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Impact of second-generation antipsychotics monotherapy or combined therapy in cytokine, lymphocyte subtype, and thyroid antibodies for schizophrenia: a retrospective study

Xiaonan Guo[1†], Lingzhuo Kong[1†], Yalan Wen[1†], Lizichen Chen[1] and Shaohua Hu[1,2,3,4,5,6,7*]

Abstract

Background Schizophrenia (SCZ) shares high clinical relevance with the immune system, and the potential interactions of psychopharmacological drugs with the immune system are still an overlooked area. Here, we aimed to identify whether the second-generation antipsychotics (SGA) monotherapy or combined therapy of SGA with other psychiatric medications influence the routine blood immunity biomarkers of patients with SCZ.

Methods Medical records of inpatients with SCZ from January 2019 to June 2023 were retrospectively screened from June 2023 to August 2023. The demographic data and peripheral levels of cytokines (IL-2, IL-4, IL-6, TNF-α, INF-γ, and IL-17 A), lymphocyte subtype proportions (CD3+, CD4+, CD8+T-cell, and natural killer (NK) cells), and thyroid autoimmune antibodies (thyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TGAb)) were collected and analyzed.

Results 30 drug-naïve patients, 64 SGA monotherapy (20 for first-episode SCZ, 44 for recurrent SCZ) for at least one week, 39 combined therapies for recurrent SCZ (18 with antidepressant, 10 with benzodiazepine, and 11 with mood stabilizer) for at least two weeks, and 23 used to receive SGA monotherapy (had withdrawn for at least two weeks) were included despite specific medication. No difference in cytokines was found between the SGA monotherapy sub-groups ($p > 0.05$). Of note, SGA monotherapy appeared to induce a down-regulation of IFN-γ in both first (mean [95% confidence interval]: 1.08 [0.14–2.01] vs. 4.60 [2.11–7.08], $p = 0.020$) and recurrent (1.88 [0.71–3.05] vs. 4.60 [2.11–7.08], $p = 0.027$) episodes compared to drug-naïve patients. However, the lymphocyte proportions and thyroid autoimmune antibodies remained unchanged after at least two weeks of SGA monotherapy ($p > 0.05$). In combined therapy groups, results mainly resembled the SGA monotherapy for recurrent SCZ ($p > 0.05$).

[†]Xiaonan Guo, Lingzhuo Kong and Yalan Wen contributed equally to this work.

*Correspondence:
Shaohua Hu
dorhushaohua@zju.edu.cn

Full list of author information is available at the end of the article

Conclusion The study demonstrated that SGA monotherapy possibly achieved its comfort role *via* modulating IFN-γ, and SGA combined therapy showed an overall resemblance to monotherapy.

Keywords Schizophrenia, Monotherapy, Combined therapy, Second-generation antipsychotics, Immunity

Introduction

Schizophrenia (SCZ) is a debilitating psychiatric disorder with an estimated lifetime risk of around 1%, constituting about 10% of the permanently disabled population [1]. Uncoordinated emotion and behavior, as well as cognitive deficits, impose a giant burden on individuals with SCZ and their families [2]. With around 70% heritability, SCZ is thought to conform to a multi-factorial polygenic threshold model [3], that is, environmental stress might increase the expression of pro-inflammatory cytokines, which are postulated to be important in SCZ development [4, 5]. Such a vulnerability-stress-inflammation model was put forward with great research interest [6]. Increasing evidence has connected the pathophysiology of SCZ with dysregulated immunity [5].

Considerable epidemiological and clinical studies have proven that various infectious agents, which trigger the inflammation and immune response in the body, are risk factors for SCZ [7]. More than the acute immune changes, lifelong and insidious immunological aberrations including cytokines (i.e., interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)) have also been unveiled for SCZ [8–13]. It was frequently reported that circulating levels of IL-2, IL-6, IL-8, TNF-α, and Interferon-γ (IFN-γ) tended to be increased in the first episode of psychosis, and were listed in the high-risk predictive factors for psychosis episodes [14–17]. Intriguingly, IL-1β, IL-2, IL-6, and TNF-α across four studies and IL-4 across three studies were also identified with positive association with negative symptoms [18]. In a meta-analysis of 2398 patients, cognitive deficits were observed to reflect elevated IL-6, IL-1β, and TNF-α levels [19]. Previous works have identified correlations between traits of lymphocytes (which can produce cytokines and also be signaled by cytokines in innate and adaptive response) and SCZ [20–23]. As indicated, CD3, CD4, and the CD4/CD8 ratio were significantly increased in a meta-analysis of sixteen studies, further proving the hypothesis of association between inflammation and SCZ [23]. It is well established that inflammation is a conservative necessity to defend against infectious agents as well as tissue damage [24]. It appears as a double-edged sword in both our peripheral body and our central nervous systems. As a relatively low-grade neuroinflammatory process was confirmed in numerous neuroimaging studies with the loss of central nervous system volume and microglial activation, it is widely hypothesized that the inflammation drives the SCZ progression [25–37]. Numerous preclinical and proton magnetic resonance spectroscopy studies also demonstrated that early infections or immune activation with elevated cytokines impact neurodevelopmental processes, including dopaminergic, glutamatergic, and GABAergic neurotransmission in animal models and patients [38–41].

Epidemiological observations have also strongly supported the association between SCZ and autoimmune diseases. A population-based study highlighted an approximate 45% increase in relative SCZ risk for individuals with a family history of autoimmune disease, and a 50% higher lifetime prevalence of autoimmune diseases in patients with SCZ [42]. In particular, compelling evidence underscored the associative prevalence between SCZ and distinct autoimmune diseases, including reduced risk of rheumatoid arthritis [43], and increased risk of autoimmune thyroiditis [44], celiac disease [45], type 1 diabetes [46], and acquired hemolytic anemia [42]. Severe autoimmune diseases that require hospitalization due to refractory infection, have been identified as a notable risk factor for SCZ. This relationship followed a dose-response pattern, suggesting a direct correlation between the severity of the autoimmune diseases and the risk of developing SCZ [47]. In addition, it was found that individuals with SCZ announced a high prevalence of autoantibodies against the whole brain or specific brain regions (including the cerebrum, septum, amygdala, frontal cortex, cingulate gyrus, and septal area), or brain-related molecules such as neurotransmitter receptors, showing the possible causal relationship with autoimmunity and SCZ [48–51].

Preliminary immune aberration evidence indicated the implication of innate and adaptive response in SCZ progression. These findings highly emphasized the participation of dysregulated peripheral and cerebral immunity in the SCZ mechanism. However, due to the heterogeneity of SCZ progression and the limited application of immune biomarkers, the specific role of immune deficit in SCZ pathophysiology remains controversial. Inspirations from effective treatment highlight the potential link between immunity and the development of SCZ [52]. It is suggested that antipsychotics (i.e., the second-generation antipsychotics (SGA)) might have intrinsic anti-inflammatory and immunomodulatory effects on some cytokines and lymphocytes [5, 53–57]. Previous research also showed that monotherapy of antidepressants, benzodiazepines (BZD), or mood stabilizers showed anti-inflammatory effects [58–60]. However, whether the SGA monotherapy or combined therapy of SGA and other psychiatric medication (including antidepressant, BZD,

and mood stabilizer) influence the immunity of patients with SCZ remains further explorations.

Here, considering the accessibility of statistics, we retrospectively analyzed cytokine levels, lymphocyte subtypes, and thyroid autoimmune antibodies in serum, to investigate how SGA monotherapy, and combined therapy of SGA with antidepressant, BZD, or mood stabilizer, influence the immunity of patients with SCZ. In the hospital, peripheral cytokines and lymphocyte proportion tests were used to examine the basic inflammation and immune situation of patients. Of note, patients with SCZ were documented susceptibility toward autoimmune thyroid disorders [44]. Considering the potential effect of autoimmunity in SCZ development and the accessibility of serum autoimmune antibody statics, data on thyroid autoimmune antibodies (thyroid peroxidase antibody (TPOAb), and antithyroglobulin antibody (TGAb)) were specially included in the study. This study potentially provides valuable insights into underlying the SCZ pathophysiology.

Materials and methods

Subjects and data acquisition

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (ITT20240569A). In terms of the retrospective, non-interventional, and anonymous nature of this research, written informed consent from patients was waived.

Based on the hospital electronic medical system, the naturalistic medical information of inpatients from January 2019 to June 2023 in the Department of Psychiatry, the First Affiliated Hospital, Zhejiang University School of Medicine, was extracted. The sampling was carried out between July 2023 to August 2023.

Inclusion criteria:

1) 15 ~ 45 years old;
2) a diagnosis with SCZ, according to *The International Statistical Classification of Diseases and Related Health Problems 10th Revision* (*ICD-10*);
3) medical history was accessible.

Exclusion criteria:

1) During pregnancy or lactation;
2) With other psychiatric disorders including acute and transient psychotic disorder, bipolar disorder, major depression disorder, and substance use including alcohol, drugs, and cigarettes;
3) Complicating physical diseases that affect immunity (cancer, autoimmune disease, chronic metabolic disease, etc.);
4) Intolerable to SGA, antidepressant, BZD, or mood stabilizer;
5) History of brain diseases, such as traumatic brain injury, cerebral tumor, encephalitis, etc.

We double-assessed the medication history in the electronic medical record and collected the data of patients with SCZ under different baseline medication conditions. Given the heterogeneity in distinct types of SCZ (i.e., first-episode and recurrent), we separated it of particular interest [61]. Based on medical history, first-episode SCZ referred to patients under acute episodes with the primary diagnosis of SCZ, and recurrent SCZ referred to relapse or exacerbation of SCZ.

To compare the effect of SGA monotherapy (single use of aripiprazole, olanzapine, quetiapine, paliperidone, clozapine, risperidone, amisulpride, or combined use of these drugs), we included patients with SCZ and divided them into four groups:

1) Drug-naïve group: patients with first-episode SCZ who never received antipsychotic treatment;
2) First-episode group: patients were primarily diagnosed with SCZ and received the SGA monotherapy for at least one week;
3) Recurrent group: patients were in the relapsed course and received the SGA monotherapy for at least two weeks;
4) Post-effect group: patients used to receive regular antipsychotic treatment including SGA monotherapy or combined therapy, but had been withdrawn for at least two weeks. (Two weeks were frequently used in clinical trials as the wash-out period [62, 63].)

Comparisons of these sub-groups were applied to observe the effect of SGA monotherapy during different courses of SCZ.

For combined therapy, antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine, venlafaxine, desvenlafaxine, and duloxetine, BZD included diazepam, lorazepam, oxazepam, clonazepam, and alprazolam, and mood stabilizer included lithium carbonate and sodium valproate. The patients with SCZ included in these sub-groups were homogeneous in the recurrent state. To dissect the role of SGA combined therapy, patients who received combined therapy for at least two weeks were divided into three separate groups according to different medications:

1) Antidepressant + SGA;
2) BZD + SGA;
3) Mood stabilizer + SGA.

For all patients involved, demographic data (sex, age, height, and weight) and the duration of schizophrenia according to the medical record were gathered. Accessible immunity-relevant blood examination results including levels of cytokines (IL-2, IL-4, IL-6, TNF-α, INF-γ, and IL-17 A), lymphocyte subtype proportions (CD3+, CD4+, CD8+T-cell, and NK cells), and thyroid autoimmune antibodies (TPOAb and TGAb) were collected. These venous blood examinations were routinely carried out on the second day of the hospital stay in a fasting state at 7 a.m. Detailed methods of the lab examination process can be found in the **Supplementary Method** [64]. The positive symptom score, negative symptom score, and total score in Positive and Negative Syndrome (PANSS) in medical records were gathered to evaluate the positive symptom, negative symptom, and the overall severity trait of SCZ. Body mass index (BMI) was defined as the weight divided by the square of the height (kg/m^2). Specifically, as reported, the ratio of CD4/CD8, which evaluated the overall cell immunity, was associated with the psychosis episode of SCZ [23]. Thus, CD4/CD8 was also calculated and compared.

Statistics analysis

All statistical analyses were performed with GraphPad Prism 9.0 and JASP 0.18.2.0. For continuous variables, normality was initially checked by the Shapiro-Wilk test. To compare the continuous variable data, One-way ANOVA was conducted on the normally distributed data for multiple comparisons, and post-hoc tests were performed using LSD correction. Kruskal-Wallis test was conducted on non-normally distributed data, and post hoc tests were performed using Dunn's test for correction. To evaluate the influence of confounding variables, including age, sex, height, weight, and BMI, analysis of covariance (ANCOVA) was employed. The immune-related markers were identified as dependent variables, groups as fixed factors, and age, sex, height, weight, and BMI as covariates. Post-hoc analysis was conducted using Bonferroni correction when the group effect was significant. To assess the correlation between the identified immune markers and the duration of disease in the whole groups, the Spearman correlation test was applied. The categorical data (i.e., sex) were analyzed by the Pearson Chi-square test. Data represented mean±SEM. $P<0.05$ was denoted as statistical significance.

Results

Groups

Altogether, 30 drug-naïve patients with SCZ, 64 patients in the SGA monotherapy group (20 first-episode SCZ; 44 recurrent SCZ), 39 patients in the combined therapy for recurrent SCZ (18 with antidepressant; 10 with BZD; 11 with mood stabilizer), and 23 recurrent patients who used to receive SGA monotherapy (had withdrawn for at least two weeks) were enrolled. (Fig. 1).

To examine the effect of SGA monotherapy in different medication states, we compared the drug-naïve patients with SCZ, SGA monotherapy for first-episode or recurrent episode groups, and SGA post-effect group together (monotherapy comparison). To identify the effect of the combined therapy, we compared the drug-naïve patients with SCZ, SGA monotherapy for recurrent SCZ, and combined therapy for recurrent SCZ (combined therapy comparison). (Fig. 2).

Demographic and clinical data

Demographic data of participants were shown in Table 1. No statistical significance was found in sex and height ($p>0.05$). However, in the monotherapy comparison, patients in the recurrent episode group were generally older, and had higher BMI, compared to both drug-naïve patients with SCZ (age: $p<0.001$, BMI: $p<0.01$) and the first-episode group (age: $p<0.01$, weight: $p<0.05$). In the combined therapy comparison, compared to the drug-naïve patients in the SGA with antidepressant / BZD groups are older (antidepressant: $p<0.05$, BZD: $p<0.001$). Patients in the SGA with antidepressant / mood stabilizer groups had bigger BMI (antidepressant: $p<0.05$, mood stabilizer: $p<0.05$). To evaluate the severity of SCZ, P score, N score, and total score in PANSS and GAS were collected and analyzed, and no group difference was found. (Table 1; p value in Table S1).

SGA therapy mainly impacted peripheral inflammation by decreasing IL-4 and IFN-γ

Figure 3 revealed the serum cytokine level. Compared with the drug-naïve, the first-episode SCZ with SGA monotherapy group displayed a down-regulation of IFN-γ ($p<0.05$) and a decreased trend of IL-4 ($p=0.07$). In the SGA for the recurrent SCZ group, levels of IFN-γ and IL-4 were both significantly reduced ($p<0.05$). No difference in cytokine levels was detected between the two groups ($p>0.05$). After antipsychotic withdrawal for at least two weeks, levels of IFN-γ rose to the baseline (compared with drug-naïve, $p>0.05$). Moreover, despite insignificance, levels of IL-2, IL-4, IL-6, IL-8, IL-17, TNF-α, and IFN-γ were generally decreased after SGA monotherapy (i.e., TNF-α was likely to significantly decrease in SGA for first-episode ($p=0.09$) and recurrent episode ($p=0.10$) group compared with the drug-naïve). (Fig. 3; p value in Table S2).

As for combined therapy, patients with recurrent SCZ received SGA treatment with antidepressant, BZD, and mood stabilizer, all showed no significant difference in cytokine levels compared with the SGA monotherapy for recurrent ($p>0.05$). Nevertheless, SGA combined with antidepressant group revealed an increasing trend of IL-6

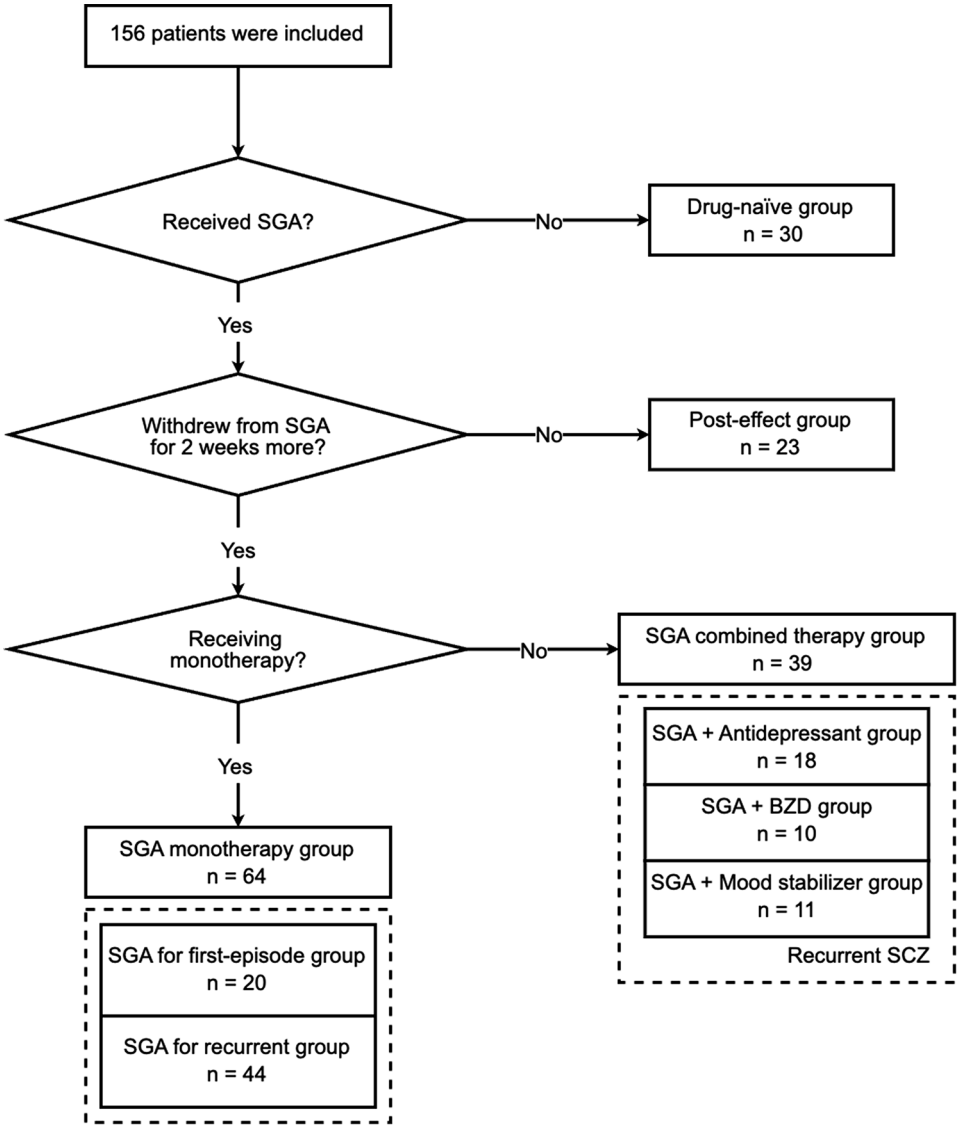

Fig. 1 The flow chart of the study

level compared with SGA monotherapy for recurrent SCZ ($p=0.08$).

Considering the confounders of demographic traits, no significant role of the involved confounders was related to the difference of therapy groups (IL-4 and IFN-γ) ($p>0.05$). Moreover, after the adjustment, the significance was consistent with the previous results. (Table S5).

First-episode SCZ with SGA monotherapy revealed elevated CD3+T-cell ratio and decreased NK cell ratio

Circulating CD4+, CD8+T-cell, and NK cell properties were analyzed. CD4+/CD8+was specially analyzed. These results were demonstrated in Fig. 4. In SGA for the first-episode SCZ group, compared with drug-naïve, the ratio of CD3+T-cell was generally elevated, specifically ($p<0.05$), and the ratio of NK cells showed a decreased trend ($p=0.05$). All of these properties in the SGA for the recurrent SCZ group showed no significance compared with drug-naïve ($p>0.05$). In addition, all of the subgroups in the combined therapy group showed no significance compared with the drug-naïve ($p>0.05$). (Fig. 4; p value in Table S3).

Given the impact of the demographic confounders, no significant difference was found in CD3+and NK cell proportion comparison ($p>0.05$). However, after adjustment of the confounders, the significance was diminished ($p>0.05$). (Table S5).

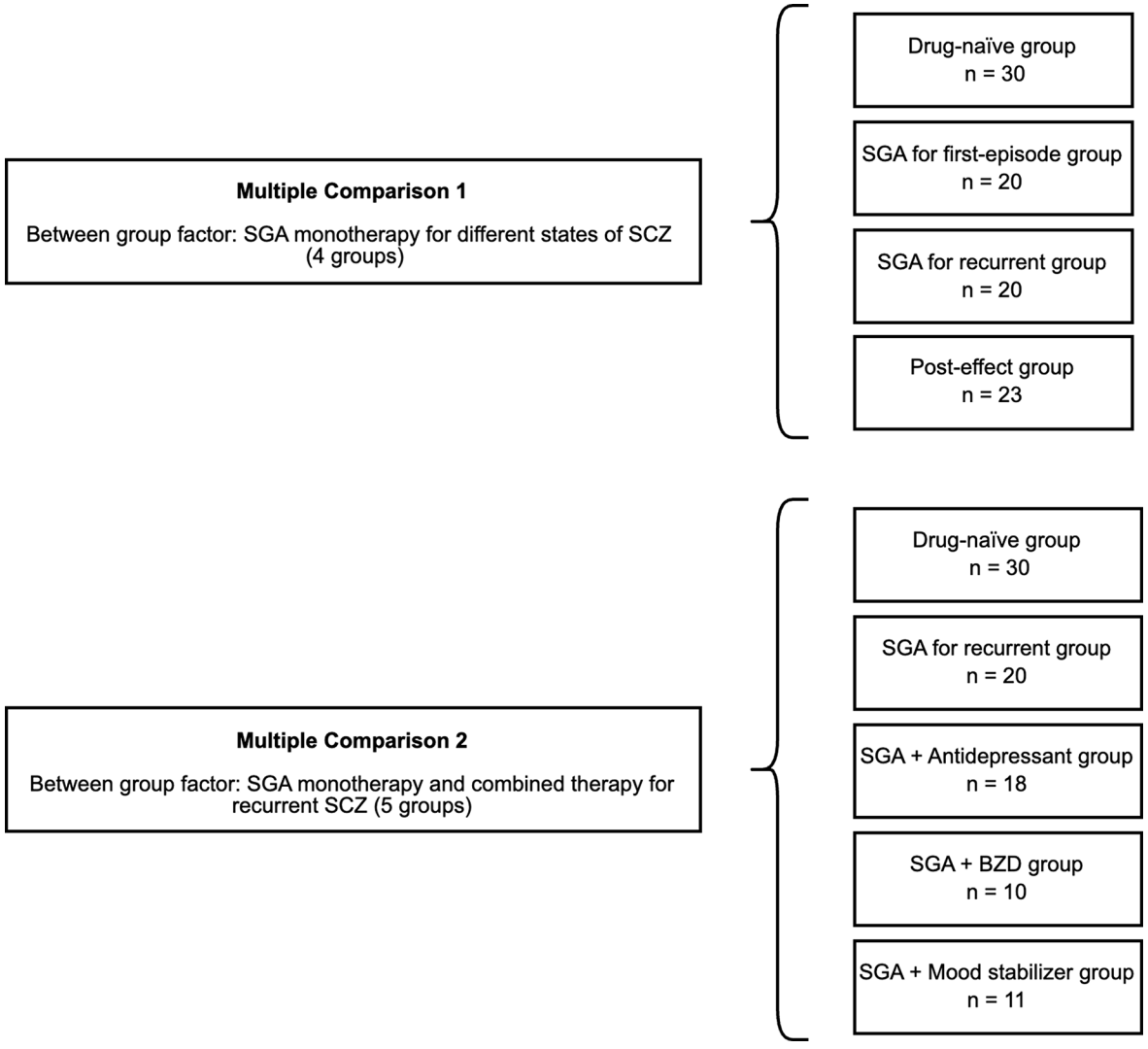

Fig. 2 The between-group factors and the used groups in multiple comparisons. Here the multiple comparison 1 aimed to reveal the effect of SGA monotherapy for different states of SCZ, and the multiple comparison 2 aimed to reveal the effect of mono- / combined- therapy for recurrent SCZ. Note that the drug-naïve group is the blank control in all the comparisons

Table 1 Demographic and clinical characteristics (mean ± SD)

	drug-naïve (*n* = 30)	**SGA for first-episode (*n* = 20)**	**SGA for recurrent (*n* = 44)**	**SGA post-effect (*n* = 23)**	**Antidepressant + SGA (*n* = 18)**	**BZD + SGA (*n* = 11)**	**Mood stabilizer + SGA (*n* = 10)**
Age (year)	18.7 ± 6.7	19.3 ± 7.5	27.1 ± 9.7	22.2 ± 7.2	26.1 ± 14.0	31.5 ± 11.9	19.4 ± 5.7
Male (%)	14.0 (0.5)	7.0 (0.4)	20.0 (0.5)	12.0 (0.5)	8.0 (0.4)	3.0 (0.3)	7.0 (0.7)
Height (cm)	166.3 ± 8.5	164.6 ± 6.7	165.0 ± 8.4	166.4 ± 7.5	166.1 ± 7.7	163.4 ± 9.1	167.0 ± 7.0
Weight (kg)	55.2 ± 10.0	54.9 ± 9.8	61.5 ± 10.1	61.3 ± 14.2	64.2 ± 13.4	59.4 ± 5.5	65.7 ± 13.7
BMI (kg/m^2)	19.9 ± 3.2	20.2 ± 2.8	22.5 ± 3.2	22.0 ± 4.1	23.2 ± 4.4	22.3 ± 2.0	23.5 ± 4.2
Disease course (Years)	1.2 ± 2.4	1.2 ± 2.4	4.7 ± 0.2	3.1 ± 2.2	2.2 ± 2.9	1.1 ± 1.5	1.7 ± 1.9
P score*	18.5 ± 4.2	23.4 ± 8.3	17.6 ± 6.3	19.3 ± 6.5	15.3 ± 5.9	17.3 ± 2.3	17.7 ± 9.7
N score	18.9 ± 5.8	22.0 ± 8.1	18.6 ± 7.4	23.2 ± 8.0	16.3 ± 3.1	18.0 ± 9.5	16.3 ± 9.0
PANSS	79.0 ± 17.9	90.0 ± 20.3	77.5 ± 18.4	92.0 ± 25.2	67.0 ± 19.3	75.3 ± 12.5	71.0 ± 30.3
GAS	48.1 ± 9.7	50.5 ± 7.6	47.7 ± 11.3	49.6 ± 10.9	49.8 ± 9.5	52.8 ± 2.3	62.5 ± 20.2

Note *P score: Positive symptom; N score: Negative symptom

Abbreviations PANSS: Positive and Negative Syndrome; GAS: Global Assessment Scale

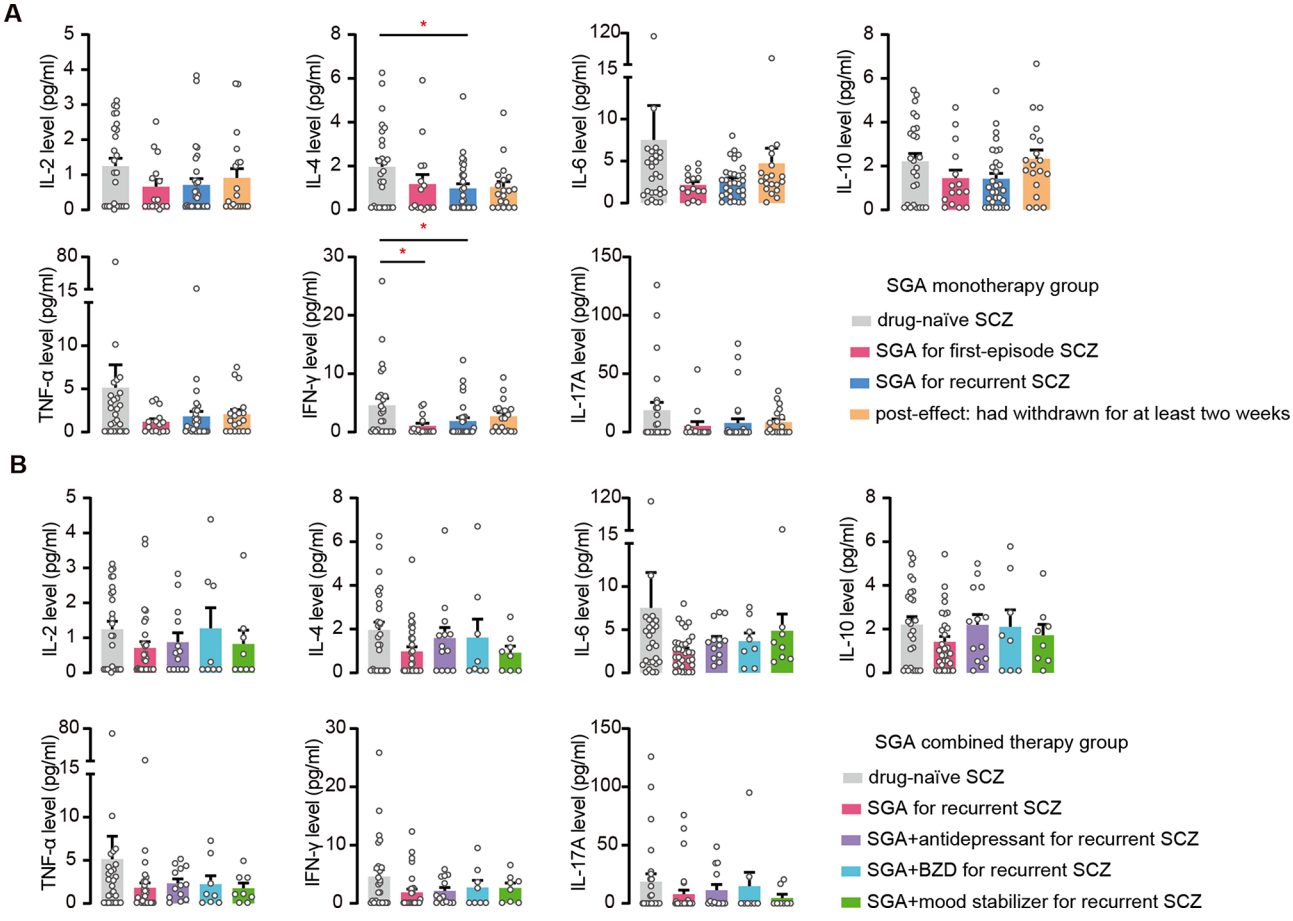

Fig. 3 Impact of SGA monotherapy and combined therapy for peripheral cytokines. (**A**) Inflammatory profiles of drug-naïve and SGA monotherapy in first-episode, recurrent and post-effect phase. (**B**) Inflammatory profiles of drug-naïve, SGA monotherapy, and SGA combined therapy with antidepressant, BZD, and mood stabilizer for recurrent SZC. (p* < 0.05, One-way ANOVA followed by LSD test or Kruskal-Wallis followed by Dunn's test)

Thyroid autoimmune antibodies were not significantly influenced by SGA monotherapy and combined therapy

Thyroid autoimmune antibody results were revealed in Fig. 5. No difference in the thyroid autoimmune antibodies was detected between each group ($p>0.05$). However, levels of TPOAb revealed an increased trend in the SGA for the first-episode group compared with the drug-naïve ($p=0.09$). (Fig. 5; p value in Table S4).

Given the impact of the demographic confounders, no significant difference was found in TPOAb and TgAb levels ($p>0.05$), which was consistent with direct comparison. (Table S5).

Disease course was irrelevant with identified immune markers

The disease course of schizophrenia was not associated with IL-2, IL-4, IL-6, TNF-α, INF-γ, IL-17 A, proportions of CD3+, CD4+, CD8+T-cell, and NK cells, TPOAb, and TGAb ($p>0.05$). (Table S6).

Discussion

Currently, the rescue role of different pharmacological therapies in the immune aberrations of SCZ remains controversial. Here, we reported the influence of SGA monotherapy and combined therapy of SGA with antidepressant, BZD, and mood stabilizer for immune profiles (cytokines, lymphocyte subtypes, and thyroid autoimmune antibodies) on patients with SCZ. This result, though preliminary, first provides the association between SGA combined therapy and various immune markers, and further adds the population-based evidence for SGA monotherapy in immunity.

Firstly, in this study, IFN-γ was significantly decreased, indicating that inactivation of T helper type-1 was induced in SGA treatment no matter the first or current episode phase. It could be inferred that SGA displayed its anti-inflammatory effect through inhibition of IFN-γ. Of note, increasing the level of IFN-γ was thought to be a reliable biomarker for treatment resistance (non-responders: $n=38$, responders: $n=30$) [65], making it reasonable for these inflammatory changes

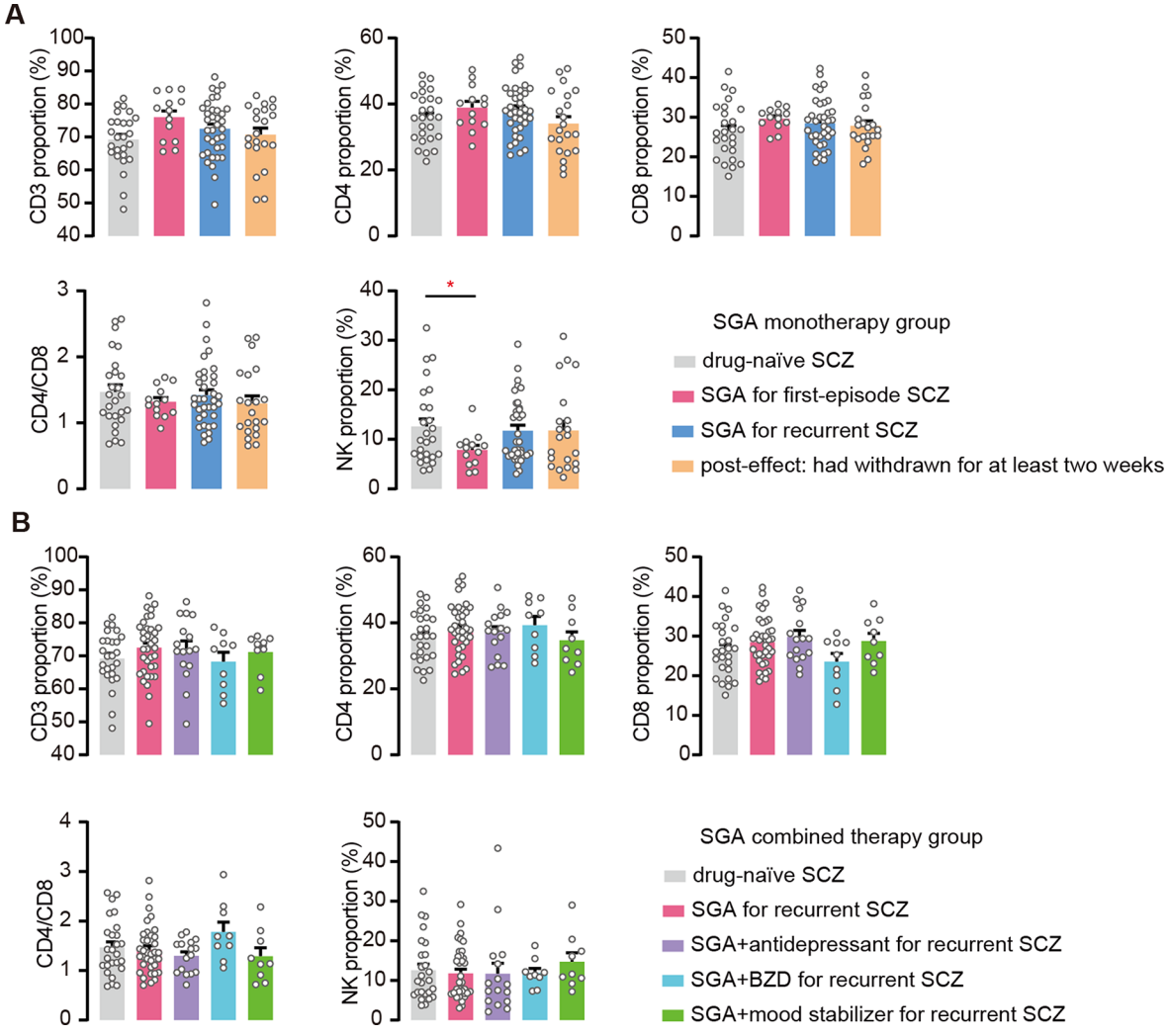

Fig. 4 Impact of SGA monotherapy and combined therapy for lymphocyte subtypes. (**A**) Lymphocyte subtypes profiles of drug-naïve and SGA monotherapy in first-episode, recurrent, and post-effect phase. (**B**) Lymphocyte subtype profiles of drug-naïve, SGA monotherapy, and SGA combined therapy with antidepressant, BZD, and mood stabilizer for recurrent SZC. ($p^* < 0.05$, One-way ANOVA followed by LSD test or Kruskal-Wallis followed by Dunn's test)

to play a protective role in SCZ. Meanwhile, IFN-γ displayed the same trend after the treatment of antipsychotics in a meta-analysis of 2 studies [53]. In addition, levels of IFN-γ rose in the drug-naïve patients when medication ceased, indicating the refractory property of SCZ. Meanwhile, anti-inflammatory IL-4 during SCZ relapse was down-regulated. Remarkably, IL-4 was found to be decreased in first-episode patients with schizophrenia after antipsychotic treatment, which is consistent with our results [66]. As indicated, IL-4 was significantly decreased in chronic schizophrenia-spectrum disorder in a high-quality meta-analysis of nine studies [13]. Therefore, the decreased IL-4 might be attributed to the chronicity of diseases instead of treatment [67, 68]. Longitudinal studies linking immune markers and schizophrenia to elucidate the cause and effect are highly required. As reported, longer disease duration with deterioration was observed in patients with SCZ with elevated levels of circulating IL-4, the level of which was highly correlated with negative symptoms across three studies [18]. Thus, the cost-effective circulating cytokine test raised the possibility of tracing the treatment efficacy in the peripheral blood of patients with SCZ. Altogether, the decrease of both pro-inflammatory and anti-inflammatory cytokines of antipsychotics may drive the general amelioration of inflammatory activity, while the lower concentrations of anti-inflammatory from antipsychotic treatment may also be its side effects.

However, whether normalizing the cytokine levels could rescue the progression of SCZ remains to be explored. Our study not only suggests a brand-new drug mechanism comforting to the immune hypothesis of SCZ but also indicates that anti-inflammatory medication might ameliorate psychiatric symptoms by correcting

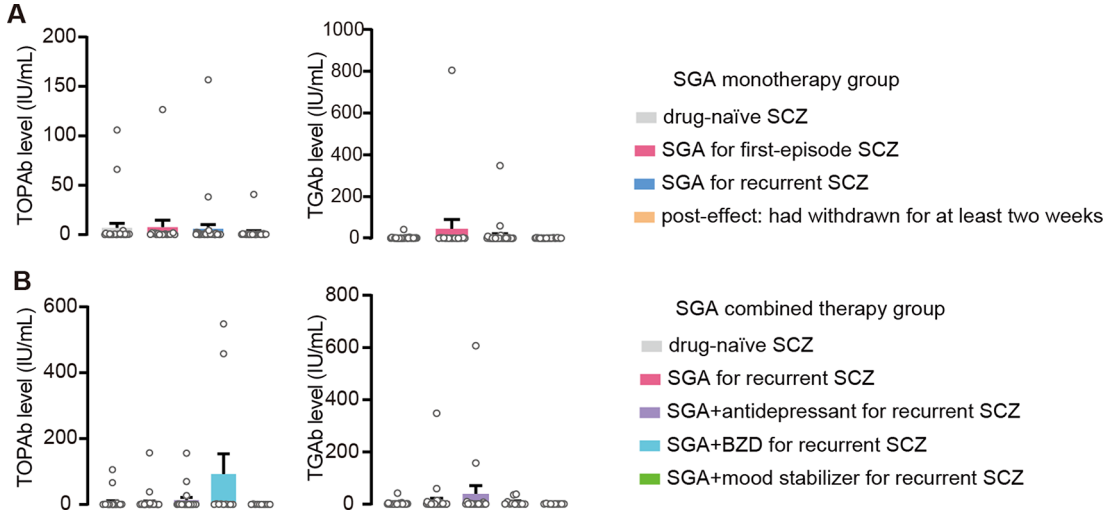

Fig. 5 Impact of SGA monotherapy and combined therapy for thyroid autoimmune antibodies. (**A**) Thyroid autoimmune antibodies profiles of drug-naïve and SGA monotherapy in first-episode, recurrent, and post-effect phase. (**B**) Thyroid-related autoimmune antibodies profiles of drug-naïve, SGA monotherapy, and SGA combined therapy with antidepressant, BZD, and mood stabilizer for recurrent SZC. (One-way ANOVA followed by LSD test or Kruskal-Wallis followed by Dunn's test)

the elevated state of pro-inflammatory factors [69]. Some anti-inflammatory drugs have promoted this idea in SCZ treatment [70]. For instance, celecoxib [71, 72], canakinumab [73], aspirin [74], long-chain omega-3 fatty acids [75], minocycline [76, 77], neurosteroid pregnenolone [78], and N-acetylcysteine [79] have been proved beneficial for SCZ improvement. However, most of these drugs were adjuncts in SCZ treatment.

Furthermore, it was demonstrated that antidepressant, BZD, or mood stabilizer also showed anti-inflammatory effects possibly through TNF-α and IL-6 [58–60]. As reported, one meta-analysis of twenty-two eligible studies suggested that the most frequently used antidepressant (i.e., selective serotonin reuptake inhibitor) treatment revealed decreased levels of pro-inflammatory markers IL-6, TNF-α, and IL-1β, and anti-inflammatory marker IL-10 in patients with major depression disorder, and no significant treatment effects on levels of IL-2, IL-4, or IFN-γ were detected [58]. Altogether, the antidepressant was recognized to restore the inflammation balance in mood disorders [80]. As for BZD, both experimental and clinical studies indicated that the central and peripheral BZD receptors, along with their ligands, formulate a novel regulatory network influencing immune function [81]. Furthermore, research conducted on fourteen healthy females documented that mood stabilizer revealed the decreased level of IL-1β, IL-2, IL-22, and TNF-α [82]. IL-22 was promisingly suggested as a research target for the specific therapeutic effects of mood stabilizers [82]. In bipolar disorder patients, it was found that ≥2 months of lithium use in euthymic populations shared a high clinical relevance with normal cytokine levels in two studies [83]. Generally, the overall immune-regulation role was revealed in various mood-regulation drugs.

While the anti-inflammation efficacy of each drug used in isolation to treat its respective adaptive condition has been extensively investigated, their collective impact on distinct cytokines when used in conjunction with SGA in the context of SCZ remains relatively uncharted territory. In contrast to the findings in previous research, in our study, no significant difference was found in the combined monotherapy, when compared to the SGA monotherapy group. It suggested that the floor effect of SGA application might cover the anti-inflammatory effect of these drugs. A possible explanation is that these drugs could display their anti-inflammatory role through the generally same approach as SGA, but the specific mechanism has not been fully explored. However, the sizes of the combined groups were limited (Antidepressant+SGA, $n=18$; BZD+SGA, $n=11$; Mood stabilizer+SGA, $n=10$), remaining further confirmation.

Remarkably, patients of recurrent SCZ who received SGA together with antidepressant represented an increasing trend of IL-6 level, compared with patients of recurrent SCZ who only received SGA intervention. It was reported that IL-6 level was correlated with depressive phenotype in SCZ across four studies [18]. However, whether IL-6 played a specific role in patients with SCZ with depression phenotype has not been fully examined [84]. Given that the combined therapy is usually prescribed to different subtypes of SCZ and the antidepressant was typically prescribed to patients with prominent negative symptoms, the disease subtype bias beyond drug effect should be carefully considered.

Altogether, a general inflammation response profile under SGA monotherapy and combined therapy, exemplified with various serum cytokine levels, was deciphered. Thus, how distinct cytokines contribute to the development of SCZ with different symptoms and how the rescue of cytokines affects the treatment effect are open questions.

As for lymphocyte subtypes, CD3+T cells are recognized as mature T lymphocytes, CD4+T cells stand for T helper lymphocytes, CD8+T cells represent T killer lymphocytes, and the NK cells are confirmed to have an important role in innate immune behavior. In our samples, only SGA monotherapy for first-episode SCZ induced the up-regulation of CD3+T cell ratio and the down-regulation of NK cell ratio, compared with the drug-naïve, which unraveled that SGA possibly displayed its antipsychotic function through the enhanced adaptive response and the dampened innate response in the first SCZ episode. A previous meta-analysis found that the NK cell ratio was significantly increased in acutely relapsed inpatients, and the ratio of CD3+T cells was significantly decreased in drug-naïve first-episode SCZ [23]. In our study, the SGA treatment displayed the specific contrast trend pattern, which was consistent with the previous study [23], but only in first-episode SCZ. This temporary immunomodulatory protection might contribute to SGA tolerance in the long time or the heterogeneity in SCZ progression. However, the differences in CD3+and NK cell proportion among the groups were no longer significant when considering the demographic traits, especially sex, suggesting that the covariates possibly confounded initial observed differences [85]. Of note, it also reported that the CD4/CD8 ratio appeared to be a state-related marker, as it was significantly increased in first-episode psychosis, and significantly decreased following antipsychotic treatment [23]. In our results, the CD4/CD8 ratio showed a nonsignificant decreased trend after SGA monotherapy in drug-naïve first-episode SCZ, which might be due to the limited number of patients and constricted effect. Meanwhile, no difference in lymphocyte types was observed in the monotherapy or combined therapy groups, compared with the drug-naïve, suggesting that pharmacological intervention might not protect patients with SCZ from immune alternating in our observation period.

Considering the potential effect of autoimmunity in SCZ development, we collected data on thyroid autoimmune antibodies (TPOAb, and TGAb). However, the serum level of TPOAb, and TGAb in patients with SCZ is far less explored. One study showed that drug-naïve patients with SCZ revealed an elevated level of TPOAb and TGAb than healthy control (SCZ: $n=288$, control: $n=100$), hinting that autoimmunity possibly changed in SCZ and thus shared the increased clinical prevalence with thyroid disorders [86]. In the treatment aspect, research on whether the SGA monotherapy or its combined therapy has a role in restoring these increased TPOAb and TGAb levels remained in infancy, lacking a unanimous conclusion. In our samples, both TPOAb and TGAb remained unchanged under SGA treatment compared with the drug-naïve. It was possible that the SGA monotherapy or its combined therapy might not influence the TPOAb and TGAb concentrations. However, it is imperative to underscore the premise that the autoimmune hypothesis of SCZ applies possibly only to some specific subgroups [87]. Thus, the role of SGA in these specific immune-derived subgroups was possibly covered up. Although more research is needed to confirm this hypothesis, such autoimmune alterations might serve as biomarkers for discerning special SCZ subgroups and help develop more accurate therapeutics.

Surging evidence has described the interaction between immunity and SCZ. However, the relationship between inflammation and autoimmunity in SCZ has not been demonstrated. The hitherto unexplained susceptibility to autoimmunity observed in SCZ might be attributed to the elevated levels of circulating pro-inflammatory cytokines, even prior to the disease onset, which possibly builds a bridge between the peripheral and the brain [88]. It was well-accepted that peripheral cytokines could communicate with the brain through various approaches such as active and passive transport, secondary messengers, and afferent nerve terminals during pathological situations [89–91]. Previous studies have also found that exposure to a variety of infections during prenatal life and childhood was associated with an elevated risk of developing SCZ [92–94]. In addition, although SCZ and autoimmunity share certain familial risk factors [42], no such association exists between SCZ and a familial predisposition of infections [95], suggesting that the prior infection possibly provokes the autoimmune mechanisms of SCZ. Meanwhile, the hypothesis also demonstrated that severe infection could cause the exhaustion of T regulatory function in autoimmunity, further lowering the threshold for glial dysregulation and promoting SCZ development [88]. Of note, IFN-γ, a cytokine modulating autoimmunity, decreased in the peripheral serum, which pinpoints another evidence for the autoimmune hypothesis. However, more evidence for the autoimmunity hypothesis is in demand in future research.

Finally, we assessed the disease course of schizophrenia with the identified immune markers in the study. However, no such association was found. It suggested that the immune markers in the study might not change with the disease course, which shed light on the application of the immune markers to represent the state-trait of disease.

There were several limitations inherent to our study. In our research, we have yet to identify all the

immunological parameters in the patients, and the patients in combined therapy groups were limited to gain a convincing effect. The relationship between antipsychotic treatment and clinical outcome is far less clarified, and the observation period is also limited. In the future, the association between the duration of schizophrenia or the number of episodes and the immune system is expected to be assessed in clinical trials. Of note, the confounder factors such as specific medicine, treatment durations, smoking, and socioeconomic status were not controlled. Thus, rigorous control (e.g., self-control before and after taking the specific medicine) trials remain to be designed. Moreover, heterogeneity among studies may indicate uncertainty or suggest diverse causes and pathogenesis of schizophrenia [96, 97], thus the caution to interpret the result should be paid. Nevertheless, it is inspiring that the immunity regulation effect of SGA was detected in patients with SCZ. In the future, far more efforts need to be paid for other autoimmune diseases and autoimmune antibodies which are critical in paving the way for improving the clinical practice for SCZ.

Taken together, our population-based retrospective research might suggest that SGA monotherapy and its combined therapy could influence the immunological processes that might have a role in the disease pathophysiology, providing the potential inspirations for underlying the development of SCZ.

Conclusion

The question of whether and how SGA monotherapy and its combined therapies impact the anti-inflammatory immunomodulatory patterns in patients with SCZ remains a subject of ongoing debate. In this study, we conducted a retrospective analysis of various immunological parameters, including the inflammatory cytokine levels, lymphocyte subtypes, and thyroid autoimmune antibodies for SGA monotherapy treatment effect in different time points (including first-episode, recurrent, and post-effect phases) and the combined therapy with antidepressant, BZD, and mood stabilizer in the recurrent episode. Our findings shed light on the complex interplay between SGAs and the immune system. It was comprehensively reported that IFN-γ was downregulated in SGA for first-episode and recurrent patients with SCZ, and after drug withdrawal, the cytokine levels returned. In the SGA monotherapy group, a higher proportion of CD3+T-cells was found in SGA monotherapy for first-episode SCZ. However, it was possibly caused by the confounders. The thyroid autoimmune antibodies remained unchanged. In combined treatment groups, results mainly resembled the SGA monotherapy for recurrent SCZ. These results indicated that SGA and other psychiatric medications could potentially achieve an antipsychotic role *via* immunity, which might be crucial in SCZ pathophysiology.

Abbreviations

TPOAb	Thyroid peroxidase antibody
TGAb	Antithyroglobulin antibody
PANSS	Positive and Negative Syndrome
BMI	Body mass index
SGA	Second-generation antipsychotics
BZD	Benzodiazepine
SCZ	Schizophrenia

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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XNG and YLW carried out data collection, did data analysis, prepared the figure, and wrote the paper; LZK designed the study, and edited the paper; LZCC did data analysis; SHH conceptualized and edited the paper. All authors read and approved the final manuscript.

Author contributions

Yu Ling: Conceptualization, Methodology, Statistic analysis, Writing - Original Dong Ying: Resources, Supervision, Project administration, Writing - Review & Editing. Shi Shuo: Investigation, Statistic analysis Liu Xin: Statistic analysis, Visualization Wang Meiling: Investigation, Methodology, Resources Jiang Guichun: Conceptualization, Methodology, Statistic analysis, Writing - Original

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (ITT20240569A).

Role of the funding source

The funders had no role in the study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit the article for publication.

Patient consent statement

Due to the retrospective, non-interventional, and anonymous nature of this study, written informed consent from patients was waived.

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Not applicable.

Human and animal rights
No animals were used for studies that are the basis of this research. All human procedures followed were in accordance with the Helsinki Declaration of 1975.

Clinical trial registration
Not applicable since this is a retrospective study rather a clinical trial.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Psychiatry, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China
[2]Nanhu Brain-computer Interface Institute, Hangzhou 311100, China
[3]Zhejiang Key Laboratory of Precision Psychiatry, Hangzhou 310003, China
[4]Liangzhu Laboratory, Zhejiang University School of Medicine, Hangzhou 311121, China
[5]Brain Research Institute of Zhejiang University, Hangzhou 310058, China
[6]MOE Frontier Science Center for Brain Science and Brain-machine Integration, Zhejiang University School of Medicine, Hangzhou 310058, China
[7]Department of Psychology and Behavioral Sciences, Graduate School, Zhejiang University, Hangzhou 310058, China

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