Neuropsychiatric Disease and Treatment

Dovepress
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ORIGINAL RESEARCH

Identification of Plasma Biomarkers in Untreated Schizophrenia Patients Using Untargeted Lipid Metabolomics

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Purpose: Schizophrenia (SCZ) is a profound psychosomatic illness with an unidentified cause and no definitive biomarkers. This study sought to investigate plasma biomarkers linked to schizophrenia by untargeted metabolomics.

Patients and Methods: A total of 50 medication-naïve SCZ patients and 25 healthy controls were eligible and participated in this study. Psychiatric symptomatology was evaluated employing the Positive and Negative Syndrome Scale. We quantified the concentration of lipid metabolites in plasma from all participants using untargeted metabolomics and classified metabolites that were significantly different between both groups. We subsequently assessed the diagnostic potential of metabolites on the basis of receiver operating characteristic curves and examined metabolites affiliated with psychotic symptomatology in SCZ patients.

Results: Fourteen metabolites exhibited compelling disparities in schizophrenia patients relative to healthy controls. Eight metabolites, including methylphosphatidylcholine, acylcarnitine, sphingomyelin, and (O-acyl)-1-hydroxy fatty acids (38:4), could significantly distinguish between schizophrenia and healthy controls, with all their areas under the curve (AUC) exceeding 0.7. The peak area under the curve (CV-AUC) for AcCa(20:4) was 0.92 ± 0.03. In schizophrenia patients, negative symptoms exhibited a negative correlation with acylcarnitines, while cognitive symptoms had a substantial positive correlation with methylphosphatidylcholine and phosphatidylcholine.

Conclusion: The findings reveal lipid metabolism dysregulation as a potential pathophysiological mechanism of schizophrenia. The identified metabolites, such as AcCa and phosphatidylcholine, serve as promising biomarkers for the diagnosis and symptom evaluation, suggesting their direct involvement in the disease's pathogenesis.

Keywords: schizophrenia, metabolomics, plasma, biomarker, phosphatidylcholines

Introduction

Schizophrenia (SCZ) is a multifaceted and incapacitating mental illness, exhibiting an international popularity rate of roughly 1%.[1] The illness is marked by an array of symptoms, encompassing delusions, hallucinations, avolition, and mood symptoms, together with cognitive impairment.[2] The diagnosis of schizophrenia is currently personal and depends on the clinical symptoms exhibited by the patient.[3] Consequently, the identification of plasma markers linked to schizophrenia is crucial for enhancing diagnostic precision and gaining a more profound understanding of the disease's etiology.[4] Although various studies employing diverse methodologies have been conducted, plasma biomarkers significantly linked to schizophrenia remain unidentified.[5]

Metabolomics represents a method that enables the concurrent identification of complete metabolites within an organism, encompassing both targeted as well as untargeted compounds.[6] In recent years, untargeted metabolomics has appeared as a viable method for classifying possible biomarkers for many disorders.[7,8] Lai et al performed a review of

Received: 30 April 2025
Accepted: 29 October 2025
Published: 3 December 2025

35 metabolomics research articles, indicating that glutamate, lactate, and citrate may function as possible biomarkers for epilepsy.[9] Hou et al conducted a systematic quantitative review of nine metabolomics studies, identifying L-glutamine and citrulline as possible biochemical markers for diabetic retinopathy.[10] Moreover, metabolomics technologies have been investigated in relation to psychiatric diseases, counting SCZ, bipolar disorder, and depression.[11–13]

Prior lipid metabolomics investigations have discovered many compounds that may function as biomarkers for schizophrenia; nevertheless, the investigations have been inconsistent. For example, Wang et al discovered that phosphatidylcholine (PC) levels were markedly reduced in patients with schizophrenia and demonstrated efficacy in detecting the condition.[14] Weber-Fahr et al similarly discovered that PCs were markedly diminished within the thalamic region of individuals with SCZ and correlated with clinical manifestations of the disorder.[15] However, Hamasaki et al demonstrated that PC levels were not considerably modified in schizophrenia (SCZ) and lacked diagnostic value as a disease biomarker.[16] Inconsistent outcomes may stem from the assay's low accuracy, patient heterogeneity, and the effects of drugs.

To mitigate these, high-resolution LC-MS was used for enhanced accuracy, strict criteria (DSM-5, medication-naïve, PANSS >60) minimized heterogeneity, and only untreated patients were recruited to avoid drug confounding. This approach highlights the novelty of our findings in unmedicated SCZ. Prior research has predominantly involved people with chronic schizophrenia, with limited investigations conducted on individuals with untreated schizophrenia. Consequently, metabolomics research on unmedicated schizophrenia patients warrants additional exploration. Consequently, further pertinent investigations are required. We conducted an untargeted metabolomics analysis of plasma samples from all participants in our trial. Our goals were 1) to diagnose likely biomarkers associated with SCZ, 2) to search for higher-performance diagnostic markers for SCZ, and 3) to research metabolomics biomarkers associated with psychiatric symptomatology.

Materials and Methods

Subjects and Sampling

This study recruited 50 subjects from Anhui Mental Health Center. The criteria for inclusion were the following: 1) Diagnosis of schizophrenia or schizophreniform disease individually validated by a pair of seasoned psychiatrists in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5); 2) life ranging from eighteen to sixty-five years; 3) completion of primary education or higher; 4) no prior administration of psychosis medications; as well as 5) overall score on the Positive and Negative Syndrome Scale (PANSS) exceeding 60. The exclusion criteria comprised 1) the presence of separate psychiatric illnesses; 2) diabetes mellitus, hyperlipidemia, or additional clinically significant comorbidities; 3) either pregnancy or ongoing lactation; 4) a past of physical therapy within the preceding 4 weeks, including modified electroconvulsive therapy as well as transcranial magnetic stimulation; as well as 5) potential barriers to valid consent among participants, independent of survey engagement. Twenty-five HCs were selected from community-dwelling healthy individuals. HCs did not fulfil the diagnostic criteria for any condition as per DSM-V and lacked a familial history of psychotic diseases.

The sample size was calculated using a power analysis for the area under the ROC curve (AUC) to ensure sufficient statistical power for detecting diagnostic biomarkers. Based on the approximation by Obuchowski et al assuming a null hypothesis AUC of 0.5 and an alternative hypothesis AUC of 0.92 (derived from preliminary metabolite analyses), a ratio of controls to patients of 0.5 (25:50), and a one-sided alpha of 0.05, the estimated power is approximately 100%.[17] This confirms that the recruited sample size (50 medication-naïve SCZ patients and 25 healthy controls) provides adequate power (>80%) to detect significant differences in AUC for the identified metabolites.

Each subject granted written informed consent, and the research received authorization from the Ethical Committee of Anhui Mental Health Center (Ethics No. HFSY-IRB-YJ-KYXM-ZL2024-014-001). This study was conducted in accordance with the Declaration of Helsinki.

Clinical Assessment

General information as well as clinical evaluations were gathered from all participants during recruiting utilising a self-constructed survey. The psychiatric symptomatology was evaluated utilising the PANSS by a pair of seasoned psychiatrists with standardized discipline. The PANSS is extensively utilized to assess the clinical manifestations of schizophrenia, with elevated scores correlating with increased symptom severity.[18] Our study employed a 5-component model for analysis, comprising positive factor, negative factor, cognitive factor, excitatory factor, and depressed factor.[19] The computed inter-observer correlation coefficient exceeded 0.8.

Specimen Collection

Blood collection protocol: 1) 10±2 h fasting; 2) ambient temperature maintained at 22–25°C; 3) antecubital venipuncture. The blood specimens were handled within four hours. Total blood specimens underwent centrifugation at 1000g for fifteen minutes at 4°C, after which the specimens were aliquoted as well as stored at −80°C up to assay.

Lipidomics Analysis

Our trials were conducted as previously outlined, and the statistics assay was facilitated by Shenzhen BGI Tech Solution Co., Ltd.[20] In summary, specimens (100 μL, precisely quantified) were augmented with internal lipid criteria (methanol solution, A454-4, Thermo Fisher Scientific, USA) subsequently accommodated with suitable quantities of water, methanol, as well as methyl tert-butyl ether for specimen treatment. Subsequently, specimens underwent ultrasonication and were centrifuged at 14,000 ×g, 10°C for fifteen minutes, after which the supernatant fluid was isolated for LC-MS assay. Specimens were compartmentalized utilising a Nexera LC-30A system equipped with a C18 column (CSH C18, 130 Å, 1.7 μm, 2.1 mm × 100 mm, Waters, USA), maintained at a process temperature of 55 °C and a flow rate of 0.4 mL/min. The lipid extracts were re-dissolved in 200 μL of a 90% isopropanol/acetonitrile solution and centrifugally separated for fifteen minutes at 14,000 ×g, subsequently, three μL of the specimen was injected. To mitigate the impact of fluctuations in the detection response, a randomized order was employed for the continuous analysis of the specimen. The Q-Exactive Plus (Thermo Fisher Scientific, San Jose, CA, USA) was employed to obtain mass spectra, with electrospray ionization (ESI) parameters calibrated and standardized for sample analyses. Simultaneously, single-point internal standard calibrations were employed to determine the standard-based amounts of distinct lipids identified using high-accuracy mass spectrometry, MS/MS spectrum matching, as well as retention durations. Lipid recognition was conducted utilising LipidSearch™ v.4.1 software (Thermo Fisher Scientific, San Jose, CA, USA).[21]

Quality control (QC) procedures were implemented to ensure analytical reproducibility. Pooled QC samples were prepared by mixing equal aliquots (10 μL) from all plasma samples and were injected every 10 experimental samples throughout the LC-MS run to monitor system stability. Internal standards (eg, A454-4 lipid standards in methanol) were added to each sample, and their recovery rates were assessed, with relative standard deviations (%RSD) for peak areas ranging from 5% to 15% across replicates, indicating acceptable reproducibility. To correct for MS drift, signal intensities were normalized using locally estimated scatterplot smoothing (LOESS) regression based on the QC samples, as implemented in LipidSearch v.4.1 software. Metabolites with %RSD > 20% in QC samples were excluded, resulting in 930 reliable metabolites for analysis.

Statistical Analyses

Statistical analyses were conducted utilizing SPSS 21.0 software (IBM-SPSS Inc., Chicago, IL, USA), employing the Kruskal–Wallis test for non-normally distributed data and one-way analysis of variance for normally distributed data. Missing or zero values in the lipid data, which accounted for approximately 3.82% of the measurements (eg, leading to the exclusion of 37 metabolites from the initial 967, resulting in 930 analyzed metabolites), were primarily due to concentrations below the limit of detection (LOD). These were classified as missing not at random (MNAR) with a left-censored mechanism, as the missingness depended on the unobserved metabolite levels themselves. To handle this, missing values were imputed using the quantile regression imputation of left-censored

data (QRILC) method, implemented in the imputeLCMD R package (version 2.0). This approach estimates a truncated normal distribution for low-abundance features via quantile regression, ensuring robust imputation without introducing excessive bias.[22] Following imputation, lipid statistics were transformed utilizing log10 to stabilize variance and approximate normality, and normalized via Pareto scaling to reduce the influence of high-intensity metabolites while preserving relative variability.

Supervised partial least squares discriminant analysis (PLS-DA) was initially employed to illustrate the inter-sample global distribution patterns and the reliability of the complete analytical procedure. A supervised OPLS-DA was subsequently employed to discern differential lipids among the groups. To avert overfitting, the OPLS-DA models underwent validation by permutation analysis conducted 200 times. Lipids exhibiting variable importance for projection (VIP) scores exceeding 1.0 in the OPLS-DA, alongside false discovery rate (FDR) values from two-tailed Student's *t*-test below 0.05 and fold change (FC) greater than 2, were classified as differentially abundant lipids. The FDR was calculated using the Benjamini-Hochberg procedure to control for multiple comparisons across the 930 metabolites, ensuring a low risk of false positives in the identification of the 14 differential candidates prior to ROC analysis.[23] Stepwise logistic regression analysis was conducted using the observed differentially abundant lipids to derive simplified potential biomarker panels. The diagnostic efficacy of the selected panels was evaluated by receiver operating characteristic (ROC) curve analysis, utilizing the R software for area under the curve (AUC) calculation and visualization (R-3.5.3). To mitigate potential overfitting, 5-fold cross-validation was applied to the single-feature logistic regression models, computing mean AUC ± standard deviation across folds. The Pearson correlation analysis was employed to evaluate the relationships associating clinical indices with discriminant lipid features. Differential metabolites were depicted by hierarchical clustering heatmaps utilising the MetaboAnalyst 5.0 network.

Results

General Demographic Information and Analysis of Variance

Table 1 encapsulates the demographic and clinical features of all subjects. No meaningful differences were observed in sex, age, or BMI when comparing SCZ patients with HCs (all $p > 0.05$). Moreover, SCZ patients exhibited a significant difference from HCs based on years of schooling ($p<0.05$). Figure 1 illustrates that PCA score plots delineate distinct metabolite profiles compared SCZ patients with healthy controls (HCs).

Table 1 Demographics and Clinical Characteristics of Participants

Characteristics	SCZ (N=50)	HC (N=25)	P
Sex, male/female	31/19	11/14	0.139
Age (yr)	33.30±9.93	32.00±9.25	0.591
Education (yr)	9.78±3.80	13.38±3.23	<0.001**
BMI (kg/m^2)	22.67±5.75	22.29±2.52	0.692
Course (mo)	48.88±74.04	NA	NA
PANSS total score	86.06±16.10	NA	NA
Positive factor	14.42±4.68	NA	NA
Negative factor	17.44±5.48	NA	NA
Cognitive factor	8.78±2.64	NA	NA
Excited factor	11.10±3.25	NA	NA
Depressed factor	6.58±2.59	NA	NA

Notes: **p<0.01. Values are presented as mean±standard deviation or number. P-values between sex difference are calculated with chi-square tests. p-values between age and BMI are calculated with *t*-tests. p-values with education are calculated with MannWhitney *U*-tests.

Abbreviations: SCZ, schizophrenia; HC, healthy control; BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; NA, not applicable.

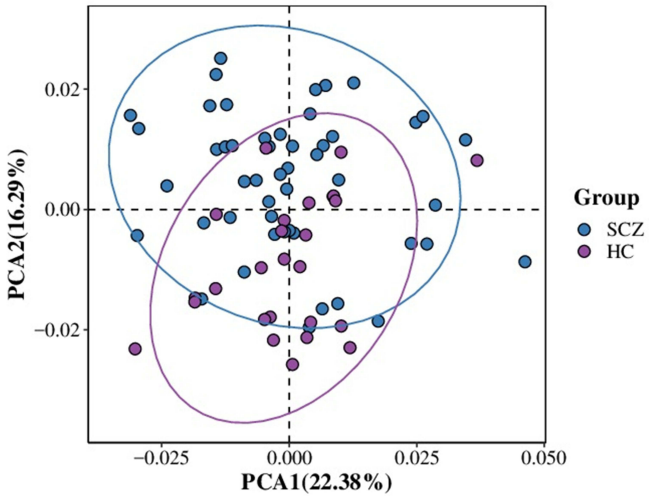

Figure 1 Score plot of principal component analysis.
Abbreviations: SCZ, schizophrenia; HC, healthy control; PCA, Principal Component Analysis.

Differential Metabolites Between Patients and HCs

This investigation involved the measurement of 967 metabolites. With the exclusion of mistakes and other variables, 930 metabolites persist. We employed OPLS-DA to examine metabolic disparities compared SCZ patients to healthy controls (Figure 2A). The score plot shows a definite difference between patients and HCs with R2Y=0.750 and Q2=−0.63 in the model (Figure 2B). This validation supports the use of the model for exploratory purposes. After screening according to p<0.05, VIP>1 and FC>2, there were significant discrepancies in 14 metabolites in plasma among SCZ and HC. A total of eight more substances were upregulated in SCZ patients compared to HC for the three isoforms of AcCa (20:4), (18:2), and (20:3) and OAHFA (38:4), the two isoforms of MePC (33:2) and (31:0), and the two isoforms of SM (d36:0) and SM (d38:3) (rep). The remaining six metabolites were downregulated in SCZ patients. The VIP plot shows the distribution of the 14 different metabolites in each specimen (Figure 3). In addition, the heatmap presents the spatial pattern of the 14 metabolites that differed between the two sets of samples (Figure 4).

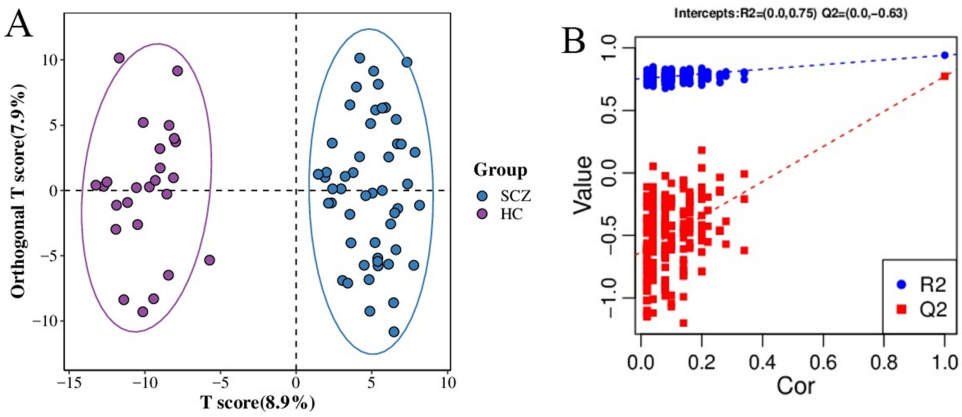

Figure 2 Metabolomic analysis between schizophrenia (SCZ) and healthy control (HC). (**A**) Score plot of orthogonal partial least squares discriminant analysis. (**B**) The plot of permutation validation: The scatter plot shows the correlation between the correlation coefficients of the permuted Y variables against the original model's R^2 (green squares) and Q^2 (blue squares) values. The vertical intercepts for R^2 and Q^2 are 0.75 and −0.63, respectively. A positive R^2 intercept (above zero) indicates that the original model is statistically significant and not overfitted, while a negative Q^2 intercept confirms the model's lack of predictive ability, as consistent with the main model's negative Q^2 value.; Cor, Correlation.

https://doi.org/10.2147/NDT.S537721

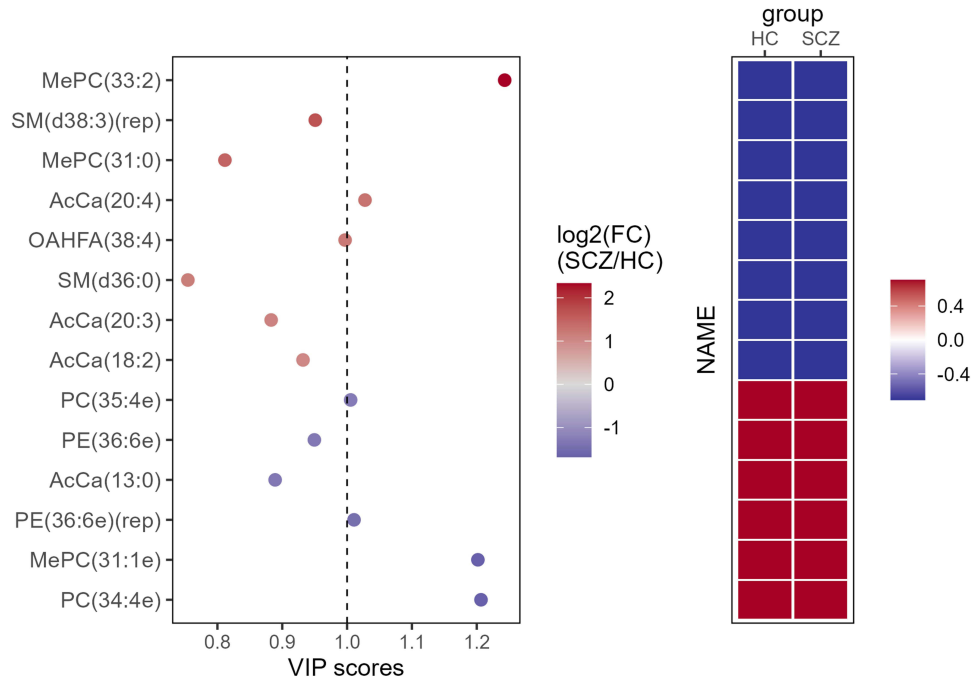

Figure 3 Variable importance in the projection (VIP) values of 14 differential metabolites. Red represents metabolites that are upregulated in the patients compared to the healthy controls. Blue means downward adjustment.

Abbreviations: AcCa, acylcarnitine; SM, sphingomyelin; PC, phosphatidylcholines; MePC, Methyl-Phosphatidylcholine; PE, Phosphatidylethanolamine; OAHFA, (O-acyl)-1-hydroxy fatty acid. VIP, Variable Importance in Projection.

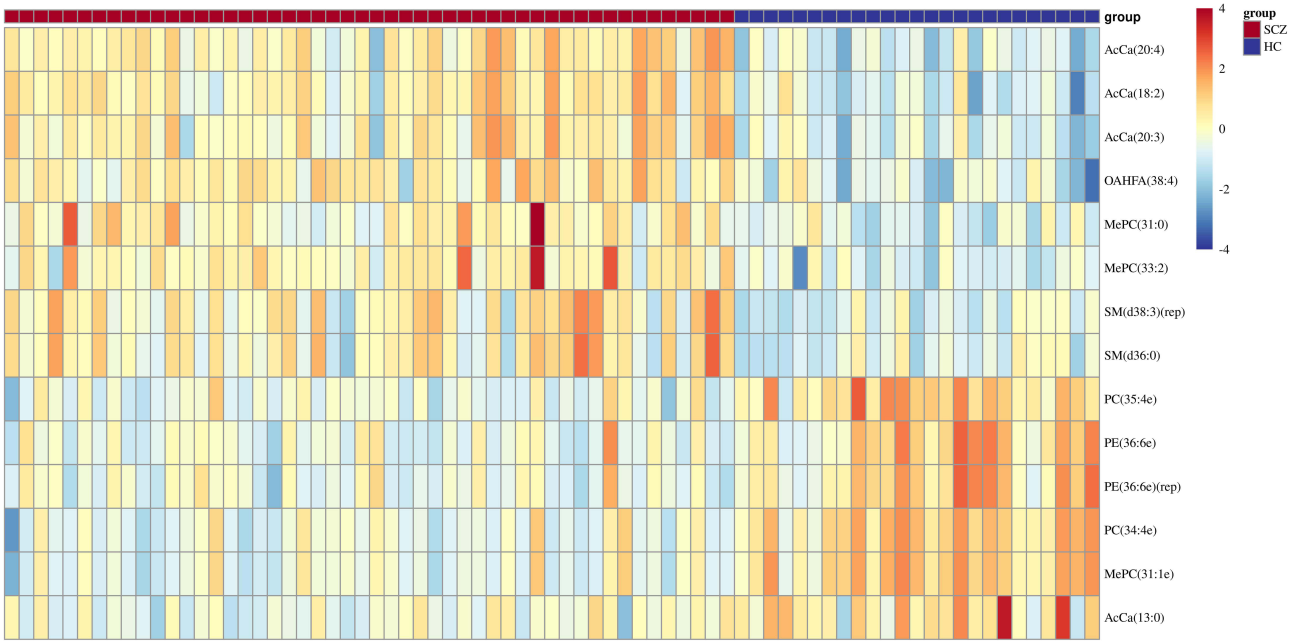

Figure 4 The heat map of 14 differential metabolites.

Validating a Diagnostic Signature Utilizing an ROC Curve

Given the significant differences in metabolites between groups, the study analyzed whether these metabolites have the promise to be diagnostic markers for SCZ. In line with the ROC curves from 5-fold cross-validation of single-feature logistic regression models, AcCa(20:4), AcCa(18:2), AcCa(20:3), OAHFA(38:4), MePC(31:0), MePC(33:2),

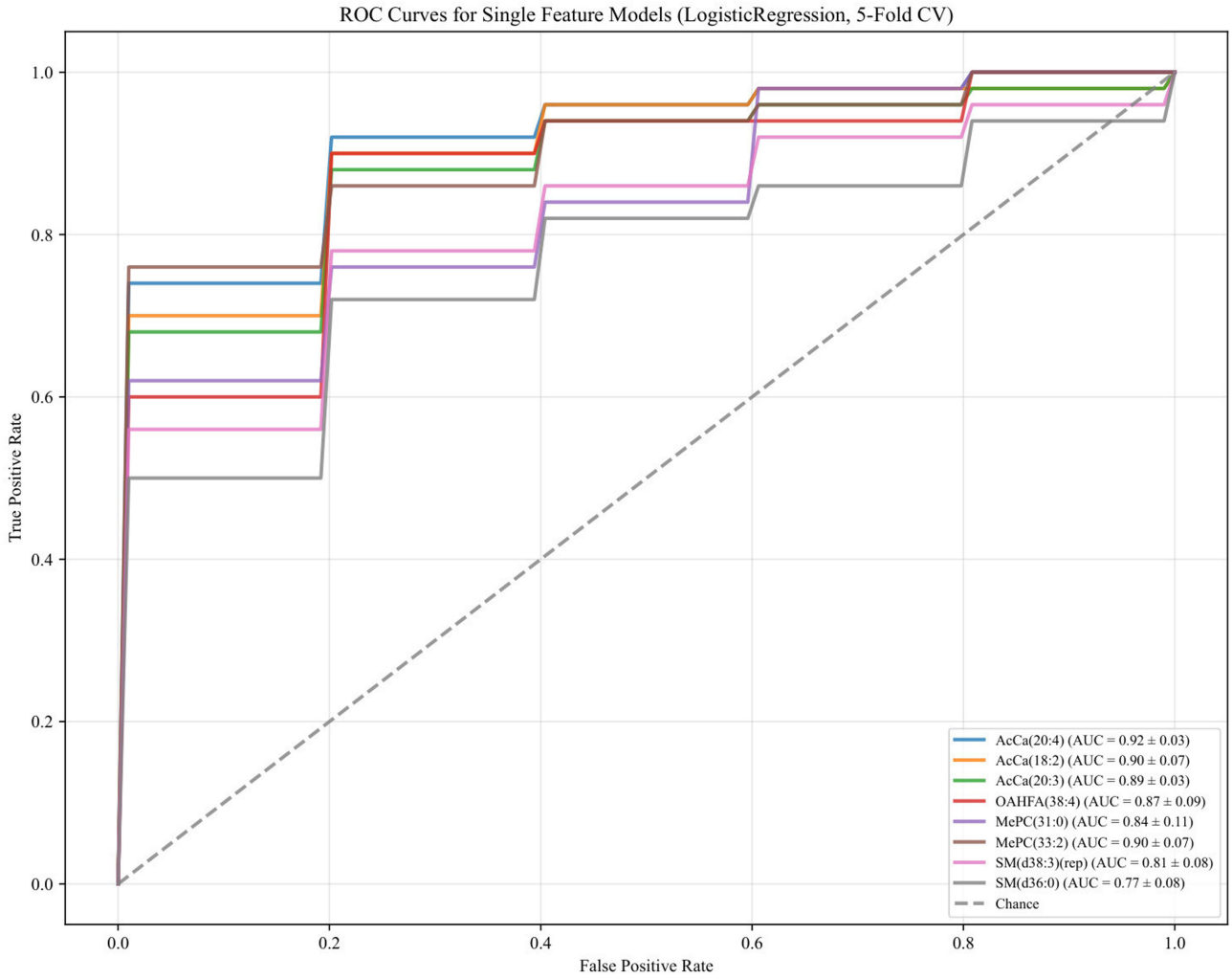

Figure 5 ROC Curves for Single Feature Models (Logistic Regression, 5-Fold CV). Receiver operating characteristic (ROC) curves for single-metabolite logistic regression models. Models were trained and evaluated using 5-fold cross-validation to assess the diagnostic potential of individual lipid metabolites for distinguishing schizophrenia patients from healthy controls. The area under the curve (AUC) values are presented as mean ± standard deviation. The dashed diagonal line represents the chance level (AUC = 0.5).

SM(d38:3)(rep), and SM(d36:0) performed well in diagnosing SCZ, demonstrating mean areas under the curve (AUC) of 0.92 ± 0.03, 0.90 ± 0.07, 0.89 ± 0.03, 0.87 ± 0.09, 0.84 ± 0.11, 0.90 ± 0.07, 0.81 ± 0.08, and 0.77 ± 0.08, respectively, with all values exceeding 0.7 and showing low variability, confirming robustness without significant overfitting (Figure 5).

Associations Between Plasma Metabolites and Symptoms

These 14 differential metabolites belong to six biological types. Correlation analyses were operated to analyze correlations between metabolites and psychiatric symptoms after combining differential metabolites of the same biotype. As shown in the table (Table 2), negative factors in PANSS were negatively correlated with plasma AcCa(20:4) ($r=-0.327$, $P<0.05$) and AcCa(20:3) ($r=-0.304$, $P<0.05$). In addition, cognitive factor scores on the PANSS scale were significantly and positively correlated with MePC(31:1e) ($r=0.327$, $P<0.05$) and PC(34:4e) ($r=0.334$, $P<0.05$) in plasma. These correlations represent weak to moderate effect sizes per Cohen's guidelines ($|r| < 0.3$ = weak, 0.3–0.5 = moderate,>0.5 strong), indicating modest clinical relationships that may reflect underlying pathophysiological links but require validation in larger cohorts.

https://doi.org/10.2147/NDT.S537721

Table 2 Associations Between Serum Differential Metabolites and Symptoms

Metabolites	PANSS Total Score	Positive Factor	Negative Factor	Cognitive Factor	Excited Factor	Depressed Factor
AcCa(20:4)	−0.025	0.273	−0.327*	−0.012	0.120	−0.275
AcCa(20:3)	−0.090	0.173	−0.304*	−0.113	0.079	0.225
PC(34:4e)	0.243	0.027	0.184	0.334*	0.070	0.066
MePC(31:1e)	0.231	0.024	0.176	0.327*	0.061	0.059

Note: *p<0.05; Effect sizes per Cohen: |r| < 0.3 weak, 0.3–0.5 moderate,>0.5 strong. The correlation between differential metabolites and symptoms was explored by correlation analysis.
Abbreviations: PANSS, Positive and Negative Syndrome Scale; AcCa, acylcarnitine; PC, phosphatidylcholines; MePC, Methyl-Phosphatidylcholine.

Discussion

The present study is an exploration of plasma metabolites affiliated with psychiatric symptoms in untreated SCZ using an untargeted metabolomics approach. In this study involving two groups of 967 metabolites, we identified 14 different metabolites. Among them, five metabolomics were PC and its methylated derivative MePC, indicating that PC may be a possible marker for SCZ. Further, SCZ by MePC, AcCa, SM, and OAHFA (38:4) showed better diagnostic ability. Finally, we found that AcCa, MePC, and PC were affiliated with clinical symptoms of SCZ.

This research revealed reduced PC levels in patients with SCZ, encompassing two subtypes: PC (34:4e) and PC (35:4e). This aligns with prior research that identified aberrant PC metabolism as the primary characteristic of SCZ.[24–26] Kaddurah-Daouk et al observed mildly reduced plasma PC concentrations in patients with schizophrenia.[27] In a prior metabolomics investigation, Schwarz et al identified diminished phosphocholines within the prefrontal cortex of schizophrenia patients.[28] Wang et al discovered predominantly increased concentrations of PC with saturated fatty acids or monounsaturated fatty acid side chains.[14] The discrepancies among these findings may stem from the varying illness conditions of the research populations, resulting in distinct pathological alterations. For instance, dysregulated PC-acylcarnitine shuttling resulted in elevated PC levels.[29] Elevated concentrations of the synthetic precursor choline may result in enhanced PC synthesis, potentially leading to increased PC levels.[30] Additional considerations must be taken into account, such as it has been observed that PC inherently displays subtype-specific differential expression patterns at the level of SCZ patients.[31] Consequently, when various research concentrates on specific PC molecular species, it is not unusual to encounter divergent outputs, which might appear conflicting. In addition, differences in metabolomics assay techniques for the effects of antipsychotic drug use can also affect the final results of research. The mechanism of abnormal PC metabolism in the SCZ is not entirely apprehended. Hasegawa et al observed that PC is a lipid exhibiting many bioactive properties known to influence pro-inflammatory signaling as well as immunological mechanisms.[32] Janssen together with Kiliaan et al discovered that PC serves as a key repository for arachidonic acid, a fundamental progenitor of bioactive molecules, and that alterations in PC levels obliquely influence signaling processes.[33] In conclusion, additional research is required to investigate the inherent mechanisms connecting the PC and SCZ.

MePC can be viewed as the product of structural modification of PC by methylation. In organisms, methylation reactions are usually catalyzed by specific enzymes. The specific physiological functions of MePC have not been fully clarified, but it may serve as an intermediate in certain metabolic processes or participate in specific signaling. Fang et al revealed a mechanism of reciprocal regulation between PC synthesis and methylation, whereby phosphatidylcholine synthesis is inhibited when key histone modifications in the methylation cycle (eg, H3K36 methylation) are absent, thereby affecting cellular metabolic adaptations.[34] Wong et al found that by supplementing exogenous phosphatidylcholine, the intracellular methylation cycle could be regulated, thereby alleviating the cell's need for endogenous methyl donors.[35] The above researches demonstrate that there is a close metabolic link between MePC and PC and that intracellular phospholipid metabolism and methylation status can be significantly affected by regulating the methylation cycle or supplementing exogenous PC.

Moreover, MePC, AcCa, SM, and OAHFA (38:4) have strong diagnostic capabilities for schizophrenia, and prior research has thoroughly examined the significance of these metabolites in the context of the disorder. AcCa is involved in bioenergetic metabolic pathways and also takes a vital part in SCZ pathogenesis.[36] Meanwhile, AcCa supplement therapy

has employed administered to SCZ patients.[37] Also in a study, it was found that patients with SCZ and depression had lower amounts of AcCa than healthy controls.[38] Cui et al identified that mid-length and long-chain acylcarnitines were typically reduced in patients with SCZ, and they also indicated that acylcarnitines have a distinguished capability for SCZ diagnosis, superior to functional near-infrared spectroscopy, uric acid as well as monoamines,[39] consistent with our findings. This result suggests that AcCa lipids may be used as possible markers for the diagnosis of SCZ and monitoring of disease progression. The current research gives clue of its diagnostic validity for schizophrenia, which requires additional verification. A genome-wide association study (GWAS) found that single nucleotide polymorphisms (SNPs) in genes associated with sphingomyelin metabolism (e.g, SMPD3) were significantly connected to the diagnosis of schizophrenia.[40] Prabakaran et al and Schwarz et al found significantly elevated levels of certain ceramides, metabolites of sphingolipids, in the white matter of the brain in patients with SCZ.[28,41] Similarly, in the study, acid sphingomyelinase (ASM) activity was found to be significantly increased in the prefrontal cortex (PFC) and ventral striatum (VS) in a rat model of amphetamine-induced psychosis, which was closely associated with the emergence of psychotic-like behavior.[40] In our study, we revealed that SM levels were significantly lower in SCZ patients, so more researches are still needed to validate whether SM is evidence-based in diagnosing SCZ patients. OAHFA is affiliated with the group of hydroxy fatty acids (HFAs), which are currently found in tear fluid and fetal sebum.[42–44] Mental disorders, including anxiety and depression, have been specifically mentioned in previous studies as contributing to the development of dry eye. Liang et al revealed that patients with dry eye had a higher risk of developing bipolar disorder, schizophrenia, neurotic disorders, and sleep disorders compared to those without dry eye.[45] We can look for clues from the hydroxy fatty acid branched chain fatty acid esters (FAHFA, fatty acid hydroxy fatty acid esters), which belong to the same family of hydroxy fatty acids (HFAs), with significant anti-inflammatory and antidiabetic physiopathological effects.[46,47]

The above results corroborate our study. The diagnostic ability of these metabolites for different SCZs advocates the Intricacy of pathogenesis and the need for more subsequent studies to improve diagnostic accuracy. Prior researches have revealed that plasma metabolites are expected to facilitate early diagnosis of SCZ. However, additional study progress is required before these discoveries may be applied clinically. A significant issue is the lack of standardization among current metabolite databases, since various laboratories frequently utilize disparate databases. This inconsistency diminishes the reproducibility of diagnostic markers in investigations, hence impacting the generalizability of the results. The findings of this research lack corroboration by independent cohorts. Emerging advancements in metabolomics technologies and methodologies for bigger independent cohorts may address this difficulty.

In addition, we detected 2 metabolites, AcCa and MePC, related to clinical signs of SCZ, which contained MePC (31:1e) and PC(34:4e). Magnetic resonance spectroscopy investigations of the cerebral cortex have identified the link connecting PC levels with psychiatric symptomatology.[15] However, Wang et al noted no significant correlation between PC and PANSS scores.[14] The varying outcomes may stem from discrepancies in metabolomics methodologies, data processing, analytical procedures, and patient demographics. Given the absence of animal models explicitly developed to examine the association between PC and mental symptomatology in SCZ, we should derive mechanistic understanding from analogous experimental animals. Fu et al present a mouse model demonstrating that disruptions in PC homeostasis result in the suppression of muscle/endoplasmic reticulum calcium ATPase activity, which may represent possible molecular machinery linked to the onset of psychotic symptoms.[48] In addition, Li et al have shown in a murine model of colitis that PC correlates with the modulation of several intestinal microbiota, containing *Lactobacillus, Faecalibacterium, Dubosiella, and Turicibacter*.[49] The identified biomarkers reflect distinct pathophysiological mechanisms in SCZ. Acylcarnitines indicate energy metabolism disruptions, with upregulation suggesting compensatory responses to mitochondrial dysfunction, potentially linked to negative symptoms via bioenergetic deficits. PC and MePC, critical for membrane integrity and signaling (eg, arachidonic acid pathways), show downregulation, which may contribute to synaptic abnormalities and cognitive deficits. These alterations support diagnosis through high AUC values (>0.9 for AcCa), enabling early detection, and correlate with symptoms, suggesting a mechanistic basis for SCZ symptomatology in medication-naïve patients.

More studies have focused on the changes of AcCa species in the SCZ, such as Kriisa et al, who demonstrated that long-chain AcCa were up-regulated and short-chain acylcarnitines were down-regulated in first-onset schizophrenia and drug-naïve patients, and that after 7 months of antipsychotic medication, the patients' levels of long-chain AcCa declined

and the concentration of short-chain AcCa increased.[50] These observations suggest disruptions in cellular bioenergetics associated with antipsychotic drugs. A possible mechanism is the inhibition of mRNA expression of carnitine palmitoyltransferase1a by atypical antipsychotic drugs.[51] Oh et al have demonstrated phosphorylation of AMP-activated protein kinases along with downregulation of several genes involved in fatty acid oxidation, particularly carnitine palmitoyltransferase 1a (CPT1a).[52] These results can be interpreted through a mechanobiological perspective, focusing on energy metabolism and phospholipid cycle abnormalities in antipsychotic-naïve individuals. For instance, CPT1a inhibition impairs fatty acid oxidation, leading to acylcarnitine accumulation and bioenergetic deficits that may underlie negative and cognitive symptoms in early, unmedicated SCZ. Similarly, phospholipid cycle disruptions affect membrane fluidity and signaling pathways, contributing to synaptic dysfunction without pharmacological confounding. However, none of the above results have been overly involved in psychiatric symptoms, and more exploratory studies are needed to follow up on AcCa's mechanism in the SCZ.

Despite the novel findings from this study, several limitations are acknowledged that should be addressed in future research. First, the relatively small sample size of 75 participants and the single-center design may limit the statistical power and the generalizability of the findings to a broader population. Despite the identification of differential metabolites, the negative Q^2 value (−0.63) in the OPLS-DA model suggests limited predictive power, which may arise from data variability, small sample size, or inherent noise in untargeted metabolomics. While the permutation test validated the model's exploratory utility by confirming no significant overfitting, future studies with larger cohorts and targeted validation are recommended to improve model robustness and confirm these findings. Second, while the cohort of medication-naive patients is a key strength, certain confounding factors, such as diet, smoking, circadian rhythm, and metabolome seasonality, were not strictly controlled for. These factors are known to influence metabolic profiles and should be carefully addressed in future research designs. Ultimately, the results require replication and validation in subsequent large-scale, multi-center investigations involving broader demographic groups to confirm the findings.

Conclusion

Our research offers innovative perspectives into metabolic problems in people with schizophrenia, specifically pertaining to psychosis demonstrates potential as a biomarker for schizophrenia, as these metabolites are effective in diagnosing the condition. Notably, the research outputs indicate that AcCa, PC, and MePC are correlated with psychiatric symptoms, suggesting these metabolites may serve as prospective targets.

Acknowledgments

This work was supported by the Anhui Clinical Medical Research Centre for Psychosomatic Diseases and the National Clinical Key Specialty Construction Project of China. We would like to thank the support of Hefei Fourth People's Hospital.

Funding

Funding this work was supported by the Scientific and technological research project of Anhui Provincial Science and Technology Department(201904a07020009), the National Clinical Key Specialty Construction Project of China, the Anhui Clinical Medical Research Center for Mental and Psychological Diseases, and the Healthcare Application Medical Research Project of Hefei City (NO. Hwk2024yb003).

Disclosure

The authors report no conflicts of interest in this work.

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