Infection and Drug Resistance

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ORIGINAL RESEARCH

Lipidomics-Based Identification of Plasma Lipid Biomarkers in Tuberculosis-Coronary Artery Disease Comorbidity

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Background: Cardiovascular disease represents the leading cause of mortality among tuberculosis (TB) patients. Both patients with tuberculosis or coronary artery disease (CAD) commonly exhibit lipid metabolism disorders. This study aims to identify specific lipids to enable early diagnosis of tuberculosis-coronary artery disease comorbidity (TB-CAD).

Methods: Blood samples were collected from hospitalized patients with TB, TB-CAD, or CAD, as well as normal healthy controls (NC), at the affiliated Changsha Central Hospital of University of South China between April 2024 and February 2025. A broad-targeted lipidomics approach based on ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) was used to identify differential lipids.

Results: The K-Means analysis showed sphingolipid, glycerolipid, and glycerophospholipid levels were decreased in patients with TB-CAD. A total of 49 differential lipids were identified to distinguish TB-CAD from the other groups. The results of receiver operating characteristic curve analysis revealed three lipids such as CE(20:0), PC(14:0_20:4) and CE(18:0) as potential biomarkers for early diagnosis of TB-CAD. The integrated diagnostic model comprising these three lipids demonstrated favorable performance, achieving AUC, sensitivity, and specificity values of 0.834, 0.900, and 0.622, respectively. KEGG analysis showed the metabolism of linoleic acid, alpha-linolenic acid, and arachidonic acid were considered pathways related to tuberculosis-coronary artery disease comorbidity.

Conclusion: This study not only identified potential biomarkers for TB-CAD diagnosis but also provided a foundation for in-depth exploration of the pathogenesis underlying tuberculosis-coronary artery disease comorbidity.

Keywords: tuberculosis-coronary artery disease comorbidity, tuberculosis, coronary artery disease, lipidomics, differential lipid

Introduction

Tuberculosis (TB) remains one of the world's major public health challenges. The World Health Organization (WHO)'s *Global Tuberculosis Report 2024* indicates that, there were about 10.8 million new TB cases globally, with an incidence rate of 134/100,000 and about 1.25 million fatal cases in 2023. Compared with 2015, the TB incidence rate and estimated number of deaths declined by 8.3% and 23%, respectively.[1] However, a substantial gap persists in achieving the targets of a 50% reduction in incidence and a 75% reduction in deaths set for 2025.[2] The development and application of novel diagnostic technologies, new drugs, advanced treatment regimens, and next-generation vaccines for TB will make TB

Received: 6 August 2025
Accepted: 8 December 2025
Published: 12 December 2025

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patients more likely to survive the infection. However, TB-associated non-communicable diseases leave these survivors with continuous disability and a higher risk of death.[3]

When tuberculosis and relevant health risk factors co-occur, these conditions can be regarded as comorbidities. These comorbidities are associated with poor tuberculosis treatment outcomes and adverse socioeconomic impacts.[4] In particular, Tuberculosis-coronary artery disease comorbidity (TB-CAD) has become a growing concern. The latest evidence from meta-analyses suggests that cardiovascular diseases are the primary contributor to all-cause mortality among patients receiving tuberculosis treatment.[5] Coronary artery disease (CAD) is the most prevalent form of cardiovascular disease,[6] and patient with latent TB infection significantly developed CAD.[7] Individuals developing TB disease face elevated mortality up to 10 years after diagnosis, Over time, major causes of death in the TB cohort shifted from TB and HIV to cardiovascular disease, cancer, and non-TB respiratory diseases.[8] With an aging global population, TB disease is becoming more common in older people, who have increased risk of multimorbidity, particularly noncommunicable diseases such as cardiovascular disease (CVD).[9] The dual disease burden of TB and CAD, coupled with their consequential economic burden, imposes severe challenges on low- and middle-income countries. *Mycobacterial* tuberculosis (Mtb) infection enhances the uptake of LDL and facilitates cholesterol accumulation via receptors expressed on macrophages.[10] As a wasting disease, tuberculosis can lead to decreased total cholesterol levels in patients due to excessive nutrient consumption. However, LDL-c is a well-established risk factor for CAD.[11] The distinct lipid profiles observed in tuberculosis and CAD highlight the necessity for more detailed lipid analysis in the diagnosis of TB-CAD comorbidity, rather than relying solely on the four standard lipid parameters (TG, TC, LDL-c, HDL-c). Identifying biomarkers for TB-CAD facilitates early diagnosis and intervention, thereby improving treatment outcomes and long-term survival.

Lipidomics, a subset of metabolomics, is a powerful approach for studying cellular lipid metabolome and identifying lipid biomarkers of diseases.[12,13] In a prospective case-control study, levels of phosphatidylcholine (PC) were generally elevated in the tuberculosis group compared to the control group.[14] Another lipidomics study demonstrated that specific plasma lipid metabolites could distinguish tuberculosis patients from other respiratory diseases and healthy controls, providing a basis for early diagnosis.[15] A prospective study on cardiovascular disease indicated that levels of CE, PC, lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE), SM, and triglyceride (TG) were associated with cardiovascular events.[16] Furthermore, several lipidomics studies on TB and CAD suggest that these two diseases may share common lipidomic metabolic abnormalities, such as alterations in lysophosphatidic acid (LPA) and CE.[15,17–23]

In this study, the potential biomarkers for TB-CAD diagnosis were identified by lipidomics analysis. This study will enhance the understanding of the biological characteristics of tuberculosis-coronary artery disease comorbidity and provide new insights for precise diagnosis of this comorbid condition.

Materials and Methods

Inclusion and Exclusion of Patients

Clinical data and blood samples were collected from TB (n = 30), CAD (n = 30), and TB-CAD comorbidity (n = 30) inpatients hospitalized at the affiliated Changsha Central Hospital of University of South China between April 8, 2024 and February 8, 2025. Normal healthy controls (n = 30) were obtained from the Health Examination Center during the same study period. In this study, the inclusion criteria for cases required an age of older than 18 years. According to previous reports, thirty patients were recruited in each group.[24]

The diagnostic and inclusion criteria of TB were as follows: (1) Positive acid-fast bacilli smear microscopy or positive *Mycobacterium tuberculosis* (MTB) culture, combined with TB-characteristic imaging findings; (2) Positive MTB nucleic acid detection, accompanied by TB-characteristic imaging findings; (3) Histopathological evidence of TB in lung tissue samples; (4) Clinically diagnosed patients of TB responding to anti-tuberculosis therapy; The diagnostic and inclusion criteria of CAD were as follows: Typical angina symptoms or imaging-confirmed asymptomatic myocardial ischemia. The definitive diagnosis of CAD requires at least one of the following: (1) Coronary computed tomography angiography (CTA) demonstrating ≥50% stenosis in any major coronary artery (left main, left anterior descending, left circumflex, or right coronary artery); (2) Invasive coronary angiography showing ≥70% stenosis in non-

left main coronary arteries or ≥50% stenosis in the left main coronary artery. The diagnostic and inclusion criteria of TB-CAD comorbidity were as follows: Patients with the diagnostic for both CAD and TB.

The patient's exclusion criteria were as follows: (1) Metabolic/Chronic Disorders, including elevated tumor markers or confirmed malignancy, diabetes, chronic kidney dysfunction and non-alcoholic fatty liver disease; (2) Immune-related diseases, including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, vasculitis syndromes and HIV infection; (3) Prolonged use of lipid-lowering medications; (4) Incomplete clinical data; (5) Refusal to provide written informed consent for trial participation.

Collection and Processing of Blood Samples

A single blood sample was collected from each enrolled patient at hospital admission using EDTA-K2 vacuum tubes. Plasma was subsequently obtained from blood by centrifugation at 3000g for 10 min at 4°C. Then, the plasma was aliquoted and stored at −80°C for future analysis.

Plasma Lipidomics Analysis

Plasma (50 μL) was mixed with 1 mL of extract solution (methyl tert-butyl ether: methanol = 3:1, containing an internal standard mixture) and vortexed for 15s. The samples were added to 200 μL of water, vortexed for 1 min, and then centrifuged at 12000 r/min (4°C) for 10 min. After the supernatant was dried, the residue was dissolved in 200 μL of the lipid resuspension solution (acetonitrile: isopropanol = 1:1). The mixture was vortexed for 3 min, centrifuged at 12000 r/min for 3 min, and the supernatant was collected for UPLC-MS/MS analysis.

Ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) analyses were performed on a UPLC system (ExionLC AD) coupled with a mass spectrometry (QTRAP®6500+). Chromatographic separation was carried out on a Thermo Accucore™ C30 column (2.1x100mm, 2.6um) at a flow rate of 0.35 mL/min. The mobile phase consisted of acetonitrile: water (60: 40, *v:v*) containing 0.1% formic acid and 10 mmol/L ammonium formate (A) and acetonitrile: isopropanol (10: 90, *v:v*) containing 0.1% formic acid and 10 mmol/L ammonium formate (B). The gradient program was as follows: 0 min, A/B (80:20, *v:v*); 2 min, A/B (70:30, *v:v*); 4 min, A/B (40:60, *v:v*); 9 min, A/B (15:85, *v:v*); 14 min, A/B (10:90, *v:v*), 15.5 min, A/B (5:95, *v:v*); 17.3 min, A/B (5:95, *v: v*); 17.5 min, A/B (80:20, *v:v*); 20 min, A/B (80:20, *v:v*). The column oven was set at 45°C. The injection volume was 2 μL.

The MS conditions of the mass spectrometer were as follows: electrospray ionization temperature, 500°C; ion spray voltage, 5500 V/-4500 V; gas 1 (GS1), 45 psi; gas 2 (GS2), 55 psi; curtain gas, 35 psi; collision-activated dissociation, medium. Each ion pair is scanned and detected based on optimized declustering potential (DP) and collision energy.

Quality Control Analysis

Quality control (QC) samples were prepared by mixing each analyzed sample. To monitor the stability during the analytical process, QC samples were injected once every 10 analytical samples.

Qualitative and Quantitative Analysis of Lipidomics Data

The lipidomics data were processed using Analyst 1.6.3 software. Based on the MWDB database (Metware, Wuhan, China), the qualitative analysis of lipids was performed by matching the retention time (RT) and parent-fragment ion pairs. The signal intensity of characteristic ions was acquired in the detector. Chromatographic peak integration and calibration were performed using MultiQuant software, with each peak area representing the relative abundance of the corresponding compound.

Data Processing and Bioinformatics Analysis

Principal component analysis (PCA) is a useful tool for omics analysis to visualize relationships between biomarkers.[25] The PCA was used to evaluate the homogeneity and reproducibility of the data quality of lipid metabolites. Orthogonal partial least squares-discriminant analysis (OPLS-DA) can effectively discriminate between classes and yield interpretable information on their differences.[26] The OPLS-DA was performed to determine the metabolic variations between groups. Variable importance in projection (VIP) values indicates the strength of influence of the corresponding lipid's

inter-group differences on the model's classification of sample groups, while *P*-values are used to denote statistical significance. The differentially expressed lipid metabolites were selected based on the criteria of VIP value > 1 and p-value < 0.05. Finally, the relative abundance of differentially expressed lipids was normalized using Unit-Variance scaling (UV), followed by K-means clustering analysis. Fourthly, the pathway analysis of these lipid metabolites was implemented using the Kyoto Encyclopedia of Genes and Genomes (KEGG).

Statistical Analysis

The Statistical analysis was performed using SPSS software (version 27). The normality of measurement data was assessed by the Shapiro–Wilk test (S-*W* test), data were considered normally distributed if p>0.05. Measurement data with approximately normal distribution were expressed as Mean ± Standard Deviation (Mean ± SD). Intergroup comparisons were performed using analysis of variance (ANOVA). When statistically significant differences (p<0.05) were observed between the four groups, Tukey's post hoc pairwise comparison test (HSD test) was conducted for pairwise comparisons between groups (p<0.05 indicated a statistically significant difference between two groups). Skewed distribution data were expressed as median with interquartile range (IQR) and analyzed by Kruskal–Wallis *H*-test. If statistical significance was identified (p<0.05), Dunn's test was subsequently applied for pairwise comparisons, where p<0.05 indicated a statistically significant difference between two groups. Categorical variables were presented as rates (%) and analyzed using Fisher's exact test. For the specific lipids detected in TB-CAD patients, receiver operating characteristic (ROC) curves were plotted for both individual and combined detection methods. Then, the area under the curve (AUC), sensitivity, specificity, Youden's index, and optimal cutoff-value were systematically calculated.

Results

Baseline Characteristics of the Study Population

The baseline clinical data of the study population were displayed in Table 1. The four groups showed no significant differences in age or gender distribution. Compared with the NC and CAD groups, the TB-CAD group showed significantly lower levels of total cholesterol (CHOL), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). Although no statistically significant difference was observed in CHOL, LDL-C and TG levels between the TB-CAD group and the TB group, a trend toward reduction was noted in the TB-CAD group. These findings indicate that tuberculosis-coronary artery disease comorbidity is associated with lipid metabolic disorders.

Results of Lipidomics Experiments

The repeatability of the analytical methods and instruments were validated by QC samples in the lipidomics analysis. As shown in Figure S1, the overlaid total ion chromatograms of the QC samples demonstrate good reproducibility in both

Table 1 Baseline Characteristics of the Study Population

Characteristics	NC	CAD	TB	TB-CAD	F/χ^2	*P* Value			
						NC vs TB-CAD	TB vs TB-CAD	CAD vs TB-CAD	All Groups
Sample size (cases)	30	30	30	30					
Age (years)	59.8±3.9	60.2±4.8	62.5±5.8	61.5±4.9	F=1.885	0.417	0.320	0.191	0.136
Gender (cases)					χ^2=2.241	0.417	0.584	0.559	0.524
Males	23(76.7%)	19(63.3%)	18(60%)	21(70.0%)					
Females	7(23.3%)	11(36.7%)	12(40%)	9(30.0%)					
CHOL (mmol/L)	5.25±1.03	4.91±0.99	4.20±0.92	3.72±1.06	F=14.142	<0.001	0.272	<0.001	<0.001
HDL-C (mmol/L)	1.39±0.30	0.88±0.30	0.99±0.29	0.90±0.39	F=16.321	<0.001	0.678	0.996	<0.001
LDL-C (mmol/L)	2.88±0.84	2.92±0.64	2.53±0.67	2.11±0.67	F=8.314	<0.001	0.100	<0.001	<0.001
TG (mmol/L)	1.55(1.17,2.11)	1.62(1.37,3.00)	1.21(0.89,1.72)	1.14(0.88,1.47)	H=21.085	0.003	0.286	<0.001	<0.001

Abbreviations: CHOL, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

peak response intensity and retention time. This result indicates that the mass spectrometer maintained a stable signal when detecting the same sample over time, confirming the excellent stability of the instrument throughout the entire analytical process.[12] The PCA scatter plot illustrates the quality control process of the experimental data. In Figure S2, the tight clustering of scatter points representing QC samples indicates the lipidomics data was stable and reliable. The OPLS-DA is a supervised model used to distinguish the metabolic variations and screen out potential biomarkers. The differential lipid metabolites in the four groups (NC, TB, CAD and TB-CAD) were analyzed by the OPLS-DA model. The OPLS-DA score plots exhibit clear separation in any two groups (Figure 1A–C). As shown in Figure 1D–F, permutation tests (200 iterations; $P<0.005$) confirmed OPLS-DA model stability (no overfitting) and robustness of identified lipid biomarkers.

The VIP score quantifies each metabolite's contribution to the group separation in the OPLS-DA model, with higher values indicating greater importance.[27] Based on the criteria of VIP > 1 and $P < 0.05$, the differentially expressed lipid metabolites were determined in the two groups. Between NC and TB-CAD groups, a total of 556 differentially expressed lipids were identified, including 46 down-regulated and 510 up-regulated lipids (Figure 2A); between TB and TB-CAD groups, a total of 176 differentially expressed lipids were identified, including 66 down-regulated and 110 up-regulated lipids (Figure 2B); and between CAD and TB-CAD groups, a total of 531 differentially expressed lipids were identified, including 24 down-regulated and 507 up-regulated lipids (Figure 2C).

K-Means Analysis of Lipidomics Data

K-means clustering is characterized by its unsupervised approach to dividing n data points into k distinct clusters, each defined by a centroid that minimizes the distances to all points in its cluster.[28] Trends in lipid relative abundance changes across experimental groups were investigated using K-means clustering analysis. The TB-CAD group showed significantly lower levels of lipid metabolites in cluster 2 (primarily sphingolipids and glycerophospholipids) than the NC and CAD groups, with a trend toward reduction compared to the TB group, whereas in cluster 5 (mainly glycerolipids), its levels were significantly lower than those in all other groups (Figure 3 and Table S1). This suggests that sphingolipids, glycerophospholipids, and glycerolipids may represent plasma lipid classes implicated in the pathogenesis of TB-CAD.

Screening and Evaluation of Lipid Biomarkers in TB-CAD

Lipidomics data also provides potential clues for the early diagnosis of tuberculosis-coronary artery disease comorbidity. The relative content of differentially lipid metabolites among the four groups were visualized using the heatmap (Figure S3). As shown in Figure 4A and Table 2, a total of 49 differentially expressed lipids were screened to distinguish TB-CAD from the other groups (NC vs TB-CAD, TB vs TB-CAD, and CAD vs TB-CAD). The diagnostic efficacy of these differential lipids was evaluated by the receiver operating characteristic (ROC) curve between the TB-CAD and the other groups, and the details of the area under the AUC, sensitivity, specificity and the Youden index were displayed in Table S2. Among 49 differentially expressed lipids, CE(20:0), PC(14:0_20:4) and CE(18:0) were selected as biomarkers on the basis of their favorable diagnostic performance for TB-CAD. CE(20:0) exhibited sensitivity, specificity, and AUC values of 0.667, 0.822, and 0.793, respectively. For PC(14:0_20:4), the corresponding values were 0.867 (sensitivity), 0.589 (specificity), and 0.792 (AUC). Similarly, CE(18:0) showed sensitivity, specificity, and AUC of 0.700, 0.811 and 0.791, respectively. Subsequently, an integrated diagnostic model was developed using logistic regression, achieving sensitivity, specificity, and AUC values of 0.900, 0.622 and 0.834, respectively (Figure 4B).The violin plots depicting the concentrations of CE(20:0), PC(14:0_20:4) and CE(18:0) among the four groups are presented in Figure 4C–E. The significantly reduced concentrations of these specific lipid metabolites (CE(20:0), PC(14:0_20:4), and CE(18:0)) in the TB-CAD group, combined with their demonstrated diagnostic performance, suggest they may serve as potential lipid biomarkers for identifying tuberculosis-coronary artery disease comorbidity.

Bioinformatics Analysis

The potential mechanisms in the pathogenesis of tuberculosis-coronary artery disease comorbidity were preliminarily explored using bioinformatics analysis. KEGG substance classification showed that lipid alterations in the TB-CAD group were primarily enriched in sphingolipid metabolism, glycerophospholipid metabolism and glycerolipid

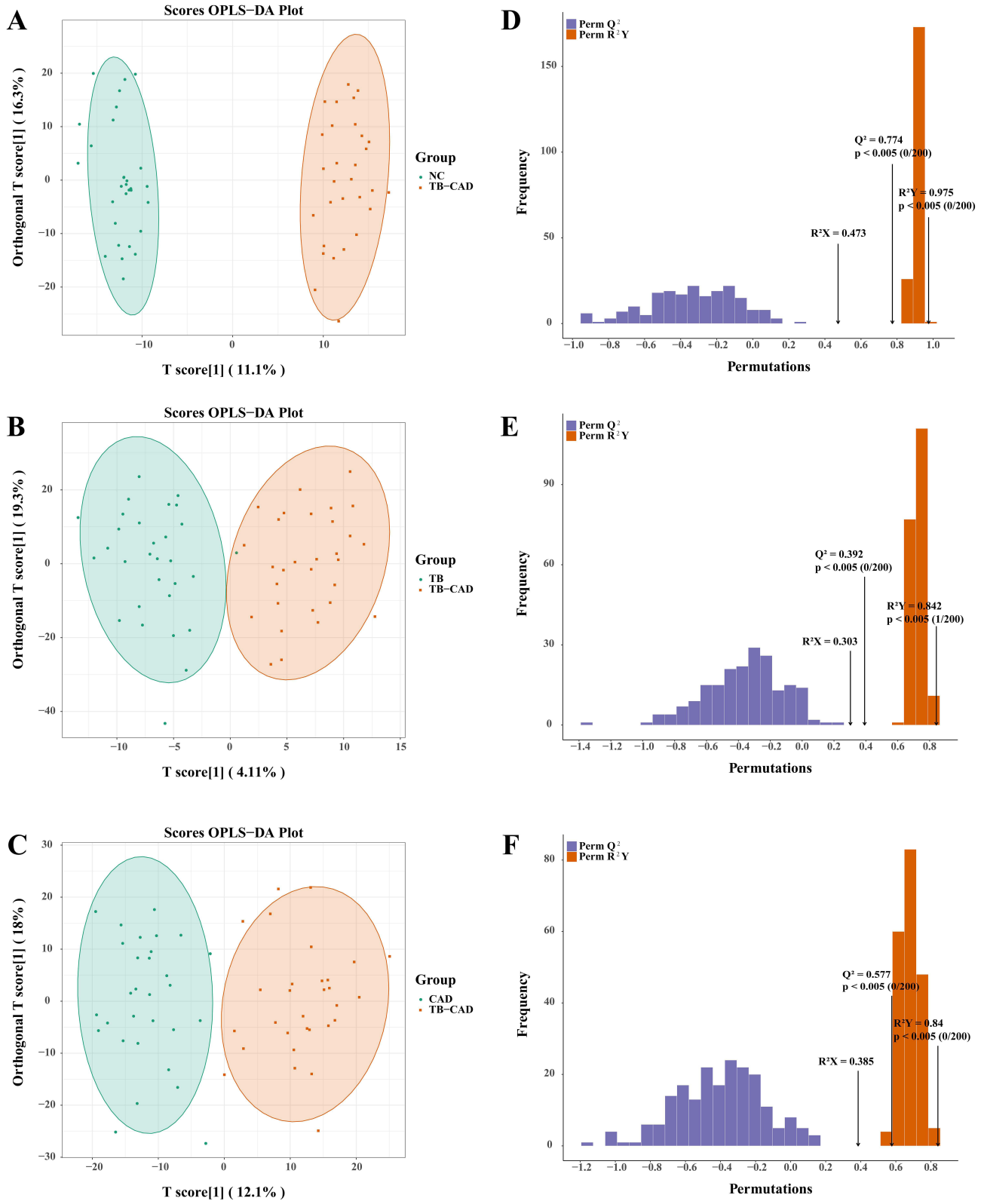

Figure 1 The OPLS-DA and permutation test plots in lipidomics analysis. (**A**) The scatter plot of NC vs TB-CAD groups, (**B**) The scatter plot of TB vs TB-CAD groups, (**C**) The scatter plot of CAD vs TB-CAD groups, (**D**) The permutation test of NC vs TB-CAD groups, (**E**) The permutation test of TB vs TB-CAD groups, (**F**) The permutation test of CAD vs TB-CAD groups.

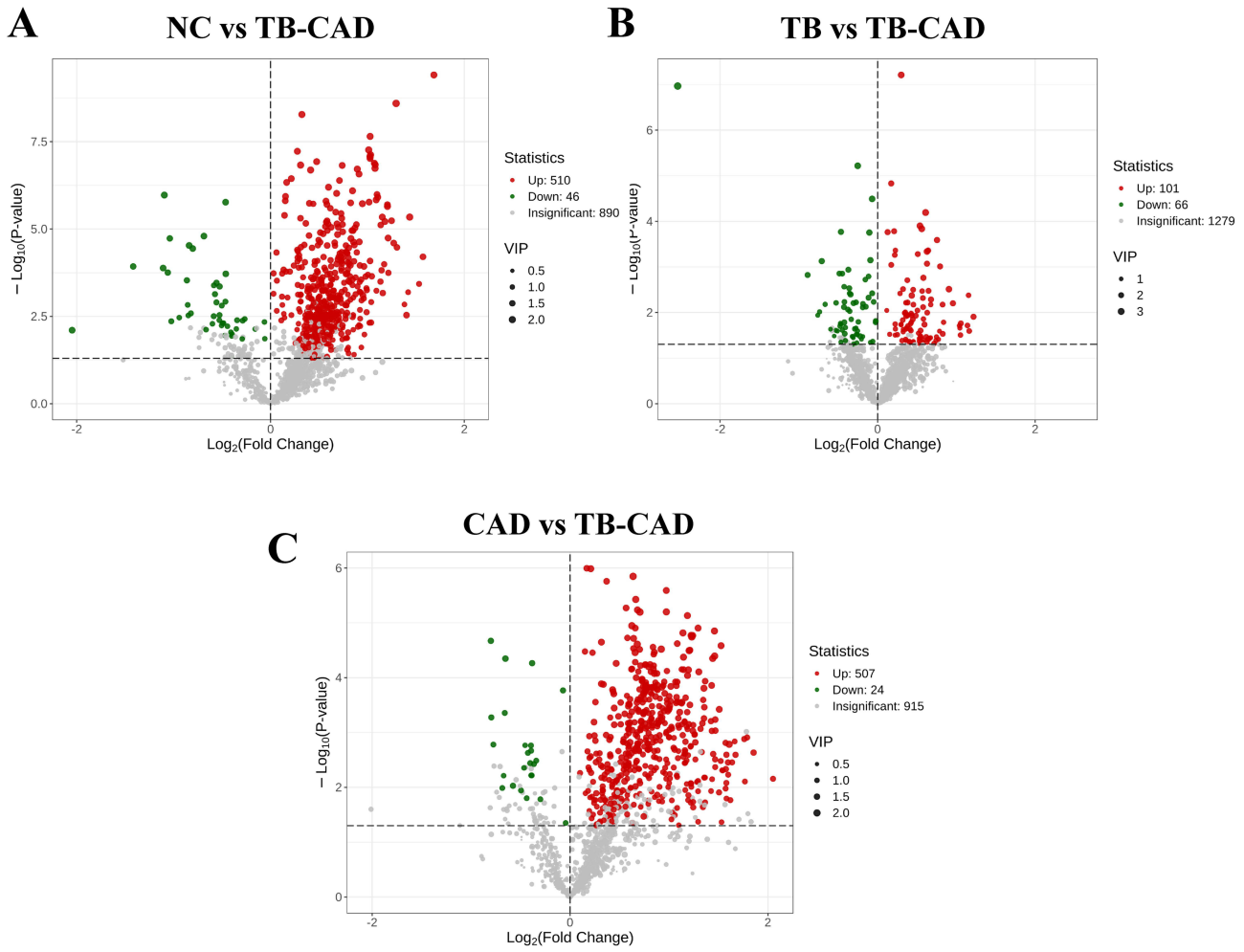

Figure 2 The volcano plot of differentially expressed lipids. (**A**) NC vs TB-CAD, (**B**) TB vs TB-CAD, (**C**) CAD vs TB-CAD.

metabolism, which is consistent with the results of k-cluster analysis (Figure 5A). KEGG pathway analysis revealed that the abnormalities of lipid metabolism in the TB-CAD group were characterized by altered linoleic acid metabolism, alpha-linolenic acid metabolism, and arachidonic acid metabolism (Figure 5B).

Discussion

Tuberculosis-cardiovascular disease comorbidity has become a focus of research. Several studies have reported a significantly elevated prevalence of CAD among TB patients.[29–32] In this study, a UPLC-MS/MS-based lipidomics approach was firstly employed to identify potential lipid biomarkers for tuberculosis-coronary artery disease comorbidity. The TB-CAD group demonstrated lower baseline levels of CHOL, LDL-C, and TG. K-means clustering analysis revealed that glycerolipids, glycerophospholipids, and sphingolipids were closely associated with the disease state or progression of TB-CAD. Among 49 differentially expressed lipids, 3 lipids such as CE(20:0), PC(14:0_20:4) and CE (18:0) were selected as potential diagnostic biomarkers for TB-CAD. These biomarkers show promise for improving the early diagnosis of TB-CAD.

Mtb infection promotes LDL uptake via receptors expressed on macrophages and facilitates intracellular cholesterol accumulation. As a wasting disease, tuberculosis leads to decreased TC levels in patients, whereas elevated TC and LDL-C are recognized risk factors for CAD.[10,11] Therefore, the decreasing trend in CHOL, LDL-C, and TG levels in the TB-CAD group may reflect metabolic disturbances associated with active tuberculosis rather than specific effects of CAD.

https://doi.org/10.2147/IDR.S558880

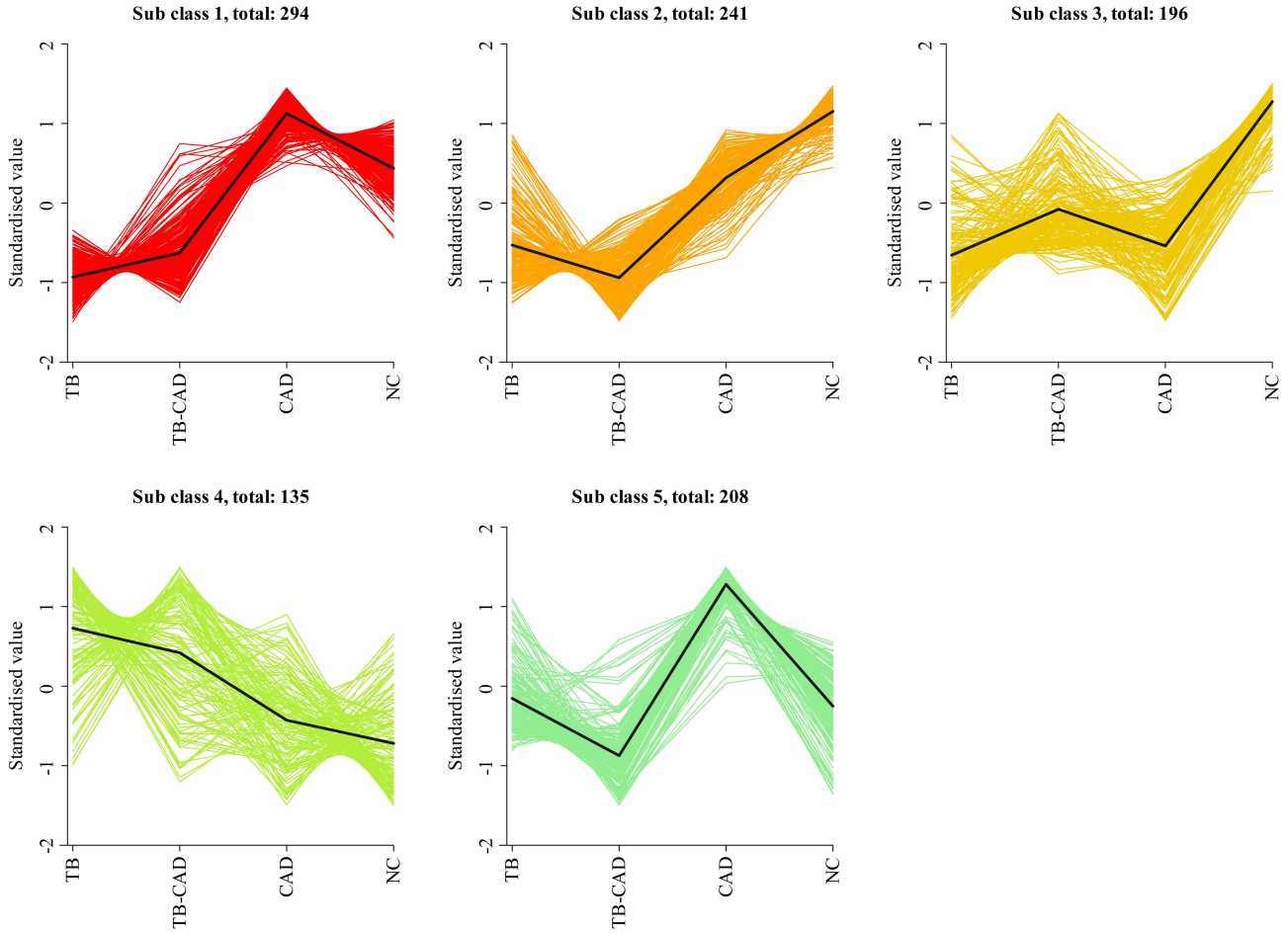

Figure 3 K-means clusters of differential lipids. The x-axis represents sample groups; the y-axis shows the normalized relative abundance of lipids; sub class denotes the number assigned to lipid subclasses exhibiting similar change trends.

Sphingolipids are bioactive components of the cell membrane that participate in and regulate diverse biological processes such as cell proliferation, survival, maturation, senescence, and apoptosis.[33] Sphingolipids play a crucial role in protecting the host from *Mycobacterium tuberculosis* (MTB) infection of macrophages.[34] Compared to the NC group, sphingolipid levels are decreased in the TB group, which may be due to MTB-produced sphingomyelinase utilizing these lipids for nutrition while modulating sphingolipid signaling pathways.[35] Previous studies indicate that sphingolipid metabolism disorders may accelerate the progression of cardiovascular disease and impair immune system function.[36–38] Therefore, tuberculosis infection can disrupt host sphingolipid metabolism, which may contribute to the development of tuberculosis-cardiovascular disease comorbidity. Glycerolipids are the major polar lipids and carbon sources of MTB. Glycerophospholipids serve not only as essential structural components of the mycobacterial plasma membrane but also as precursors for the outer envelope.[39] Compared to the TB group, the TB-CAD group demonstrated a downward trend in glycerolipids and glycerophospholipids, indicating more active MTB in TB-CAD patients. The metabolic disorders of glycerophospholipids and glycerides are closely associated with the pathogenesis of cardiovascular diseases.[40,41] This study revealed that the glycerolipid and glycerophospholipid levels were decreased in the TB-CAD group in comparison with the TB and CAD groups. We speculate that this phenomenon may be attributed to TB-induced acceleration of CAD progression or could be a consequence of the TB-CAD disease state, which requires further experimental validation.

The ROC curve showed that CE(20:0), PC(14:0_20:4) and CE(18:0) were capable of discriminating TB-CAD from other groups. Previous studies have reported CE(20:3) as a biomarker for diagnosing TB,[15] while this study identified CE (20:0) as a biomarker for TB-CAD, suggesting that the degree of unsaturation in CE may be a key factor in differentiating TB from TB-CAD. CE are the main components of intracellular lipid droplets.[42] Their accumulation

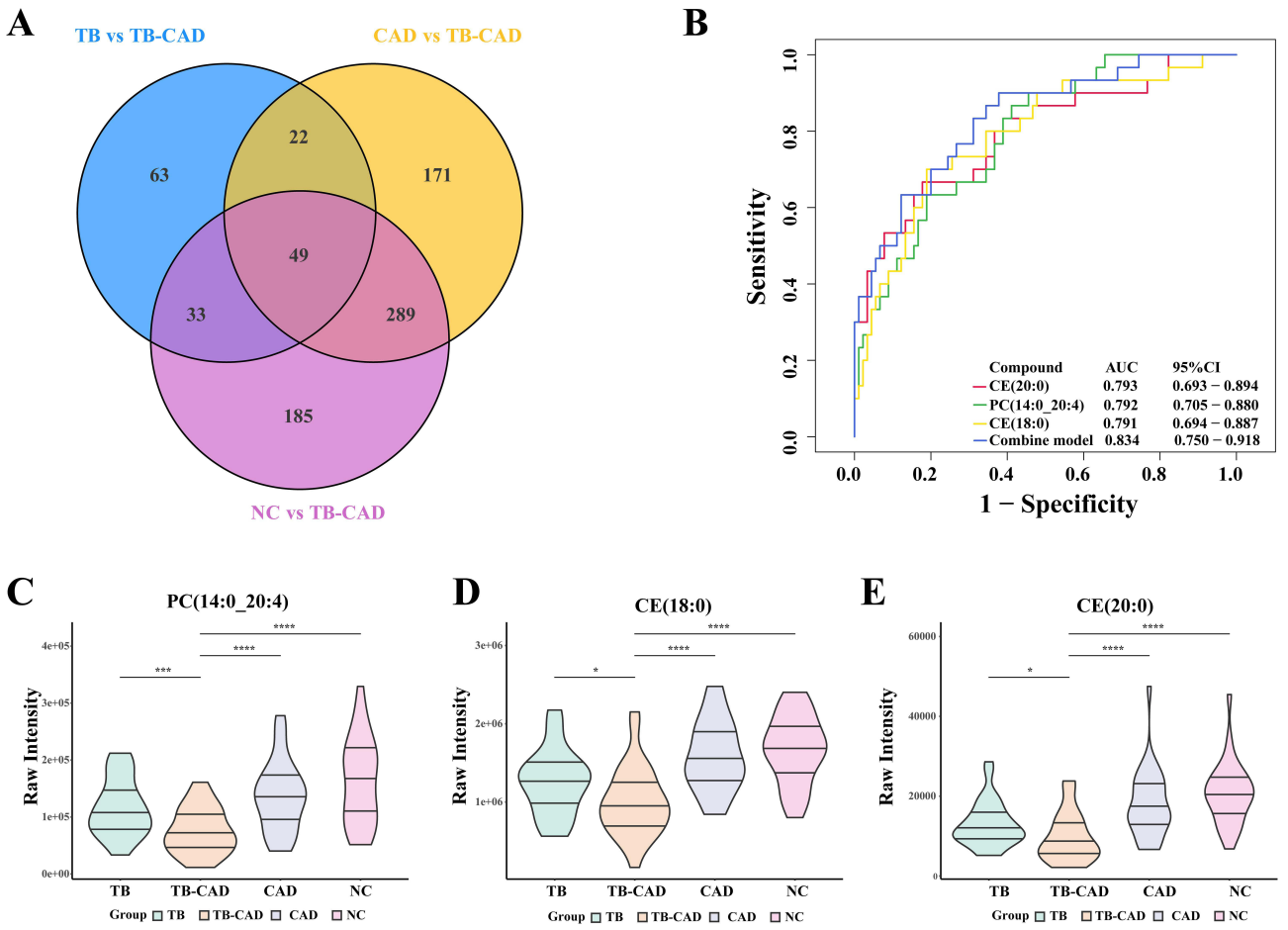

Figure 4 Screening and evaluation of potential lipid biomarkers in TB-CAD. (**A**) Venn diagram of differential lipids between TB-CAD and other groups (NC vs TB-CAD; CAD vs TB-CAD; TB vs TB-CAD), (**B**) ROC curve of the diagnostic model comparing the TB-CAD group to the other three groups, (**C**) violin plot of PC(14:0_20:4), (**D**) violin plot of CE(18:0), (**E**) violin plot of CE(20:0). *, $P < 0.05$; ***, $P < 0.001$; ****, $P < 0.0001$.

promotes the formation of foam-like macrophages, which represents a key shared cellular event in both tuberculous granulomas and CAD.[10,43,44] A review disclosed that the CE(18:0) can improve the predictive efficacy for cardiovascular disease.[45] Another study report that CE with a low carbon number and a low double-bond content has strong predictive value for cardiovascular diseases.[46] Under conditions of nutrition deprivation, MTB utilizes CEs as carbon sources to promote intracellular survival and caseous necrosis formation.[47] PC(14:0_20:4) contains arachidonic acid (C20:4), a crucial precursor for eicosanoid inflammatory mediators.[48] KEGG analysis showed that the arachidonic acid metabolism pathway may be associated with the pathogenesis of TB-CAD. These results indicate that the arachidonic acid metabolic pathway may be affected by tuberculosis infection, generating numerous pro-inflammatory mediators. Meanwhile, inflammatory activity is recognized as a core factor in the development and progression of CAD.[49] Therefore, PC(14:0_20:4) may serve as a diagnostic biomarker indicative of the inflammatory cascade in TB-CAD comorbid conditions.

This study has several limitations. First, the single-center design resulted in a relatively limited sample size. Second, as this study was primarily based on cross-sectional analysis, elucidating the pathogenesis of TB-CAD comorbidity requires further longitudinal cohort studies. Third, the model's specificity of 0.622 is suboptimal, limiting its standalone clinical utility due to a substantial risk of false positives. Therefore, it could be strategically employed as an initial screening tool to identify high-risk TB-CAD patients for subsequent confirmatory tests. This two-step approach would help reduce the overall healthcare burden. In future research, we will collaborate with multiple centers to expand the

https://doi.org/10.2147/IDR.S558880

Table 2 The Differentially Expressed Lipids Between the TB-CAD Group and the Other Groups

NO	Lipids	NC vs TB-CAD			CAD vs TB-CAD			TB vs TB-CAD		
		VIP	FC	Trend	VIP	FC	Trend	VIP	FC	Trend
1	CE(18:0)	1.79	1.67	Up	1.98	1.58	Up	1.53	1.25	Up
2	CE(17:1)	1.01	1.25	Up	1.36	1.27	Up	1.74	1.25	Up
3	Carnitine C20:4	1.27	1.35	Up	1.01	1.34	Up	2.01	1.57	Up
4	CE(20:3)	1.15	1.31	Up	1.50	1.43	Up	2.70	1.54	Up
5	CE(14:0)	1.16	1.44	Up	1.35	1.45	Up	1.99	1.35	Up
6	CE(18:3)	1.32	1.43	Up	1.02	1.24	Up	2.00	1.40	Up
7	DG(18:0_18:1)	1.02	1.64	Up	1.52	2.77	Up	1.69	1.45	Up
8	Cer(t20:1/38:2(2OH))	1.26	1.58	Up	1.66	2.22	Up	1.71	1.34	Up
9	CE(20:5)	1.52	1.77	Up	1.91	1.90	Up	1.27	1.37	Up
10	LPC(0:0/18:0)	1.14	1.32	Up	1.04	1.20	Up	1.73	1.28	Up
11	Cer(d18:1/28:2)	1.55	1.46	Up	1.34	1.24	Up	2.11	1.73	Up
12	LPC(16:0/0:0)	1.18	1.24	Up	1.14	1.18	Up	1.92	1.25	Up
13	TG(18:0_16:1_20:1)	1.05	1.47	Up	1.34	1.84	Up	1.54	1.29	Up
14	LPC(14:0/0:0)	1.12	1.34	Up	1.07	1.36	Up	2.29	1.50	Up
15	SM(d18:2/14:0)	1.48	1.39	Up	1.48	1.33	Up	2.02	1.30	Up
16	TG(14:0_18:0_18:2)	1.00	1.60	Up	1.35	1.88	Up	1.69	1.46	Up
17	Cer(d16:1/21:0)	1.35	1.47	Up	1.16	1.35	Up	1.95	1.46	Up
18	CE(17:2)	1.40	1.47	Up	1.28	1.30	Up	1.60	1.24	Up
19	CE(20:0)	1.97	2.11	Up	1.77	1.84	Up	1.73	1.32	Up
20	DG(14:0_18:1)	1.02	1.88	Up	1.40	3.39	Up	1.98	1.77	Up
21	TG(17:1_17:1_24:6)	1.41	1.95	Up	1.64	2.36	Up	1.48	1.44	Up
22	DG(18:1_20:3)	1.58	1.98	Up	1.70	2.70	Up	1.83	1.56	Up
23	PC(16:0_22:5)	1.49	1.45	Up	1.84	1.56	Up	1.47	1.25	Up
24	PI(18:0_19:0)	1.09	1.28	Up	2.11	1.56	Up	1.99	1.42	Up
25	PE(20:0_18:0)	1.19	1.34	Up	1.25	1.26	Up	1.85	1.37	Up
26	PG(16:1_20:3)	1.38	1.37	Up	1.56	1.58	Up	3.00	1.53	Up
27	Chenodeoxycholic acid	1.45	1.36	Up	1.24	1.23	Up	1.52	1.17	Up
28	PC(16:0_20:2)	1.51	1.37	Up	1.60	1.54	Up	2.82	1.45	Up
29	PC(18:0_20:3)	1.25	1.34	Up	1.42	1.25	Up	1.21	1.23	Up
30	PC(17:0_20:3)	1.47	1.36	Up	1.71	1.63	Up	2.87	1.47	Up
31	PC(14:0_20:4)	1.81	2.15	Up	1.54	1.80	Up	2.19	1.54	Up
32	PG(9:0_22:4)	1.54	1.51	Up	1.16	1.26	Up	1.80	1.29	Up
33	PC(14:0_22:6)	1.77	2.02	Up	1.64	2.12	Up	1.90	1.55	Up
34	PC(18:0_22:4)	1.01	1.32	Up	1.30	1.49	Up	2.17	1.56	Up
35	PC(16:1_20:3)	1.07	1.38	Up	1.10	1.58	Up	2.21	1.60	Up
36	PC(20:3_20:4)	1.55	1.72	Up	1.45	1.80	Up	2.34	1.69	Up
37	PE(14:0_22:4)	1.63	2.20	Up	1.31	1.77	Up	1.94	1.49	Up
38	PI(18:0_20:0)	1.00	1.29	Up	1.59	1.47	Up	1.69	1.48	Up
39	Cer(d18:1/19:1(2OH)	1.05	0.78	Down	1.05	0.76	Down	1.69	0.78	Down
40	Cer(t17:1/22:2)	1.56	0.49	Down	1.39	0.67	Down	1.44	0.75	Down
41	DG(16:0_18:0)	1.41	1.09	Up	1.64	1.12	Up	1.59	0.96	Down
42	Carnitine C6-2OH	1.52	1.22	Up	1.65	1.29	Up	1.90	0.88	Down
43	DG(16:0_16:0)	1.57	1.10	Up	1.86	1.16	Up	2.06	0.92	Down
44	TG(16:1_18:1_18:2)	1.04	1.37	Up	1.59	1.56	Up	1.13	0.81	Down
45	Cer(t14:1/21:0)	1.72	1.72	Up	1.65	1.60	Up	1.29	0.72	Down
46	Cer(t26:1/12:1(2OH))	1.46	1.53	Up	1.43	1.38	Up	1.26	0.70	Down
47	HexCer(t18:1/20:0(2OH))	1.61	1.62	Up	1.43	1.51	Up	1.73	0.72	Down
48	DG(16:2_18:2)	1.73	2.14	Up	1.58	1.79	Up	1.12	0.66	Down
49	PE(13:0_19:2)	1.33	1.05	Up	1.33	0.95	Down	2.71	0.95	Down

Notes: "Up" denotes a higher lipid level in the control groups (NC, CAD, or TB) relative to the TB-CAD group. "Down" signifies a lower lipid level in the control groups relative to the TB-CAD group.

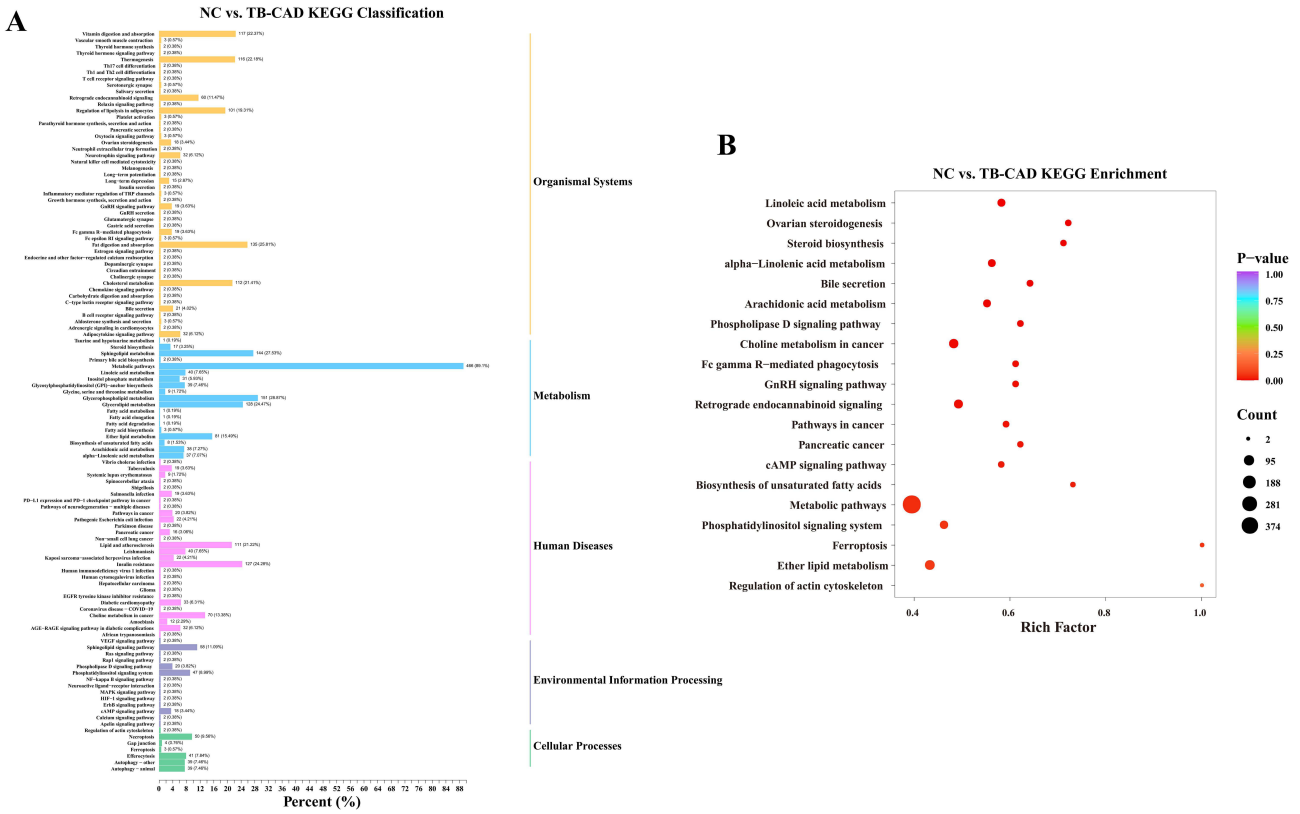

Figure 5 KEGG pathway classification and enrichment analysis of the differential lipids between the NC and TB-CAD groups. (**A**) KEGG substance classification, (**B**) bubble chart of KEGG pathways.

sample size and integrate key clinical parameters with the biomarkers to enhance the performance of the diagnostic model.

Conclusion

Patients with TB-CAD comorbidity demonstrate a series of characteristic alterations in lipid metabolism, primarily characterized by decreased levels of sphingolipids (only a trend toward reduction compared to TB), glycerolipids, and glycerophospholipids relative to other groups. The CE(20:0), PC(14:0_20:4) and CE(18:0) were screened as biomarkers to distinguish TB-CAD from TB, CAD, and NC. The combined diagnostic model demonstrated superior performance. This study identifies potential lipid biomarkers for the early diagnosis of TB-CAD comorbidity and provides lipidomic evidence to support further longitudinal studies into the underlying disease mechanisms.

Data Sharing Statement

The datasets analyzed for the current study are not publicly available due to the requirement of obtaining official permission to access the data but are available from the corresponding author (Yiping Leng, lyp0626@aliyun.com) upon reasonable request.

Ethical Statement

This ethical approval was granted by the Medical Ethics Sub-committee of Changsha Central Hospital (Ethics Approval Number: 2023-037-01) and were performed according to the Declaration of Helsinki's ethical principles.

https://doi.org/10.2147/IDR.S558880

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.

Funding

This work was supported in part by the National Science Foundation of China (NSFC) Projects 82170475 (LYP), Hunan Provincial Natural Science Foundation of China 2023JJ30065 (DP), The Science and Technology Innovation Program of Hunan Province 2021SK53408 (LYP), Scientific Research Project of Hunan Provincial Health Commission B202303016916 (LYP) and D202303086260 (SL), Hunan Province Degree and Graduate Education Reform Research Project 2022JGYB171 (DP), National Key Clinical Specialty Scientific Research Project (Z2023045) (PY), The Science and Technology Innovation Program of Hunan Province (2023SK4071) (PY), Changsha Natural Science Foundation (kq2208438) (PY) and (kq2502332) (YP), Scientific Research Project of Education Department of Hunan Province (23B0438) (YP).

Disclosure

The authors report no financial and non-financial benefits have been received or will be received from any party directly or indirectly related to the subject of this article.

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