

Untargeted Plasma Lipidomics Reveal Perturbed Metabolites of Glycerophospholipids, and Sphingolipids in Moderate-to-Severe Acne

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Background: Acne vulgaris (AV) is a common inflammatory disorder involving the pilosebaceous unit. The study aimed to explore the plasma lipidome signatures and identify specific lipid biomarkers in moderate-to-severe acne patients.

Patients and Methods: Untargeted plasma lipidomic analysis using ultra-high performance liquid chromatography system (UHPLC) coupled to q-extraction plus was employed on 30 moderate-to-severe acne patients aged between 16–25 years and 30 healthy controls. Multivariate data analyses were used to identify the distinguishing lipid metabolites.

Results: All 1449 species of 37 lipid subclasses were identified from the MS data. There were apparent differences in plasma lipid profiles between acne groups and control groups. With variable influence on projection (VIP) > 1.0 and P-value < 0.05, 26 significantly different lipid metabolites were identified. These metabolites consisted mainly of glycerophospholipids (GPs), sphingolipids (SPs), and glycerolipids (GLs). Combining with AUC ≥ 0.800 as the elected criteria, we obtained five differential lipids with good diagnostic performance for acne severity, including 2 sphingomyelins (SM), 1 phosphatidylglycerol (PG), 1 trihexosylceramide (Hex3Cer), and 1 Phosphatidylcholine (PC). Among them, PG (44:0) had the highest AUC values.

Conclusion: Our study revealed the plasma lipidome signature of patients with moderate-to-severe acne. The results will provide a novel light into the perturbed lipid metabolism leading to the development of acne.

Keywords: moderate-to-severe acne, lipidomics, sphingolipids, glycerophospholipids

Introduction

Acne vulgaris (AV) is a common inflammatory disorder involving the pilosebaceous unit and affects skin sites with a high density of sebaceous glands, such as face, back, and chest.^{1,2} It affects approximately 85% of world's population aged 12 to 25 years.³ Typical acne lesions include open and closed comedones, inflammatory papules, pustules, and nodules.⁴ AV is a multifactorial disease, and its precise pathogenesis remains unknown. Four factors are believed to play a pivotal role in the formation of acne lesions, including excessive sebum, disturbed keratinization within the follicle, altered bacterial colonization with *Cutibacterium acnes*, and inflammation.^{5–7}

Metabolomics is a newly developing omics after genomics, transcriptomics, and proteomics analysis.^{8,9} It uses advanced analytical chemistry techniques and complicated statistical methods to comprehensively measure large numbers of small molecule metabolites found in biofluids, tissues, and cells. As a subfield of metabolomics, lipidomics aims to comprehensively and systematically reflect the alterations in lipid profiles and related metabolic pathways within organisms under various physiological or pathological conditions.¹⁰ To date, lipidomics has been employed to study some dermatological diseases such as psoriasis,¹¹ atopic dermatitis,¹² urticaria,¹³ and hidradenitis suppurativa.¹⁴

Several lipidomics studies have revealed an association between lipid metabolite alterations and acne. Through skin surface lipidomics, Zhou et al¹⁵ revealed that the variation of triacylglycerols (TGs), phytosphingosine, and sphinganine was closely related to the severity of acne in adolescents. In addition, skin surface lipids sampled from young males with acne had significantly higher phosphatidylserine levels.¹⁶ In a rat acne model, 96 different lipid species were identified by a skin lipidomics study.¹⁷ Targeted lipidomics of serum sphingolipids in patients with acne has also been performed.¹⁸ However, no untargeted lipidomics studies have been conducted focusing on the plasma of moderate-to-severe acne.

In this study, an untargeted lipidomics analysis using an ultra-high performance liquid chromatography system (UHPLC) coupled with q-extraction plus was adopted to examine of the total plasma lipids in moderate-to-severe acne patients. Our aim is to reveal the discrepancies in lipid metabolites of moderate-to-severe acne patients and screen for potential biomarkers.

Materials and Methods

Patient Population

The patient group consisted of 30 patients aged between 16–25 years who visited our department from 10 January 2016 to 5 September 2021. The Global Acne Grading System (GAGS) criteria was used to estimate the disease severity of acne.¹⁹ The control group consisted of 30 gender- and age-matched healthy subjects. Exclusionary criteria for all participants were recent (within one month) treatment with topical and systemic medications, history of smoking, history of alcohol abuse, presence of systemic diseases, and psychiatric diseases. The study was conducted in accordance with the principles in the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. Each participant was fully informed of the purpose of the study and signed an informed consent form.

Main Reagents and Instruments

Reagents

Methanol (Thermo Fisher, USA), acetonitrile (Thermo Fisher, USA), propanol (Thermo Fisher, USA), formic acid (Fluka, German), ammonium formate (Sigma-Aldrich, USA), Internal Standards (SPLASH[®] LIPIDOMIX MASS SPRC STANDARD, AVANTI, 330707-1EA), and Methyl Tert-Butyl Ether (MTBE) (Sigma-Aldrich, USA).

Instruments

UHPLC Nexera LC-30A ultra performance liquid chromatography system (SHIMADZU, Japan), Q Exactive plus mass spectrometer (Thermo Scientific, USA), the chromatographic column: Waters, ACQUITY UPLC CSH C18, 1.7 μ m, 2.1 mm \times 100 mm column and Low temperature high-speed centrifuge (Eppendorf 5430R, German).

Sample Collection and Preparation

Plasma sample from each participant was collected in vacuum tubes (5 mL) containing EDTA anticoagulant, then centrifuged and stored at -80°C . Each sample (50 μ L) was spiked with 20 μ L internal standards and then homogenized with 240 μ L methanol and 200 μ L water. Following the addition of 800 μ L of MTBE, the mixture was subjected to ultrasound followed by sitting still for 30 min. The solution was centrifuged (14,000 g, 15 min, 10°C) to extract the top layer, which was then dried under nitrogen. For Liquid Chromatograph-Mass Spectrometer (LC-MS) analysis, the lipid extracts were redissolved and vortexed in 200 μ L of an isopropanol solution. Thereafter, 90 μ L of the re-resolution was collected and centrifuged (14,000 g, 15 min, 10°C). The supernatants were collected for further analysis. By pooling equal amounts of lipid extracts from all samples, quality control (QC) samples were prepared.

Liquid Chromatograph-Mass Spectrometer/Mass Spectrometer (LC-MS/MS) Analysis

Lipidomic analysis was conducted by Shanghai Applied Protein Technology Company. Reversed phase chromatography was selected for LC separation using the CSH C18 column. Solvent A was acetonitrile–water (6:4, vol/vol) with 0.1 mM ammonium formate and 0.1% formic acid, and solvent B was isopropanol–acetonitrile (9:1, vol/vol) with 0.1 mM ammonium formate and 0.1% formic acid. The initial mobile phase consisted of 30% solvent B, which was kept for 2 min, and then linearly increased to 100% solvent B for 23 min, followed by equilibrating in 5% solvent B for 10 min.

The autosampler was kept at 10°C. Signal fluctuations were detected randomly to avoid bias due to instrumentation errors. To evaluate and monitor the reliability and stability of the experimental data, sampling of the queue was performed every eight samples by using one QC sample.

Following ultra-HPLC separation, samples were analyzed using a Q Exactive™ plus mass spectrometer. The chromatographic conditions were in accordance with a previous report.²⁰

Data Processing and Statistical Analysis

To process the raw data, the LipidSearch software version 4.2 (Thermo Scientific™, USA) was used. Adducts of +H, +NH₄ were chosen for positive mode searches, and -H, +HCOO were chosen for negative mode searches. For the data extracted from LipidSearch, the ion peak with a value of > 50% missing from the group was deleted. After normalization and integration using the Perato scaling method, the processed data were imported into SIMPCA-P 16.1 (Umetrics, Umea, Sweden) for orthogonal partial least squares discriminant analysis (OPLS-DA). Significantly different lipids were identified based on a combination of statistically significant thresholds of variable influence on projection (VIP) values obtained from the OPLS-DA model and two-tailed Student's *t*-test.

Results

Clinical Characteristics of the Subjects

A total of 30 moderate-to-severe acne patients (Group P) and 30 healthy subjects (Group C) were enrolled in the study. Detailed clinical characteristics are described in Table 1. No statistically significant differences between acne and healthy controls in age, sex distribution, or body mass index were found.

Different Lipidomic Profiles Between the Moderate-to-Severe Acne and Healthy Groups

All 1449 species of 37 lipid subclasses were identified from the Mass spectrometry data (Figure 1). The main lipid metabolite subclasses in the plasma samples included phosphatidylcholine (PC), TG, and sphingomyelin (SM). OPLS-DA, a supervised multivariate model, was constructed to analyze the lipidomic data and search for features that may discriminate between Group P and Group C. An apparent distinction between them was observed in the OPLS-DA model, which indicated

Table 1 Characteristics of Group P and Group C

Characteristics	Group P (n=30)	Group C (n=30)	P-value
Age			0.49
Range	16–25	18–24	
Gender			0.76
Female	6 (20%)	7 (23%)	
Male	24 (80%)	23 (77%)	
Body mass index	22.49 ± 2.11	22.76 ± 1.99	0.62
Duration (year)		NA	NA
Median	3		
Range	1–8		
GAGS	28.6 ± 5.06	NA	NA
Moderate (19–30)	19 (63%)		
Severe (31–38)	11 (37%)		

Abbreviations: Group P, moderate-to-severe acne group; Group C, healthy subject group; NA, not available; GAGS, Global Acne Grading System.

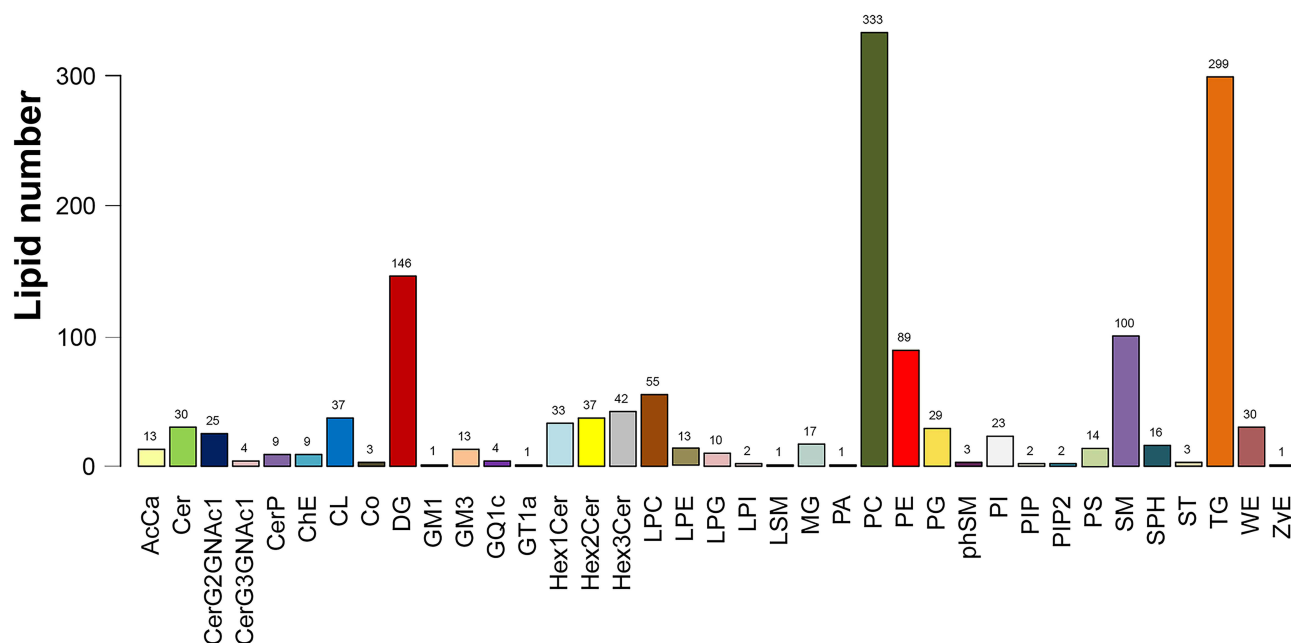


Figure 1 Classification of the identified lipids.

significant alterations in the plasma lipidomic profile of Group P (Figure 2A). The model was evaluated by monitoring the model R2 (goodness of fit) and Q2 (predictive ability) values and permutation tests ($n = 200$) were performed on R2 and Q2 as shown in Figure 2B ($R2 = 0.6647$, $Q2 = -0.6375$). The permutation test indicated the OPLS-DA model is reliable. The volcano plot displayed significant changes in the plasma metabolite profiles for Group P. Overall, 113 lipid metabolites were upregulated, and 78 were downregulated compared to those in Group C (Figure 2C).

Screening and Identification of Significantly Altered Lipid Metabolites for Acne

VIP reflected the significance of those variables in the OPLS-DA model and was used to select the significant variables. With $VIP > 1.0$ and $P\text{-value} < 0.05$, 26 significantly different lipid metabolites were identified (15 up-regulated and 11 down-regulated lipids) (Table 2). These lipid species mainly belonged to Glycerophospholipids (GPs) ($n=9$), Sphingolipids (SPs) ($n=12$), and Glycerolipids (GLs) ($n=2$). Their relationships were revealed by correlation analysis (Figure 3). Furthermore, to visualize the distribution of relative levels of 26 differential lipids in each group, the identified lipid data were analyzed using a clustering heatmap (Figure 4).

ROC Curve Analysis

To further evaluate the diagnostic performance of the identified lipid species, OPLS-DA-based ROC analysis was performed. The area under the ROC curves (AUC) was calculated to evaluate the reliability and discriminatory power of the potential biomarkers. With $AUC \geq 0.800$ as the elected criteria, five differential lipids were identified with good diagnostic performance for acne, including 2 SMs, 1 PG, 1 Hex3Cer, and 1 PC. Among them, PG (44:0) had the highest AUC values (0.941 (95% CI: 0.886–0.996)), indicating outstanding diagnostic ability for acne, whereas Hex3Cer (d32:1) had relatively lower AUC values ($AUC = 0.807$, 95% CI: 0.697–0.916) (Figure 5).

Discussion

Lipids provide the structural basis of the cell membrane bilayer. Moreover, they were involved in various biological processes, such as cell proliferation, apoptosis, angiogenesis, immunity, and inflammation.^{21–23} Based on “Comprehensive Classification System for Lipids”, eight categories of lipids can be obtained: fatty acids (FA), sphingolipids (SP), glycerolipids (GL), glycerophospholipids (GP), saccharolipids (SL), sterol lipids (ST), polyketides (PK), and prenol lipids (PR).^{24,25} Currently, lipid dysregulation has been identified in many diseases, including diabetes,

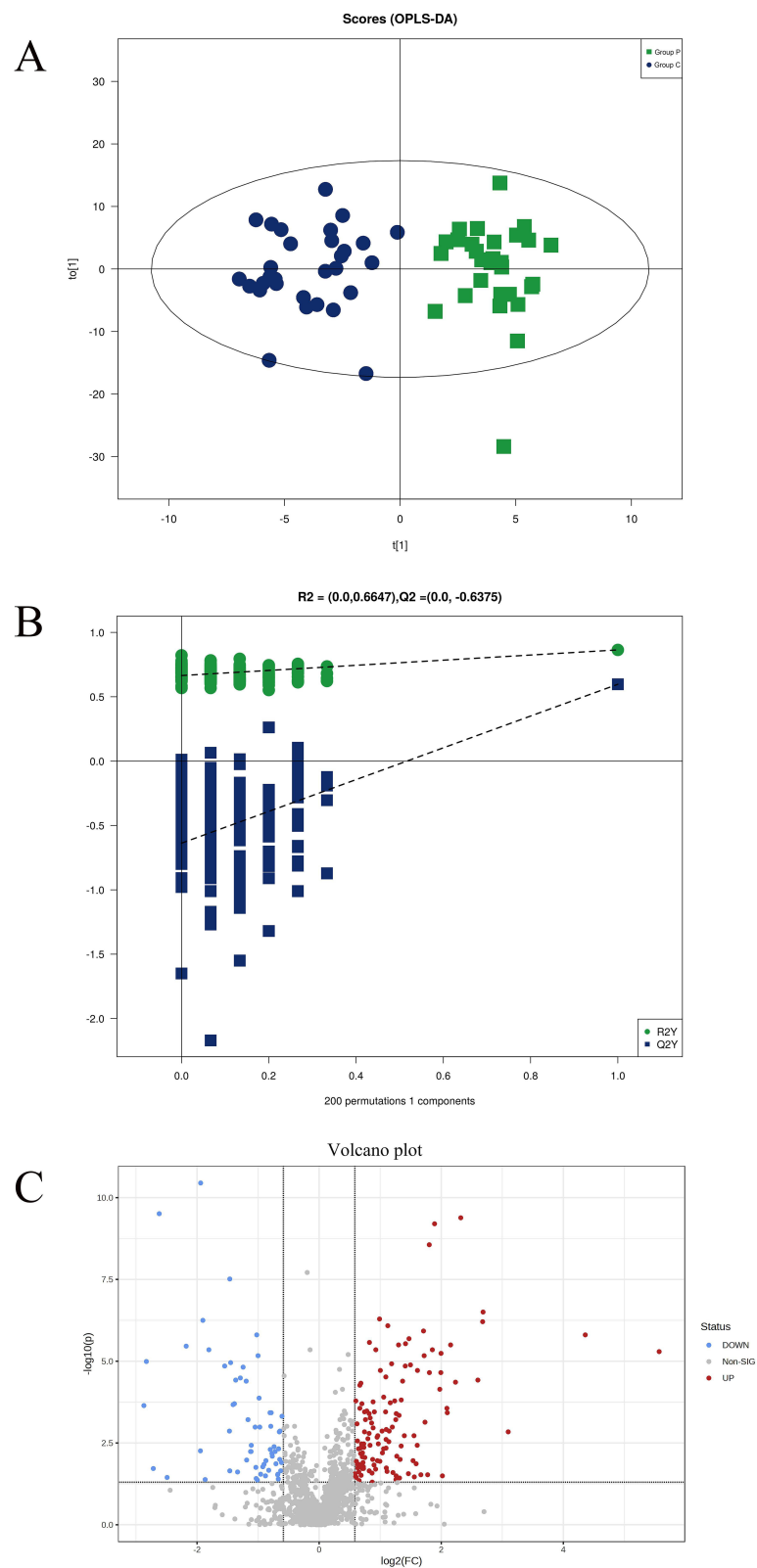


Figure 2 Separation between Group P and Group C by detected ions. **(A)** Supervised OPLS-DA model based on all Group P and Group C samples differentiating the two groups. **(B)** Permutation test for OPLS-DA model. **(C)** Volcano plot based on all detected ions that presented distribution of these ions, differential metabolic features were selected by criteria of P-value < 0.05, and fold change >1.5 or <0.67.

Table 2 Identification of Significantly Altered Plasma Lipids Between Group P and Group C

Lipid	VIP	Fold Change	P-value	Variation	Cal Mz	RT(Min)
PE (40:7e)	5.362	1.178	4.43E-03	Up	798.541	10.341
PI (18:0_20:4)	1.017	1.347	1.84E-02	Up	885.550	9.162
PC (34:1)	3.648	1.388	5.49E-03	Up	760.585	10.992
TG (16:0_16:0_18:1)	3.496	4.265	9.06E-03	Up	850.786	17.838
SM (d42:2)	2.428	1.299	5.36E-04	Up	857.675	12.528
SM (d34:1)	2.013	1.131	2.65E-02	Up	747.566	8.944
Hex3Cer (d32:1)	1.809	3.496	2.69E-05	Up	1013.673	7.409
SM (d42:3)	1.602	1.178	7.70E-03	Up	855.660	11.542
phSM (t36:1)	1.559	1.214	7.62E-04	Up	763.596	10.344
SM (d36:1)	1.413	1.215	8.37E-03	Up	775.597	10.224
SM (d36:2)	1.273	1.260	2.03E-03	Up	773.581	9.129
SM (d38:1)	1.089	1.214	5.38E-03	Up	803.628	11.459
SM (d42:1)	1.005	1.985	1.20E-07	Up	859.691	12.978
ChE (18:1)	8.060	1.171	2.48E-02	Up	668.634	17.671
WE (2:0_20:3)	3.664	3.008	3.12E-03	Up	352.321	2.016
WE (2:0_22:5)	2.154	0.137	2.71E-03	Down	376.321	1.629
GM3 (m34:0)	1.340	0.845	3.94E-03	Down	568.360	2.627
TG (18:1_18:2_18:3)	2.750	0.670	3.00E-02	Down	896.770	16.495
Hex2Cer (m40:5)	1.465	0.437	4.31E-05	Down	920.647	17.650
SM (d40:1)	1.364	0.544	1.57E-02	Down	787.669	13.125
PC (36:1)	2.407	0.745	4.67E-02	Down	810.598	10.977
PC (16:0_20:3)	9.538	0.221	2.89E-07	Down	828.576	10.078
PC (8:1e_10:1)	1.292	0.816	1.22E-02	Down	520.340	1.512
CL (78:2)	1.283	0.361	1.42E-03	Down	771.573	10.989
LPC (18:2)	1.245	0.363	6.20E-04	Down	564.331	2.161
PG (44:0)	1.210	0.260	1.19E-07	Down	891.705	17.753

Abbreviations: VIP, Variable influence on projection; Cal Mz, Calculators mass to charge ratio; RT, Retention time; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; PC, Phosphatidylcholine; TG, Triacylglycerol; SM, Sphingomyelin; Hex3Cer, Trihexosylceramide; phSM, phytosphingosine; ChE, Cholesteryl Ester; WE, Wax Ester; GM3, Ganglioside, monosialo trihexosyl ceramide; Hex2Cer, dihexosylceramide; LPC, Lysophosphatidylcholine; CL, Cardiolipin; PG, Phosphatidylglycerol.

respiratory diseases, and Alzheimer's disease,^{26–28} suggesting that dysregulated lipids may serve as an important biomarker and be associated with the development of these diseases. In this study, we demonstrated that plasma lipidomic profiles are substantially changed in moderate-to-severe acne patients compared to healthy controls. Besides, 26 differential lipid metabolites were identified between the two groups. They consisted mainly of GPs, SPs, and GLs.

GPs, also known as phospholipids, are critical components of the lipid bilayer of cellular membranes and play a central role in cell signaling and metabolism.²⁹ Previous studies have shown that in skin lipids, GPs were increased in

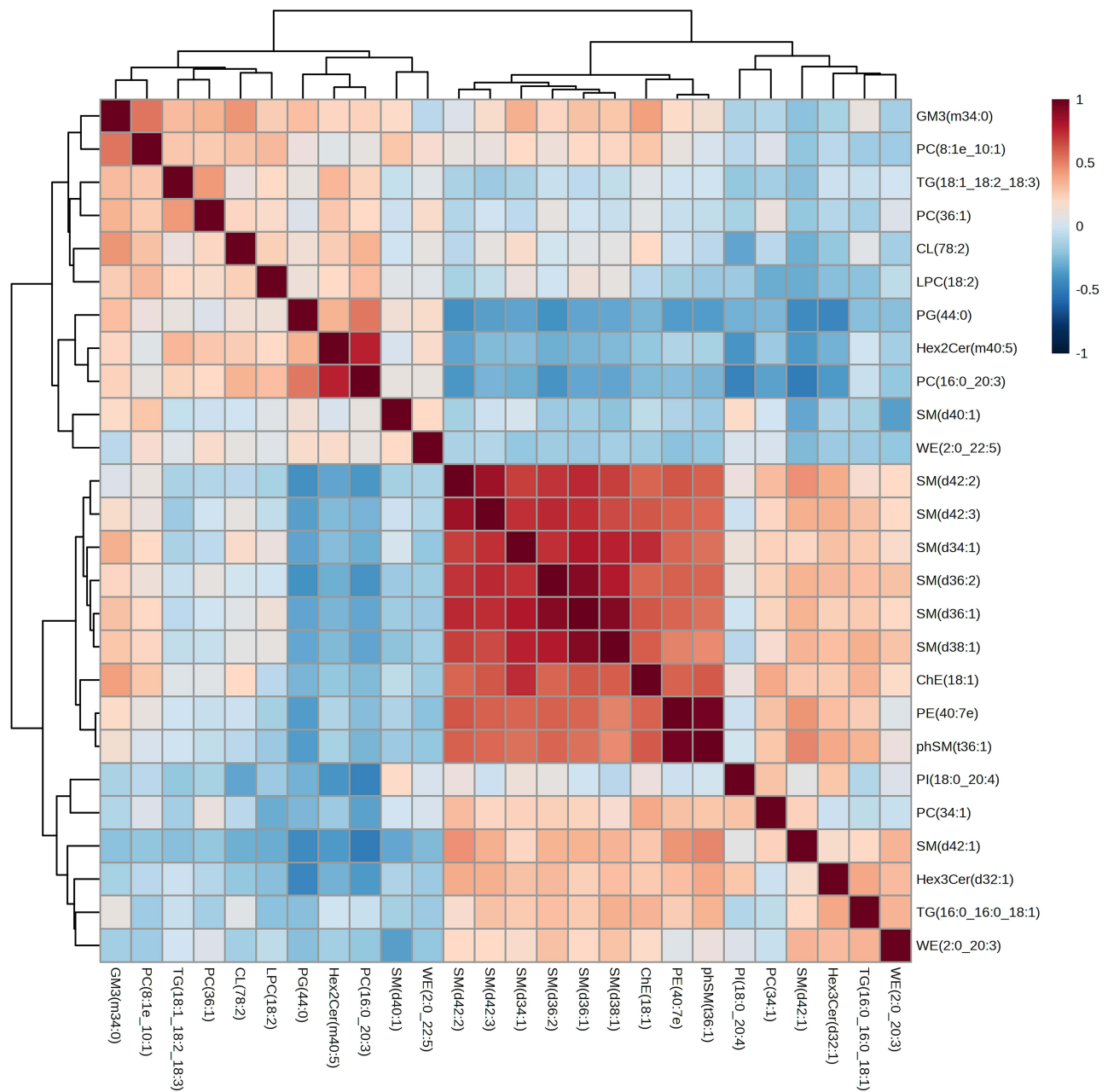


Figure 3 Correlation clustering-heatmap of selected lipid between Group P and Group C.

young male acne patients and decreased in infantile acne patients.^{16,30} Besides, Chen et al found elevated GPs in the skin sample of a rat acne model.¹⁷ However, there are no studies on blood GPs of acne. In our study, plasma lipid profiling identified a series of 9 GPs with significant alterations. Three GPs were elevated (PC) (34:1), phosphatidylethanolamine (PE) (40:7e), phosphatidylinositol (PI) (18:0_20:4), and six GPs were decreased (lysophosphatidylcholine (LPC) (18:2), PC (36:1), PC (8:1e_10:1), PG (44:0), PC (16:0_20:3), cardiolipin (CL) (78:2)). The lipid metabolites obtained were mainly from the PC, PG, and PE subgroups. PC constitutes the major component of biological membranes in eukaryotic cells, and its degradation and biosynthesis are essential to regulate cell cycle processes.³¹ A previous study demonstrated that PC species can regulate the differentiation of keratinocytes. Therefore, the alteration in PC levels suggests a defect in the process, resulting in disturbed keratinization. Notably, the levels of PG (44:0) were decreased. Previous studies have

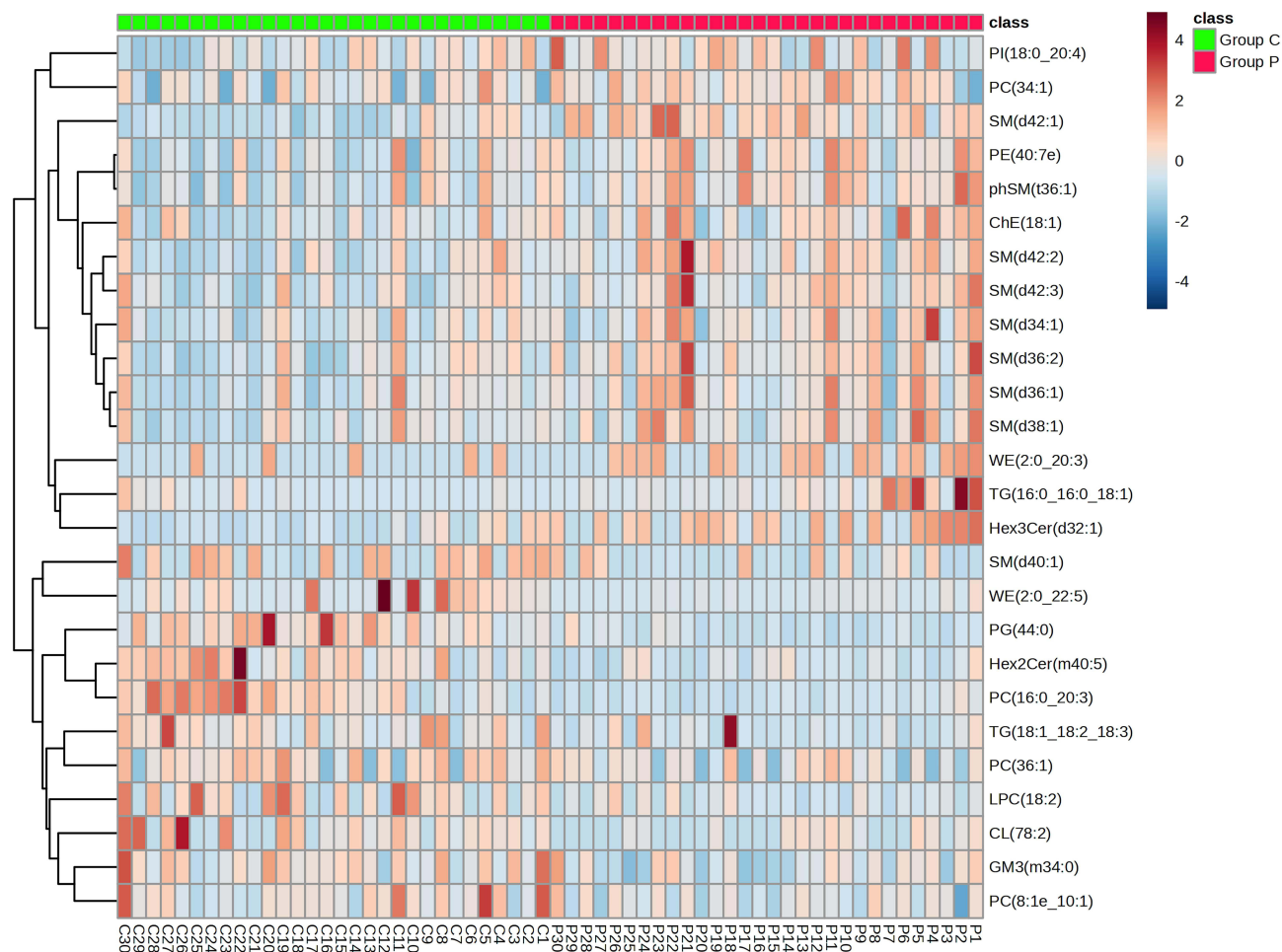


Figure 4 Clustering of differential lipids in Group P and Group C by heatmaps.

shown that PG can inhibit keratinocyte inflammatory mediator expression.^{32,33} We postulate that decreased PG (44:0) level may be related to acne inflammation.

SPs occur in the plasma membranes of all eukaryotic cells and play an essential role in maintaining the skin barrier.³⁴ Through untargeted metabolomics, our previous study revealed sphingolipid metabolic pathway was significantly perturbed in a rabbit acne model.³⁵ Similarly, Chen et al conducted a skin lipidomics study of a rat acne model, and metabolic pathway analysis showed that the sphingolipid metabolism pathway had the highest impact factors.¹⁷ However, studies on blood sphingolipids in acne patients remain limited. In this study, 12 SPs were markedly altered in moderate-to-severe acne patients. Of note, seven SMs increased, including SM (d34:1), SM (d36:1), SM (d36:2), SM (d38:1), SM (d42:1), SM (d42:2), and SM (d42:3). This result was in agreement with our previous untargeted metabolomics study showed that sphingolipid metabolic pathway was significantly perturbed in moderate-to-severe acne patients.³⁶ Besides, Kaya et al revealed that circulating levels of C16 SM were increased in patients with acne compared to healthy controls.¹⁸ SMs are the most abundant circulating lipids. In vitro, SM can stimulate the proliferation of keratinocytes.³⁷ Therefore, we hypothesize that the elevated plasma SMs may be involved in the pathogenesis of acne by regulating abnormal keratinization processes.

GLs are the principal constituent of cell membranes and extracellular protective layers such as the stratum corneum. They are classified as monoacylglycerol (MG), diacylglycerol (DG), or triacylglycerol.³⁸ TGs are the most abundant lipids in the body synthesized from glycerol and fatty acids (FAs), which can be hydrolyzed into DG and FAs by lipase reaction. Most previous studies have mainly measured total TG levels in patients with acne.^{39–41} However, no studies

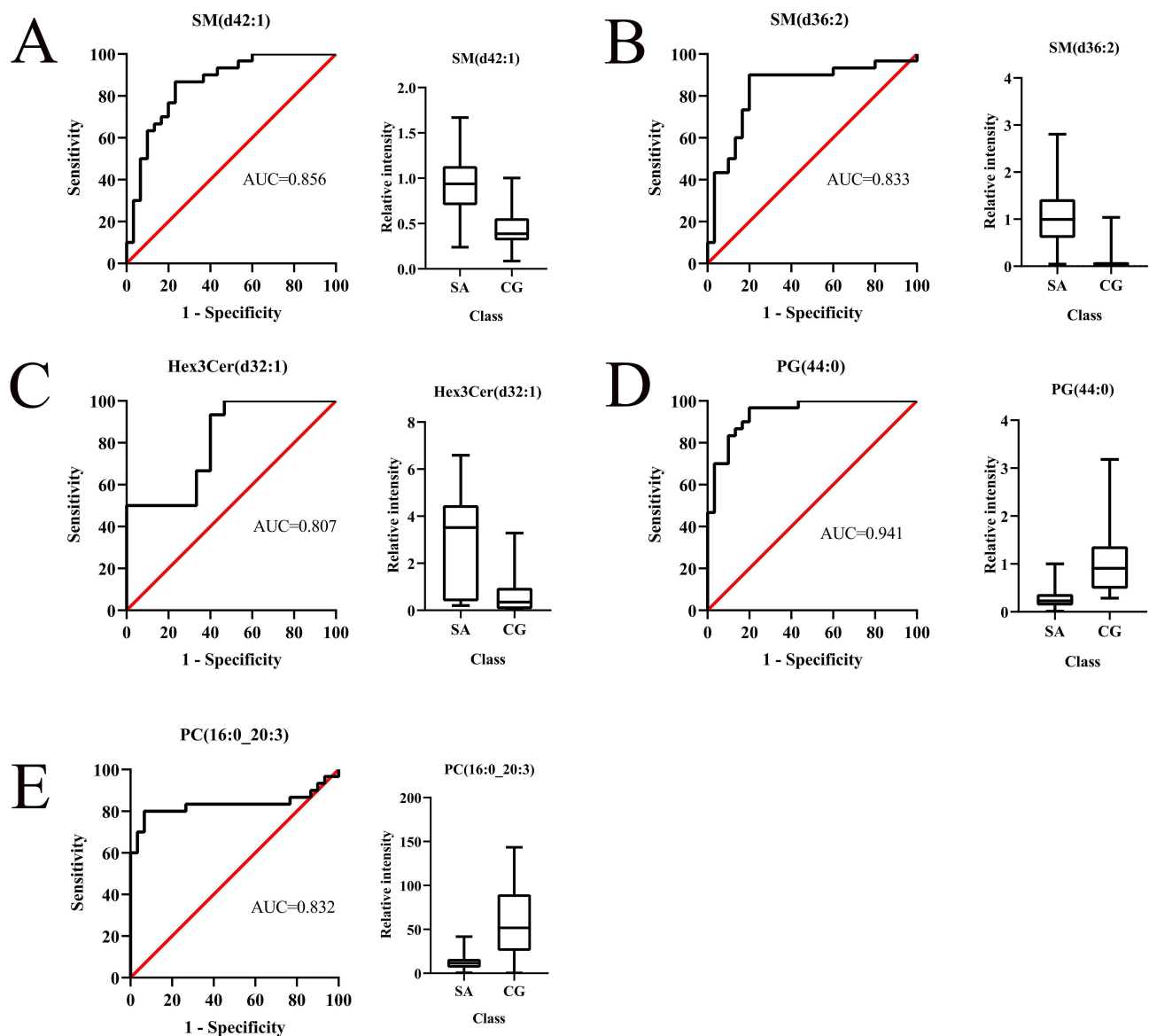


Figure 5 ROC curves and boxplots for the top 5 differential lipids of highest diagnostic value. (A): SM (d42:1); (B): SM (d36:2); (C): Hex3Cer (d32:1); (D): PG (44:0); (E): PC (16:0_20:3).

have examined the association between plasma TGs species levels and acne. In the present study, we found elevated levels of TG (16:0_16:0_18:1) and decreased levels of TG (18:1_18:2_18:3) in moderate-to-severe acne patients.

According to the ROC analysis results, five lipid species had an AUC value of more than 0.800. They were defined as the potential lipid biomarkers of moderate-to-severe acne and can be regarded as the complement of the existing protein or gene biomarkers. Among them, SM (d42:1), SM (d36:2), and Hex3Cer (d32:1) were significantly increasing in moderate-to-severe acne patients, while PG (44:0) and PC (16:0_20:3) were significantly decreasing compared with healthy controls. However, further investigation in larger sizes, even involving cell biology, is required to confirm these potential lipid biomarkers.

Conclusion

Based on plasma lipidomics, we demonstrated the difference in plasma lipid profiles between moderate-to-severe acne patients and healthy controls. 26 significantly different lipid metabolites, mainly belonging to GP, SP, and GL, were identified. However, this study had some potential limitations. The sample size was relatively small. In addition,

traditional blood lipid profiles, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and TG levels, were not measured. Overall, our research provides a novel light into the perturbed lipid metabolism leading to the development of acne.

Abbreviations

AV, Acne vulgaris; GAGS, Global Acne Grading System; TLR, Toll-like receptors; UHPLC, Ultra-high performance liquid chromatography system; PCA, Principal component analysis; OPLS-DA, Orthogonal partial least squares discriminant analysis; AUC, Area under the curve; ROC, Receiver operating characteristic; VIP, Variable influence on projection; SP, Sphingolipid; GP, Glycerophospholipids; GL, Glycerolipid; PC, Phosphatidylcholine; PE, Phosphatidylethanolamine; PG, Phosphatidylglycerol; PI, Phosphatidylinositol; LPC, Lysophosphatidylcholine; CL, Cardiolipin; SM, Sphingomyelin; Hex3Cer, Trihexosylceramide; DG, Diacylglycerol; TG, Triacylglycerol; FA, Fatty acids.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. Informed written consent was obtained from all study patients and/or from their parents if the study participant was under 18 years of age.

Consent for Publication

All patients signed the informed consent.

Acknowledgments

We thank all the patients for participating in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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