBIL(umol/L)	12.6(10.9–15.0)	9.8(6.9–13.4)	8.7(6.9–13.4)	**0.004**	0.596
DBIL(umol/L)	2.2(1.8–2.7)	2.1(1.3–3.0)	1.9(1.7–2.7)	0.558	0.829
TG(mmol/L)	1.0(0.7–1.5)	1.1(0.7–1.4)	1.1(0.7–1.3)	0.667	0.868
CHO(mmol/L)	5.3(4.5–6.8)	4.8(4.5–5.4)	4.5(3.4–5.2)	**0.025**	0.394

(*Continued*)

Table 2 (Continued).

Variables	Healthy controls	SCZ group	SCZ-C group	P^a	P^b
HDL-C(mmol/L)	1.51±0.04	1.37±0.07	1.17±0.06	**<0.001**	0.063
LDL-C(mmol/L)	3.25±0.14	3.19±0.10	3.12±0.21	0.862	0.781
Apoa(g/L)	1.6(1.4–1.8)	1.2(1.0–1.3)	1.0(0.9–1.2)	**<0.001**	0.057
Apob(g/L)	1.16±0.05	0.91±0.03	0.88±0.06	0.654	0.987
Urea(mmol/L)	4.66±0.15	4.15±0.14	3.57±0.31	0.056	0.078
Cr(umol/L)	68.0(60.5–75.5)	67.7(58.7–72.9)	72.3(63.0–103.3)	0.120	**0.048**
UA(umol/L)	301.1(259.8–361.3)	335.3(271.5–370.0)	315.5(253.0–475.8)	0.256	0.451
CK(U/L)	79.5(68.5–106.8)	86.6(68.5–129.9)	178.5(69.0–473.0)	**0.047**	0.092
LDH(U/L)	170.9(153.0–192.8)	142.0(129.5–176.7)	184.7(144.5–204.4)	**0.006**	**0.023**
CKMB(U/L)	10.0(8.1–12.4)	10.7(7.4–13.4)	9.9(7.3–15.0)	0.994	0.869

Notes: Data are presented as mean ± SD or median (IQR). *P* values are acquired by Kruskal–Wallis *H*-test and one-way ANOVA test. P^a: comparison between the healthy controls, SCZ and SCZ-C groups. P^b: comparison between the SCZ and SCZ-C groups. Bolds: statistical significance.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase; ALB, albumin; GLO, globin; TP, total protein; TBIL, total bilirubin; DBIL, direct bilirubin; TG, triglyceride; CHO, cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; apoA, apolipoprotein A; apoB, apolipoprotein B; Cr, creatinine; UA, uric acid; CK, creatine kinase; LDH, lactate dehydrogenase; CK-MB, creatine kinase-MB.

Table 3 Comparison of Serum Biochemical Tests of Four Subgroups

Variables	SCZ drug free	SCZ treated	SCZ-C drug free	SCZ-C treated	*P*
AST(U/L)	24.4(20.0–28.9)	23.0(18.4–29.8)	28.2(18.0–73.0)	31.0(22.3–60.7)	0.065
ALP(U/L)	76.0(63.0–90.8)	80.0(65.8–107.6)	79.0(60.5–96.1)	72.0(61.8–81.8)	0.241
Cr(umol/L)	69.0(54.4–72.9)	66.3(58.4–76.0)	71.0(62.3–79.0)	72.3(63.2–106.3)	0.217
LDH(U/L)	144.0(136.0–182.8)	144.0(129.2–170.4)	168.0(121.0–298.7)	185.4(161.0–202.6)	0.146

Notes: Data are presented as median (IQR). *P* values are acquired by Kruskal–Wallis *H*-test.

Changes of Lymphocyte Subsets and Mitochondrial Mass in Different Groups

The SCZ-C group had significantly lower $CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$ T-cell counts than SCZ group (694.4 [361.3–1364.9] vs 1494.0 [1241.3–1868.9], $p<0.001$; 315.7 [201.3–699.6] vs 759.9 [638.8–1029.4], $p<0.001$; 317.2 [161.9–565.5] vs 605.3 [447.5–753.6], $p<0.001$). Meanwhile, the mitochondrial mass of $CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$ T-cell was higher in the SCZ-C group compared to SCZ group (199.89 ± 40.59 vs 89.21 ± 6.07, $p<0.001$; 563.45 ± 144.61 vs 186.85 ± 11.46, $p<0.001$; 442.96 ± 86.82 vs 196.66 ± 15.42, $p<0.001$) (Table 4).

Table 4 Comparison of T Cell Sub-Populations Between Groups

Variables	Healthy controls	SCZ group	SCZ-C group	P^a	P^b
CD3+(%)	69.01±9.01	67.31±9.08	65.25±8.96	0.281	0.407
CD3+CD4+(%)	37.33±6.37	36.68±7.49	31.87±10.85	0.059	0.066
CD3+CD8+(%)	28.2(22.0–31.6)	24.8(21.6–29.5)	24.9(21.8–30.1)	0.436	0.510
CD3+ count	1494.0(1241.3–1868.9)	1277.6(1071.7–1531.5)	694.4(361.3–1364.9)	**<0.001**	**<0.001**
CD3+CD4+ count	759.9(638.8–1029.4)	712.2(607.2–838.2)	315.7(201.3–699.6)	**<0.001**	**<0.001**
CD3+CD8+ count	605.3(447.5–753.6)	494.9(414.4–612.8)	317.2(161.9–565.5)	**<0.001**	**<0.001**
CD3+ SCMM	89.21±6.07	142.16±7.78	199.89±40.59	**<0.001**	**<0.001**
CD3+CD4+ SCMM	186.85±11.46	333.17±20.82	563.45±144.61	**<0.001**	**<0.001**
CD3+CD8+ SCMM	196.66±15.42	240.62±18.23	442.96±86.82	**<0.001**	**<0.001**

Notes: Data are presented as mean ± SD or median (IQR). *P* values are acquired by Kruskal–Wallis *H*-test and one-way ANOVA test. P^a: comparison between the healthy controls, SCZ and SCZ-C groups. P^b: comparison between the SCZ and SCZ-C groups. Bolds: statistical significance.

Abbreviation: SCMM, single-cell mitochondrial mass.

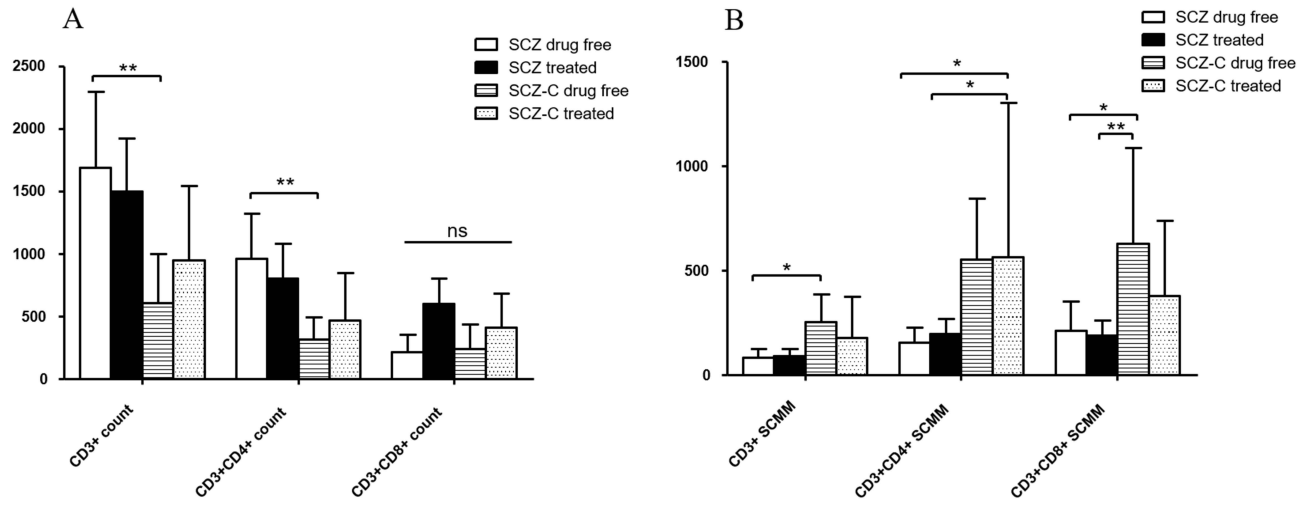

Figure 2 Comparison of T lymphocyte counts and SCMM of four subgroups (SCZ drug free, SCZ treated, SCZ-C drug free and SCZ-C treated).
Notes: (**A**) Comparison of T cells ($CD3^+$ T cells, $CD3^+CD4^+$ T cells, and $CD3^+$ $CD8^+$ T cells) between groups. (**B**) Comparison of the T-cell SCMM ($CD3^+$ T cells, $CD3^+CD4^+$ T cells, and $CD3^+$ $CD8^+$ T cells) between groups. *p<0.05; **p<0.005; ns, no significance; SCMM, single-cell mitochondrial mass.

Interestingly, in comparison to the SCZ drug-free group, the $CD3^+$ and $CD3^+CD4^+$ T-cell counts reduced in the SCZ-C drug-free group (p<0.01) (Figure 2A). Also, we found increased mitochondrial mass of $CD3^+$ and $CD3^+CD8^+$ T-cell in SCZ-C drug-free group compared to SCZ drug-free group (p<0.05) (Figure 2B). Additionally, the $CD3^+CD4^+$ SCMM of SCZ-C treated group was significantly higher than SCZ drug-free and SCZ treated groups (p<0.05) (Figure 2B).

Relationship Between Laboratory Data and PANSS Scores

To further determine whether there were any relationships between the laboratory data and symptoms of psychosis of SCZ patients, we analyzed the association between laboratory data and PANSS scores. In SCZ-C group, PANSS-P score was found to be positively correlated with $CD3^+$ (r = 0.542, p = 0.014) and $CD3^+CD4^+$ (r = 0.565, p = 0.009) cell counts, and negatively correlated with SCMM of $CD3^+$ (r = 0.474, p = 0.035) and $CD3^+CD4^+$ (r = 0.519, p = 0.019) T cells (Figure 3A). Otherwise, we found no significant correlations between clinical laboratory data and PANSS scores in SCZ group (Figure 3B).

A

	PANSS-N	PANSS-P	PANSS-G	PANSS-T
AST	-0.123	0.415	0.167	0.286
ALP	-0.040	-0.212	-0.238	-0.252
Cr	0.184	-0.067	-0.078	-0.025
LDH	-0.203	0.343	0.078	0.136
CD3+ counts	-0.390	0.542*	0.265	0.174
CD3+CD4+ counts	-0.350	0.565*	0.227	0.150
CD3+CD8+ counts	-0.387	0.518	0.194	0.106
CD3+ SCMM	0.286	-0.474*	-0.105	-0.062
CD3+CD4+ SCMM	0.313	-0.519*	-0.092	-0.046
CD3+CD8+ SCMM	0.160	-0.316	-0.069	-0.059

B

	PANSS-N	PANSS-P	PANSS-G	PANSS-T
AST	-0.056	0.029	0.010	-0.070
ALP	0.352	-0.089	0.086	0.111
Cr	-0.372	-0.158	-0.502	-0.469
LDH	0.405	-0.020	0.246	0.206
CD3+ counts	-0.329	0.094	-0.204	-0.196
CD3+CD4+ counts	-0.208	0.170	0.059	-0.004
CD3+CD8+ counts	-0.241	-0.040	-0.364	-0.289
CD3+ SCMM	0.204	-0.123	0.143	0.102
CD3+CD4+ SCMM	0.185	-0.180	0.021	0.025
CD3+CD8+ SCMM	0.182	-0.069	0.215	0.129

Figure 3 Spearman correlation analysis between laboratory data and PANSS scores in the SCZ and SCZ-C group.
Notes: (**A**) Correlation analysis in SCZ-C group. (**B**) Correlation analysis in SCZ group. Positive correlations are shown in red, negative correlations are shown in green, and the color intensity is proportional to the correlation coefficient. AST, aspartate aminotransferase; ALP, alkaline phosphatase; Cr, creatinine; LDH, lactate dehydrogenase; SCMM, single-cell mitochondrial mass; PANSS: positive and negative syndrome scale. *p<0.05.

Discussion

Due to the rapid spread and uncertainty of the virus, COVID-19 still remains a major public health problem. In particular, the association between COVID-19 and mental disorders appears to be bidirectional.[24] Psychiatric patients might be at higher risk of COVID-19 infection, and COVID-19 survivors have an increased risk of adverse mental health outcomes.[25] Some previous work discussed the impact of the COVID-19 pandemic on schizophrenia patients[4,5] and proposed recommendations to mitigate the adverse consequences of COVID-19 on persons with schizophrenia.[13]

The first finding of this study was that the serum levels AST, ALP, LDH and Cr were significantly higher in SCZ-C group than SCZ groups, but no significant differences were found in drug free and treated patients of the two groups. SARS-CoV-2 infection can increase liver enzymes by affecting liver function. Inflammation and liver toxicity induced by multidrug therapy may be the main causes of elevated liver enzymes observed in COVID-19 patients.[26] Additionally, kidney injury and heart failure are also common in patients with COVID-19.[27,28] In the present study, we found abnormally higher levels of AST and ALP in the SCZ-C group, while such a difference was not observed in serum ALT and GGT levels. On the other hand, we need to pay more attention to heart damage in schizophrenia patients with COVID-19, when the levels of myocardial enzymes such as LDH were much higher than in patients who were not infected with SARS-CoV-2. Studies have demonstrated that LDH may be the prognostic factors for severity and adverse outcomes of COVID-19.[17] The level of Cr was also increased remarkably in SARS-CoV-2-positive schizophrenia patients, which are the signs for kidney dysfunction. However, it is widely accepted that abnormal serum biochemical levels and liver dysfunction in SCZ patients could also be caused by antiviral medication use, unbalanced diet, excessive smoking and alcohol consumption.[29–31] Due to the limited sample size of this study, future research needs to encompass a broader range of schizophrenia patients and take into account important confounders such as smoking, alcohol use and eating habits.

Next, we compared the blood T-cell subpopulations and SCMM using flow cytometry between the SCZ-C group and the SCZ group. The results showed that the cell counts of $CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$ T lymphocytes were significantly lower in the SCZ-C group, compared to the SCZ group. A previous study revealed that the decline in lymphocyte counts was one characteristic of COVID-19,[32] which was in line with our results. Furthermore, we found that the SCMM of T lymphocytes was significantly higher in schizophrenia patients with COVID-19 than in those without COVID-19. SCMM can sensitively reflect the function of cell mitochondria, which is a new index in the evaluation of cell mitochondrial function.[22] Some researchers revealed that mitochondrial dysfunction might be associated with mental disorders.[33] In addition, acute recurrence of schizophrenia might be related to elevated levels of mitochondrial damage in peripheral blood T lymphocytes.[34] Recent studies have demonstrated that mitochondrial function was severely impaired in lymphocytes of COVID-19 patients.[19] The higher SCMM in peripheral blood T lymphocytes reflects abnormal mitochondrial metabolism, which can result in decreased energy generation.

Previous studies have demonstrated that biochemical changes were associated with antipsychotic drug use.[35] Therefore, we further divided these patients into four subgroups according to drug taking. No statistically differences of AST, ALP, LDH and Cr levels were found between drug-free and treated groups between SCZ and SCZ-C patients. In drug free group, the $CD3^+$ and $CD3^+CD4^+$ cell counts were significantly lower in SCZ-C group than SCZ group. Studies have found that lymphocytes were significantly decreased in COVID-19 patients,[36] which were consistent with our study. Furthermore, we found that the $CD3^+$ and $CD3^+CD8^+$ SCMM in SCZ-C drug free group were higher than SCZ drug free group. Recent studies have shown that the $CD3^+CD8^+$ SCMM may act as a diagnostic biomarker of COVID-19 progression.[19] According to our study, mitochondria may represent critical mediators and serve as strategic therapeutic targets in schizophrenia patients who were infected with SARS-CoV-2.

At the end of the study, we conducted a correlation analysis of laboratory data and PANSS scores in the SCZ-C and SCZ groups. We found that the PANSS-P score was positively correlated with the $CD3^+$ and $CD3^+CD4^+$ cell counts and negatively correlated with the SCMM of $CD3^+$ and $CD3^+CD4^+$ in SCZ-C group. Otherwise, no correlation was found

between the laboratory data and the positive, negative, or general symptoms in SCZ group. Previous studies have discussed mitochondrial dysfunction in COVID-19 patients.[37] Furthermore, many studies have suggested a relationship between mitochondrial damage and PANSS scores.[34,38] To some extent, mitochondrial damage in lymphocytes can be used as a biomarker of treatment response, which may be helpful for the treatment of schizophrenia patients infected with SARS-CoV-2. We assume that mitochondrial therapy may be useful in alleviating positive symptoms in SARS-CoV -2-positive schizophrenia patients.

This retrospective study was the first to explore the biochemical characteristics, including the mitochondrial mass of T lymphocytes and serum biochemical levels, of SARS-CoV-2-positive schizophrenia patients. Our study is not exempt from limitations, some of which are inherent to retrospective studies. The relatively small sample size because of missing data might have reduced the statistical power and increased the risk of bias. Furthermore, important confounders that affect biochemical indicators, such as smoking, alcohol use and medication situations, should also be taken into account. Future research should address these limitations by increasing sample sizes.

Conclusion

Our data confirmed that schizophrenic patients with COVID-19 present significant mitochondrial damage in T lymphocytes and a sharp increase in serum AST, ALP, Cr and LDH levels. Positive correlations were found between the cell counts and SCMM of $CD3^+$ and $CD3^+CD4^+$ T cells and PANSS-P scores. This is the first study to characterize the biochemical values in SARS-CoV-2-positive schizophrenia patients, and we expect the findings to provide useful evidence for the treatment of these individuals.

Ethics Approval & Patient Consent Statement

This study was approved by the Xiamen Xianyue Hospital Ethical Committee (No. 2022-KY-034). And, because this was a retrospective cohort study, the Ethics Committee authorized the exemption of patients from informed consent. Attention was paid to minimal risk of patient data confidentiality, and the study was conducted in accordance with the Declaration of Helsinki.

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Disclosure

All authors have no conflicts of interest to declare in this work.

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