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# Identifying serum lipidomic signatures related to prognosis in first-episode schizophrenia

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## Abstract

**Background** Antipsychotic medications are crucial for alleviating symptoms of schizophrenia (SCZ). However, treatment responses vary across individuals, and few reliable biomarkers currently exist to predict the clinical outcome. Therefore, we aim to identify potential lipid markers for treatment outcomes in patients with first-episode SCZ.

**Methods** Pre-treatment serum samples were obtained from 95 participants who underwent an 8-week treatment regimen with antipsychotic drugs. Untargeted liquid chromatography-mass spectrometry (LC-MS) was used to acquire serum lipidomic profiles, correlating them with treatment responses at 8 weeks to identify potential lipid signatures. The antipsychotic treatment response was quantified using the percentage change on the Positive and Negative Syndrome Scale (PANSS) scale.

**Results** By combining LASSO regression and Random Forest regression, we identified 8 positively associated and 2 negatively associated baseline lipids related to the PANSS reduction rate. In the further analysis of logistic regression, we identified three candidate lipids, PC (18:2e_19:0), PE (53:7), and TG (16:2e_19:0_20:5), which could together distinguish poor and good responders, with an AUC of 0.805 (95% CI, 0.715–0.894).

**Conclusions** Our findings suggest that this set of lipid biomarkers may have the potential to predict the outcome of antipsychotic drug treatment. Further validation and larger studies are needed to evaluate their potential for clinical applications.

**Clinical trial number** Not applicable.

**Keywords** Schizophrenia, Prognosis, Lipidomic profiling, Biomarker

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## Introduction

Schizophrenia (SCZ) is a severe and highly heterogeneous mental illness with an unclear etiology that is characterized by profound disturbances in thinking, feeling, and behavior [1]. Antipsychotics are the mainstay of clinical management for relieving symptoms of SCZ [2]. Previous studies showed that while the majority of patients achieve symptom control with standardized treatments, approximately 30% remain unresponsive to these pharmacological interventions at the time of first treatment [3], which is a significant contributor to treatment delays and costly healthcare burdens. The underlying causes of the individual differences in treatment responses are not fully understood. In clinical practice, current approaches for treating SCZ typically rely on an iterative trial-and-error process. Therefore, there is an urgent need for reliable candidate biomarkers to predict outcomes and guide treatment decisions made by attending physicians [4].

Lipids play crucial roles in the brain, including signaling, energy metabolism, neuroprotection, and membrane composition. Dysregulation of lipid metabolism, particularly in phospholipids, sphingolipids, and fatty acids, has been implicated in the pathophysiologic mechanisms of SCZ [5, 6]. Notably, abnormal lipid patterns are observed not only in the central nervous system (CNS) [7], but also in peripheral cells such as erythrocytes [8]. Similar findings have been reported in unmedicated first-episode SCZ patients [7, 9], suggesting that specific lipid disturbances emerge early in the disease and are not solely attributable to the effects of antipsychotic drugs. Research indicates that lipid dysregulation may stem from abnormal catabolism of membrane phospholipids and inflammatory responses, which can be partially reversed by therapeutic intervention [10, 11]. Additionally, antipsychotic drugs have been shown to modulate lipid metabolism-related gene expression [12]. These findings suggest that lipids may be a potential biomarker for predicting response to antipsychotic drug treatment in SCZ.

Significant progress has been made in the research on lipid biomarkers for predicting treatment response in SCZ. Previous studies have demonstrated associations between treatment outcomes and lipids such as fatty acid supplementation and lipid levels, including total cholesterol (TC) and triglyceride (TG) [13–16]. However, these studies have focused only on specific lipid classes rather than a comprehensive lipid profile. Lipidomics, a rapidly evolving branch of high-throughput metabolomics techniques, enables the precise identification and quantification of intact individual lipid molecular species [17]. This approach offers a potent and unbiased method for identifying lipid-specific biomarkers associated with diseases [18]. Although several studies have explored lipidomic features and their changes in SCZ [19–21], none have delved into the impact of baseline lipid profiles on treatment response, especially in terms of identifying biomarkers.

Given these gaps in the current research, we hypothesized that lipid profiles could function as prospective biomarkers for predicting responses to antipsychotic therapy. Following this hypothesis, this study employed lipidomics technology to quantify lipids in baseline serum samples from the first-episode SCZ cohort in the prospective SMART-CAT trial, aiming to identify potential serum lipid biomarkers associated with treatment outcomes.

## Methods

### Subjects

All included subjects were drawn from the SMART-CAT trial, a sequential randomized trial carried out in China to assess antipsychotic therapies in first-episode SCZ [22], approved by the Institutional Review Board of Shanghai Mental Health Center (SMHC). The subjects were enrolled based on the following inclusion criteria: a DSM-5 diagnosis of SCZ, age range of 16 to 45 years, initial onset lasting no longer than 3 years [23], either drug-naïve or receiving antipsychotic medication treatment for less than 2 weeks [24], a total score on the Positive and Negative Syndrome Scale (PANSS) of greater than 70 and a score at least 4 on at least one of the following items: delusion, conceptual disorganization, hallucinations, grandiosity, or suspiciousness/persecution. The exclusion criteria included individuals with a diagnosis of mental retardation, any other serious psychiatric or neurological disorders (including chronic, recurrent schizophrenia or treatment-resistant schizophrenia), substance abuse, pregnancy or lactation, unstable clinical status (e.g., extreme agitation, stupor, or suicide behavior), or those who had received modified electric convulsive therapy.

### Study design

Enrolled patients were randomized to be assigned to receive five different antipsychotics (olanzapine, risperidone, perphenazine, amisulpride, aripiprazole) treatment for a period of 8 weeks. The flowchart and the detailed doses of antipsychotics are listed in the supplementary material (Supplementary Fig. 1 and Supplementary Table 1). A protocol consisting of sociodemographic information, anthropometric measurements, and the assessment of clinical symptoms using the PANSS and the Clinical Global Impression (CGI)-severity scale was responded to by each participant at baseline and 8 weeks later. The PANSS scale includes 7 items measuring positive symptoms, 7 items measuring negative symptoms, and 16 items measuring general psychopathology, providing a comprehensive measure of symptomatology [25]. The CGI scale consists of the CGI-Severity and

CGI-Improvement that assess symptom severity and improvements from baseline [26]. These scale assessments were administered by two trained clinicians with demonstrated interrater reliability (intraclass correlation coefficient > 0.8). A total of 95 patients who completed the 8-week course of treatment, had their clinical symptoms evaluated, and had given serum samples were included in the final analysis of this study. Their treatment efficacy threshold was defined as a reduction of 40% or more in the total PANSS scale score in this study, which usually implies a significant improvement in clinical symptoms [27, 28]. This threshold for categorizing responders and non-responders is also used in clinical trials of drugs, and assessment of treatment response [22, 29], which facilitates more intuitive treatment decisions made by clinicians. Individuals achieving this reduction were allocated to responders, whereas those not meeting this criterion were classified as non-responders. The percentage decrease in total PANSS scores is calculated as follows. All participants voluntarily participated in the study and provided their informed consent.

$$PANSS\ reduction\ rate = \frac{PANSS\ baseline\ score - PANSS\ endpoint\ score}{PANSS\ baseline\ score - 30} \times 100\%$$

## Lipidomics

This study employed non-targeted liquid chromatography-mass spectrometry (LC-MS) for lipid analysis. To prepare the serum sample, five milliliters of venous blood were drawn into anticoagulant-free tubes from all patients before therapy using the normal venipuncture procedure, following at least 8 h of fasting. The blood sample was centrifuged (3000 rpm) for 15 min in order to extract the serum after it had been still for an hour at 4 °C. After transferring a volume of 100 µL of the serum sample into 1.5 mL Eppendorf tubes with the proper internal standard volumes, 240 µL pre-cooling methanol and 100 µL water were added. Subsequently, 800 µL of methyl tert-butyl ether (MTBE) was added before ultrasonication for 20 min at 4 °C. After rest for 30 min at ambient temperature, the mixture was centrifuged at 14,000×g for 15 min at 10 °C. Following nitrogen drying, the upper organic phase was redissolved in 200 µL 90% isopropanol/acetonitrile, centrifuged at 14,000×g for 15 min at 10 °C, and the supernatant was eventually collected. Additionally, an equal volume of supernatant was mixed from each set of samples to form a Quality Control (QC) sample, which was introduced after every 10 injections for evaluation of the stability of the system and the performance of the instrument.

A non-targeted LC-MS system consisting of an ultra-high performance liquid chromatography (UHPLC) Nexera LC-30 A (SHIMADZU, Japan) coupled to a Q-Exactive Plus mass spectrometer (Thermo Scientific) was used to accomplish this lipid analysis. The ready 3 µL samples were directly injected into the CSH C18 column (waters, 1.7 µm, 2.1 mm× 100 mm) that was preheated to 45 °C for separation. The initial conditions for the column's eluted flow rate, which was 300 µL/min, were 30% mobile phase B and 70% mobile phase A. Following that, there was a linear gradient that took 23 min to 100% mobile phase B, after which 30% was maintained for 10 min. The mobile phase A consisted of an acetonitrile-water solution (acetonitrile: water = 6:4, vol/vol) containing 0.1% formic acid and 0.1 mM ammonium formate, while mobile phase B was an acetonitrile-isopropanol solution (acetonitrile: isopropanol = 1:9, vol/vol) with 0.1% formic acid and 0.1 mM ammonium formate.

Following the separation of the samples by UHPLC, MS analyses were carried out using electrospray ionization (ESI) in the positive and negative ionization modes, individually. The ESI parameters are set as follows: 45 arb of sheath gas, 15 arb of auxiliary gas, 1arb of sweep gas, heater temperature of 300 °C, capillary temperature of 350 °C, $MS^1$ scanning range of 200–1800. The positive and negative ion spray voltages were 3.0 kV and 2.5 kV, respectively. The mass-to-charge ratio (m/z) data of lipid molecules were obtained via a sequential process that started with a full scan ($MS^1$ scans) and followed by the collection of ten product ion spectra ($MS^2$ scans) utilizing Higher-energy Collisional Dissociation (HCD). For the $MS^1$ scans, the resolution at m/z 200 was set to 70,000. The $MS^2$ scan resolution was set at 17 500 at m/z 200. LipidSearch software version 4.2 (Thermo Scientific™) was used to process the raw data from the Q-Exactive Plus instrument.

## Statistical analysis

### *General remark*

All statistical analyses were performed using SPSS (version 27) and R (version 4.4.1). Student's t-tests for continuous variables and chi-squared tests for categorical data were used to compare clinical data. Continuous variables are reported as mean ± standard deviation (SD), and categorical data are represented by a number (percentage). For non-normally distributed lipid molecules, correlation analysis by Spearman and differences between groups were assessed using the Mann-Whitney U test, with a p-value < 0.05 considered statistically significant, and multiple tests were corrected for false discovery rate (FDR) using the Benjamini-Hochberg procedure. The k-Nearest Neighbors method from the R package "impute" (version 1.80.0) was used to impute lipid molecules with ≤ 50% missing values, whereas lipid species with > 50% missing values were filtered out. The percentage of missing values for lipid species with missing data is provided in the Supplementary Materials.

#### *Lipid selection*

To eliminate the impact of variable scale differences, all lipid data were standardized using *Z-score* transformation (R package "scale"). Because categorization based on the change in PANSS may reduce sensitivity and the efficacy of statistical tests, we used the PANSS reduction rate as a continuous variable for lipid feature selection. Spearman correlation analysis was performed for initial screening, with lipids meeting the significance threshold of $p < 0.05$ retained for further analysis. Subsequent lipid selection and shrinkage were based on the intersection of the results from Absolute Shrinkage and Selection Operator (LASSO) regression (R package "glmnet") [30] and Random Forest (RF) regression (R package "randomForest") [31]. The LASSO regression was validated using 10-fold cross-validation to ensure the independence of the training and testing sets and prevent overfitting. For RF regression, the top 20 lipids were selected based on the percentage increase in mean squared error (%IncMSE). Additionally, logistic regression was applied to identify potential lipid markers that distinguished the responders from non-responders. The performance of the final selection was evaluated using the Receiver Operating Characteristics (ROC) curve and the related Area Under the Curve (AUC). The details of each approach and variable selection are provided in Supplementary Methods.

## Results

### Baseline demographic information and clinical characteristics

The drug distribution information, demographics, and clinical features of every patient are shown in Table 1. A total of 95 patients with first-episode SCZ were included in this study and were randomized to receive one of five different antipsychotic treatments. Eight weeks later, 60 patients (PANSS reduction rate ≥ 40%) were allocated to responders, while the remaining 35 patients (PANSS reduction rate < 40%) were classified as part of non-responders. No statistically significant differences were found in the distribution of medications between responders and non-responders ($p = 0.135$). Moreover, there were no significant differences between the two patient groups in terms of age, gender, years of education, duration of untreated psychosis (DUP), all items in PANSS, CGI-S, and body mass index (BMI) ($p > 0.05$).

**Table 1** Drug distribution, demographic data, and clinical characteristics

| | Responders | Non-responders | $t/\chi^2$ | *p* |
|---|---|---|---|---|
| | *N* = 60 | *N* = 35 | | |
| Olanzapine [n (%)] | 12 (20.0%) | 10 (28.6%) | / | / |
| Risperidone [n (%)] | 13 (21.7%) | 3 (8.6%) | / | / |
| Perphenazine [n (%)] | 9 (15.0%) | 11 (31.4%) | / | / |
| Amisulpride [n (%)] | 15 (25.0%) | 5 (14.3%) | / | / |
| Aripiprazole [n (%)] | 11 (18.3%) | 6 (17.1%) | 7.01 | 0.135 |
| Age (years) | 27.52 ± 6.86 | 26.60 ± 7.83 | 0.60 | 0.553 |
| Male [n (%)] | 16 (26.7%) | 12 (34.3%) | 0.62 | 0.432 |
| Education (years) | 14.72 ± 2.68 | 13.89 ± 2.81 | 1.43 | 0.155 |
| DUP (month) | 8.98 ± 11.8 | 8.96 ± 10.44 | 0.01 | 0.991 |
| PANSS total score | 86.68 ± 15.62 | 89.00 ± 12.22 | -0.72 | 0.471 |
| PANSS positive score | 24.86 ± 5.08 | 26.03 ± 4.40 | -1.09 | 0.277 |
| PANSS negative score | 17.70 ± 8.27 | 18.34 ± 6.82 | -0.37 | 0.710 |
| PANSS general score | 43.07 ± 8.02 | 44.63 ± 6.91 | -0.92 | 0.359 |
| GCI severity score | 5.26 ± 0.77 | 5.47 ± 0.62 | -1.29 | 0.199 |
| BMI ($kg/m^2$) | 22.04 ± 3.86 | 20.72 ± 3.99 | 1.56 | 0.122 |

DUP, Duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; GCI, Clinical Global Impression; BMI, body mass index. Data were expressed as mean ± SD or number (percentage)

### Lipidomic analyses

A total of 1892 lipid molecules were kept for downstream analysis in pre-treatment serum samples analyzed using non-targeted LC-MS. Principal component analysis (PCA) was used to perform a preliminary analysis of the overall data structure of these lipid molecules. The results of this analysis failed to reveal distinct intrinsic characteristics capable of differentiating the two groups (Fig. 1A). The Spearman correlation analysis identified 158 lipids that were significantly correlated with PANSS reduction rate, where 152 showed positive correlations and 6 showed negative correlations (Fig. 1B and Supplementary Table 2). Subsequently, the LASSO regression analysis, using the optimal lambda value determined through 10-fold cross-validation, screened 23 lipids with non-zero coefficients (Fig. 1C and D). Meanwhile, RF regression identified the top 20 lipids based on importance scores, reflecting their contribution to predicting PANSS reduction rate (Fig. 1E). Intersecting the top 20 lipids from the RF model with the non-zero coefficient lipids from the LASSO analysis, a total of 10 lipids were shared between them that were correlated with PANSS reduction rate, including 2 negatively correlated and 8 positively correlated lipids. Figure 1F shows the Spearman correlation matrix for the 10 selected lipids, with only 2 triglycerides (TG) markers highly correlated with each other (Spearman' $r = 0.71$).

### Evaluation of biomarker efficacy

To further explore lipid biomarkers capable of distinguishing responders from non-responders to antipsychotic treatment, we included the 10 selected lipids in a logistic regression analysis, which essentially meets the 10 events per variable (EPV) rule [32]. As shown in Fig. 2, PC (18:2e_19:0)(OR = 2.520, 95%CI:1.197–5.305), PE (53:7) (OR = 2.035, 95%CI:1.031–4.018) and TG (16:2e_19:0_20:5) (OR = 2.351, 95%CI:1.025–5.393) presented a significant positive association with better treatment response ($p < 0.05$). Hex2Cer (t38:6) also demonstrated potential value as a biomarker for predicting

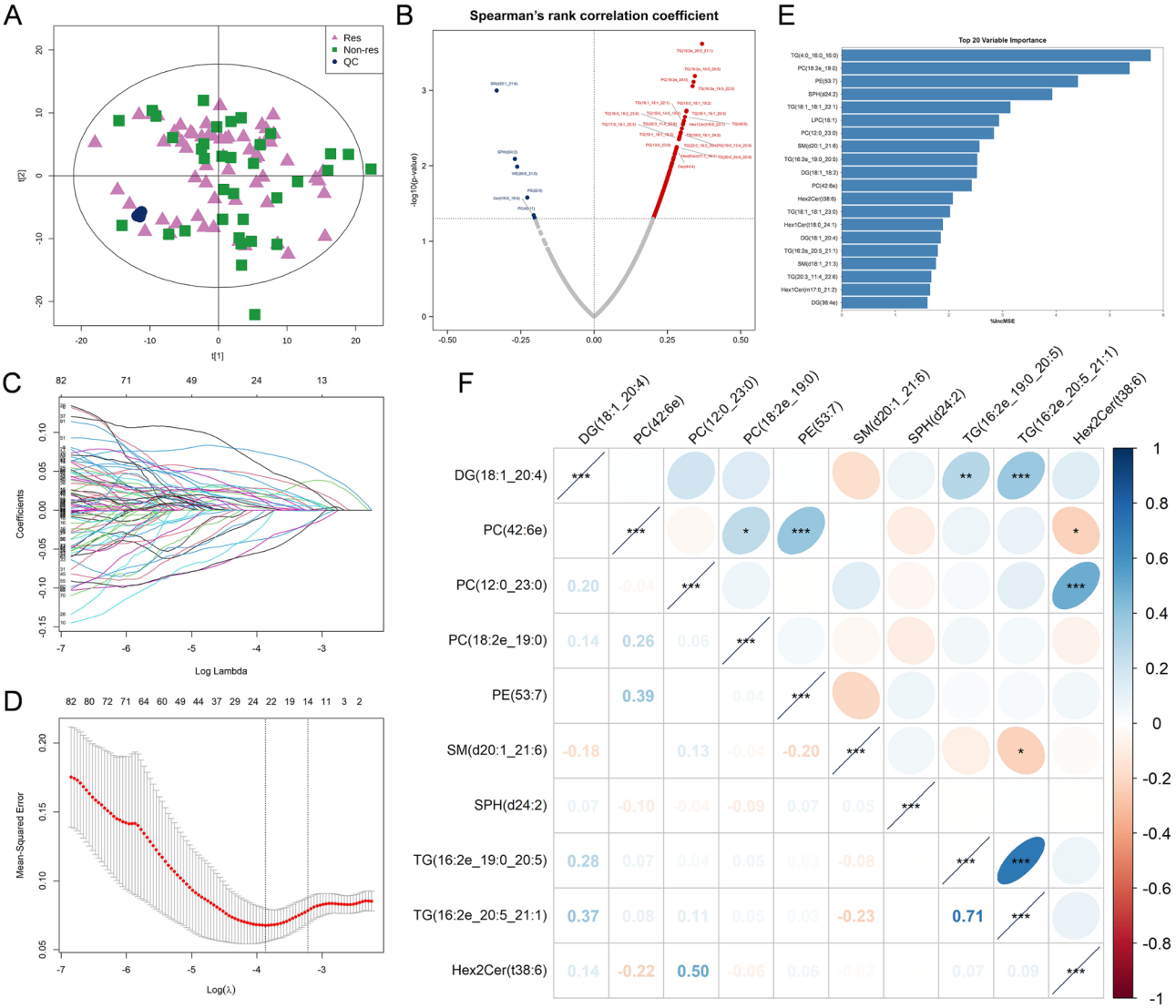


**Fig. 1** **(A)** Principal component analysis (PCA) for Responders and Non-Responders. R2X (cumulative) = 0.563. Purple triangles indicate subjects who responded well to treatment (Res). Green squares denote subjects who did not respond to treatment (Non-res). Blue circles represent QC samples. **(B)** Spearman correlation and significance between the lipids expression levels and PANSS reduction rate, represented in a volcano plot. Red dots indicate a significant positive correlation, only the top 20 are labeled. Blue dots indicate a significant negative correlation. **(C)** LASSO coefficient path plot. **(D)** The 10-fold cross-validation curve identified the optimal λ value at 0.021, which yielded 23 non-zero coefficients. **(E)** The importance values of the top 20 lipids in Random Forest regression. **(F)** Correlation matrix of Spearman correlation coefficients for the 10 selected lipids

treatment (OR = 2.129, 95%CI: 0.924–4.907), but it lacked statistical significance ($p = 0.076$). Compared to the non-responder group, the better-responding patients had higher levels of PC (18:2e_19:0), PE (53:7), and TG (16:2e_19:0_20:5) ($p < 0.05$) (Fig. 3A, B and C). According to the ROC curve analysis, the lipid biomarker panel showed good discriminatory power with an AUC of 0.805 (95%CI, 0.715–0.894), specificity of 82.9%, and sensitivity of 71.7%, and it had a significantly improved discriminatory performance over the sex-age panel (Fig. 3D). To further assess the reliability and robustness of the panel's discriminatory ability, a 5-fold cross-validation was performed with a mean AUC of 0.787 (Supplementary Fig. 2). In addition, we used gender-specific stratification in Spearman correlation analysis to investigate the relationship between three categories of lipids and both age and BMI (Supplementary Fig. 3). The *p*-values and R-values indicate that no significant correlations were observed for any of the variables, suggesting that lipid profiles were not significantly influenced by age, gender, or BMI in distinguishing treatment response.

## Discussion

This study aimed to determine specific lipids within the lipid profiles as potential biomarkers for differentiating responses to antipsychotic medication treatment in

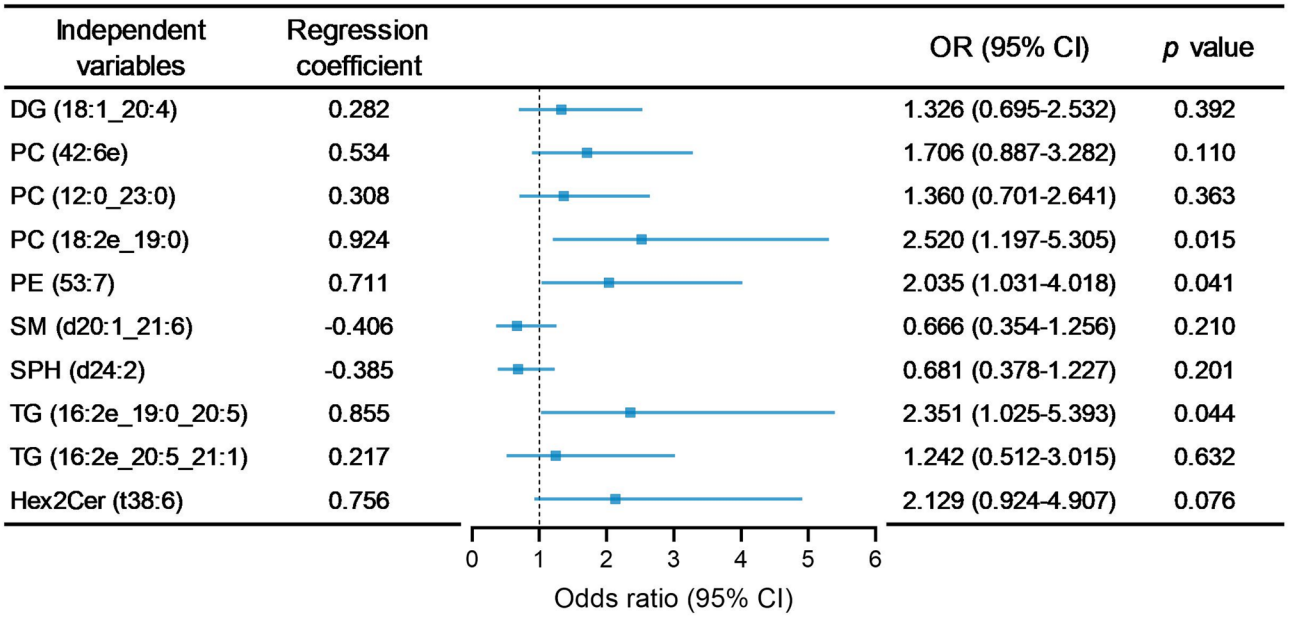


**Fig. 2** Forest plots for logistic regression analysis of the 10 selected lipids in distinguishing Responders and Non-responders

first-episode SCZ patients. In this study, we selected lipids by integrating the results from LASSO and RF regression, which is a common machine-learning approach for variable selection in high-dimensional data [33, 34]. 23 lipids were identified by LASSO and 20 by RF, with 10 lipids overlapping by both approaches. It is not unexpected that the results differ between these approaches, as RF is an ensemble learning algorithm based on decision trees, considering non-linear relationships or other complex interactions between lipids, while LASSO is a variant of linear regression. Combining both algorithms allows the selection of more stable and reliable lipid markers [35]. To obtain the optimal lipid biomarker, we identified a set of three potential lipid biomarkers based on logistic regression to distinguish responders from non-responders with high accuracy. They respectively originate from phosphatidylcholine (PC), phosphatidylethanolamine (PE), and triglyceride (TG).

Lipids play an important role in a variety of human diseases. In particular, it has been showed that a broad class of phospholipids with phosphate groups, including phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylethanolamines (PE), phosphatidylinositol (PI), and phosphatidylglycerol (PG), are essential in neuronal and synaptic growth and remodeling [36]. In our study, we explored biomarkers of treatment response by baseline lipid profiling and found that patients with higher PC (18:2e_19:0) presented a more positive response to antipsychotic medication. Other studies have also shown that the change in PC levels was associated with therapeutic response to antipsychotics. Specifically, patients who responded well to risperidone showed increases in several other PCs, including PC (40:5), PC (O-42:1), PC (38:5), PC (O-32:2), PC (P-38:1), and PC (38:4). While among poor responders, PC (40:8) and PC (40:7) experienced a decrease [19]. Moreover, Leppik et al. (2020) found that the aberrant levels of certain PCs in drug-naïve SCZ were improved by antipsychotics [37]. Another research that used $^{31}$P magnetic resonance spectroscopy found a negative association between the PANSS overall score and PC concentrations in the temporal cortex [38]. These results indicated that PC may be involved in the course of disease and the mechanisms of action of antipsychotics. The PC is the most prominent subgroup among mammalian cell membranes, its dysregulation has been observed in both peripheral and brain tissue samples from patients with SCZ [37–40]. A potential mechanism of PC dysregulation may be due to excessive oxidative stress and impaired membrane lipid homeostasis [41]. Furthermore, Haszto et al. (2020) indicated that decreased de novo synthesis of PCs may contribute to its etiology [42]. However, the precise mechanisms by which different kinds of PCs are involved in the action of antipsychotic medications remain unclear.

We found that a higher baseline PE (53:7) level in first-episode SCZ was associated with a better treatment response. Similarly, another study identified correlations between baseline levels of PE (50:5n3), PE (dm18:1n7), and PE (dm18:1n9) and early clinical treatment response measured by changes in the CGI scale [11]. These findings collectively highlight the potential role of PE in the SCZ treatment from different perspectives. Reduced PE levels in SCZ patients have been observed in both postmortem and other vivo studies [21, 40, 43, 44],

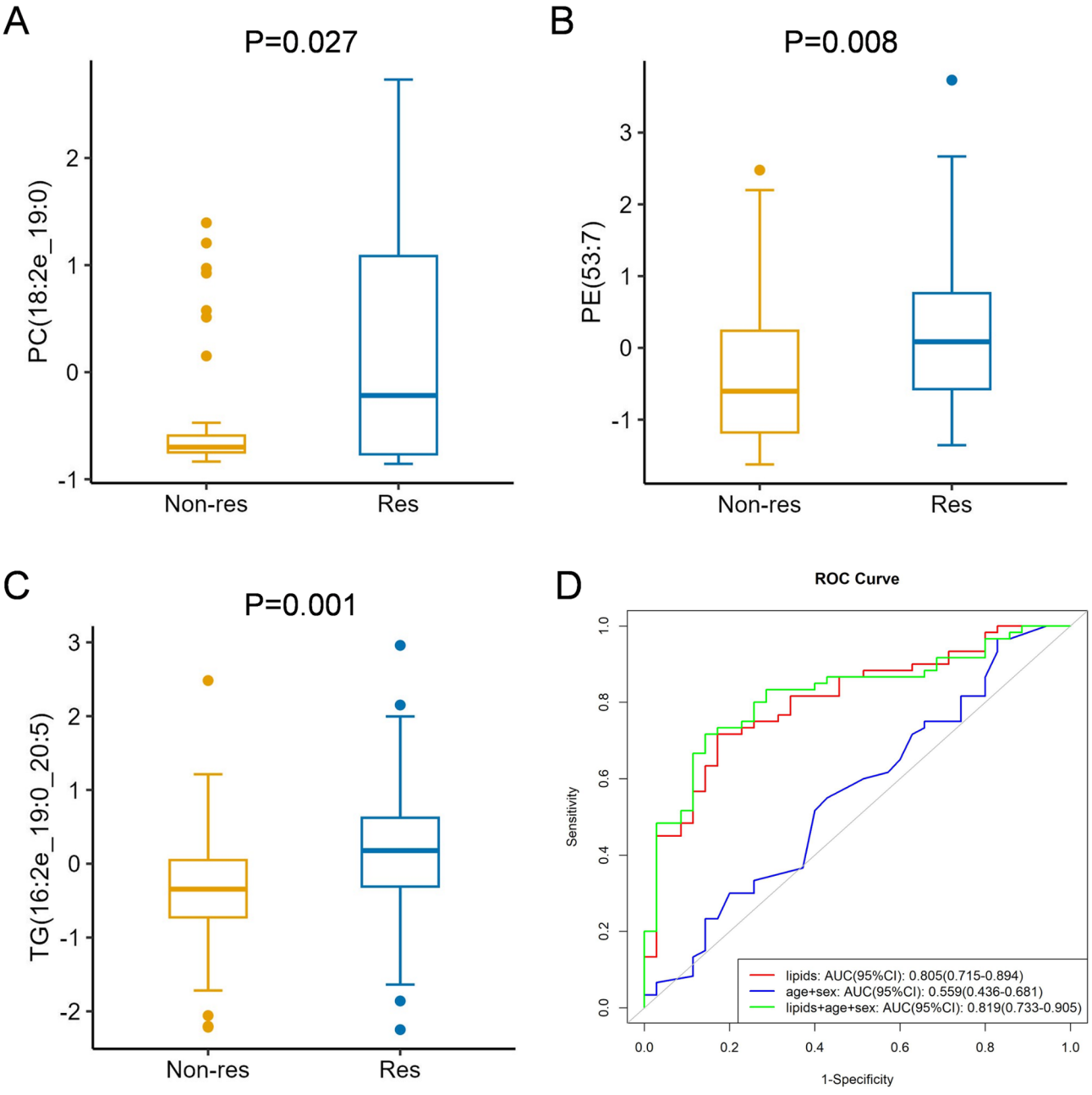


**Fig. 3** (**A**, **B**, **C**) Expression level of three lipid biomarkers in the Non-responders and Responders. (**D**) ROC curve analysis for distinguishing between Responders and Non-responders

supporting the critical role of lipid metabolic dysfunction in the pathophysiology of SCZ. The potential cause of these abnormalities may involve membrane phospholipid transporters or degradative enzymes involved in phospholipid metabolism, leading to altered phospholipid distribution [45]. Antipsychotic treatment has been shown to modulate abnormal levels of PE. One study showed that the decreased level of PE in SCZ patients was reversed following treatment with risperidone and olanzapine [11]. Rodent studies have also shown that atypical antipsychotics can ameliorate stress-induced deficits in PE levels in the prefrontal cortex and hippocampus [46]. Furthermore, Ghosh et al. (2020) reported that patients who responded well to risperidone treatment had elevated levels of PE (20:0) after treatment [19]. These findings suggest that the therapeutic effects of antipsychotics may involve the regulation of lipid homeostasis, especially the restoration of PE function. Although the precise mechanism by which PE levels impact treatment response remains unclear, it may be related to better membrane stability.

Elevated serum TG levels in individuals with SCZ are predominantly attributed to insulin resistance associated with antipsychotic medication therapy. Surprisingly, however, patients with higher blood lipids may be linked to better responses to treatment. In our study, patients with higher TG (16:2e_19:0_20:5) had a better response to antipsychotics, which is in line with a randomized, double-blind trial that found an increase in serum TG and cholesterol (TC) levels being associated with lower ratings on the PANSS negative subscale and overall PANSS score [47]. Patients with untreated SCZ who started an 8-week olanzapine therapy regimen showed comparable results [48]. Research by Sharma et al. (2014) showed early rise in blood TG was strongly connected with a 2–4 weeks and 8–12 weeks clinical improvement, according to a prospective research that involved random delivery of first- or second-generation antipsychotic drugs [49]. Furthermore, a case report illustrated that a patient who reacted favorably to clozapine had a return of symptoms following a 7-week treatment of atorvastatin, which significantly lowered serum total TC and TG levels. Following the cessation of atorvastatin, the patient's serum TC and TG levels increased, and there was a marked improvement in symptoms [50]. Although the precise mechanism by which increased TG levels improve drug response is not fully understood, research suggests that serum lipids may influence treatment outcomes by changing the pharmacokinetics of antipsychotic drugs [16, 50]. Increased serum lipids may act as a physiological reservoir for these medications, encapsulating antipsychotics in lipoprotein particles and potentially facilitating their transport across the blood-brain barrier.

Lipidomics study is undeniably important for disease processes and discovering biomarkers. However, there are some limitations in this study. Firstly, although the discriminatory performance of candidate lipid biomarkers was preliminarily validated using 5-fold cross-validation, more representative external validation was lacking. Secondly, the small and predominantly female sample size limits careful subgroup analysis, especially regarding specific antipsychotics and gender. Lastly, as the mining and visualization of quantitative lipidomic data is inherently exploratory, the complex mechanisms behind these results were not elucidated. Therefore, further studies with larger sample sizes are warranted to validate the predictive ability of these biomarkers on different antipsychotic medications and to explore their underlying mechanism.

## Conclusions

In summary, our study identified three potential candidate lipid biomarkers through a comprehensive analysis of lipidomics. These lipids are expected to identify antipsychotic treatment responses in patients with SCZ. Subsequent investigations were needed to replicate these findings in more extensive groups and explore the mechanisms by which these lipid signatures impact treatment outcomes, potentially revealing innovative therapeutic targets within the lipid metabolic pathways associated with SCZ.

### Abbreviations

| | |
|---|---|
| DG | Diglyceride |
| Hex2Cer | Dihexosylceramides |
| PC | Phosphatidylcholine |
| PE | Phosphatidylethanolamine |
| SPH | Sphingosine |
| SM | Sphingomyelin |
| TG | Triglyceride |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06802-7.

Supplementary Material 1

Supplementary Material 2

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### Author contributions

Mengyi Luo, Suzhen Zhang and Jingxin Xue: Conceptualization, Formal Analysis, Methodology, Software, Investigation, Writing - Original Draft; Xuan Li, Tianhao Gao, Zhaolin Zhai, Chang Lu, and Yuke Dong: Data Curation, Visualization, Investigation; Kaiming Zhuo, Qiong Xiang, Qing Kang and Shunying Yu: Resources, Supervision; Chunhong Shao and Dengtang Liu: Conceptualization, Funding Acquisition, Resources, Supervision, Writing - Review & Editing. All authors reviewed the manuscript.

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### Data availability

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

## Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Shanghai Mental Health Center. All participants provided written informed consents. All procedures carried out in the study comply with the Declaration of Helsinki for experiments involving humans.

**Consent for publication**
No individual data is presented, and consent to publication is therefore not applicable.

**Competing interests**
The authors declare no competing interests.

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