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Research Article

Lipidomics Profile Changes of Type 2 Diabetes Mellitus with Acute Myocardial Infarction

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The morbidity and mortality of cardiovascular disease (CVD)/acute myocardial infarction (AMI) of type 2 diabetes mellitus (T2DM) patients are extremely higher than those without T2DM. Biomarkers can be used to predict the occurrence of acute myocardial infarction, thus effectively reducing the incidence of CVD events, particularly in T2DM patients. Lipids have been shown to be biomarkers and potential therapeutic targets for human diseases. The aim of our study was to investigate the prognostic value of lipid biomarkers for predicting AMI in T2DM patients. A total of 420 subjects were recruited in this research. Liquid Chromatography-Electrospray Ionization-Quadrupole Time of Flight-Mass Spectrometer- (LC-ESI-QTOF-MS-) and Liquid Chromatography/Mass Spectrometer- (LC/MS-) based metabolomic methods were applied to characterize metabolic profiles in each plasma sample. In the first untargeted set, 40 T2DM patients with AMI, 40 T2DM patients without AMI, and 40 control subjects were gender- and age-matched. Eight lipid metabolites showed a significant difference among three groups. Then, in the second set, targeted metabolic profiling assays for these 8 lipid biomarker concentrations in plasma were performed; another 100 T2DM patients with AMI, 100 T2DM patients without AMI, and 100 control subjects were selected independently. Receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curves (AUC) was calculated to determine the potential biomarkers. ROC curve analysis showed that the AUC value of lysophosphatidylcholine (LysoPC) 18:0 is more than 0.7, indicating that LysoPC 18:0 may be a potential sensitive and specific biomarker for T2DM with AMI. The changed plasma concentrations of lipids were significantly associated with T2DM with AMI, which showed great value to be biomarkers, though it requires a prospective cohort study for further validation.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide [1], and acute myocardial infarction (AMI) is a fatal cardiovascular event, at least seven million patients died because of AMI in 2012 [2]. Meanwhile, type 2 diabetes mellitus (T2DM) is a growing health burden of the whole world [3]. It is reported that CVD has a clear relationship with T2DM; it is a major complication of diabetes [4]. T2DM patients have been shown to have a five higher incidence of AMI compared with people without T2DM [5–7]. Estimating and validating the biomarkers of AMI in those T2DM patients are major concerns.

Metabolomics is defined as the use of high-throughput techniques to detect small molecule metabolites; the metabolic profiling represents the phenotype of the cellular response to pathophysiological stimuli or genetic modification [8]. Lipid profiles play important roles in regulating cellular functions and are involved in human physical and pathological conditions, T2DM for example [9]. The metabolomic approach has indeed been used to find novel biomarkers and pathophysiologic pathways in coronary artery disease (CAD) successfully [10]. Lipidomics, the large-scale study of pathways and networks of cellular lipids in biological systems, is an emerging field of basic and translational research [11, 12].

Lipid metabolism is known to be dysregulated in T2DM, and traditional lipid markers, such as total cholesterol (TC), high-density lipoprotein cholesterol (HDL), triglycerides (TG), and low-density lipoprotein cholesterol (LDL), are used to assess the risk of future cardiovascular events [13, 14]. However, these biomarkers alone do not reflect the

complex alteration of lipid metabolism in T2DM and distinct lipid species in CVD/AMI.

The aim of this study is to investigate the lipid profiling changes in T2DM patients with AMI and identify the prognostic value of lipid biomarkers in predicting AMI in T2DM patients.

2. Subjects and Methods

2.1. Study Population. This study was designed as a three population-based case-control study. All the subjects were recruited from Beijing Chaoyang Hospital, whose clinical information was collected in March 2015-April 2017. AMI diagnosis is based on the assessment of symptoms and analysis of the surface electrocardiogram and serum biomarkers [15]. Diabetes was defined if the participants reported having been diagnosed with T2DM by a physician and also reported meeting at least one of the following criteria: (1) fasting glucose ≥ 7.0 mmol/L, (2) oral glucose tolerance test ≥ 11.1 mmol/L, and (3) use of antidiabetic medication.

AMI patients with a definite diagnosis of T2DM for less than 10 years were recruited in the group of T2DM with AMI; patients with a definite diagnosis of T2DM for more than 10 years without any cardiovascular (CV) events were recruited in the group of T2DM; and the control group is from the outpatients' clinic. Patients were excluded if they had any of the following: smoking or drinking addiction history within five years, liver or kidney dysfunction, psychiatric disorder, substance abuse disorder, recent acute surgery operation, a central neurological condition, pregnant female, or any other conditions which were concerned that could interfere with the final result altering the lipid pattern. Informed consent was obtained from each participant. This study was reviewed and approved by the Research Ethics Committees in Beijing Chaoyang Hospital.

2.2. Clinical Data. Clinical data were obtained from the participants and hospital database system. Anthropometric measurements were taken by trained personnel. A detailed medical history was collected, including history of CV events and T2DM, family history, smoking and alcohol drinking habits, major surgical procedures, antibiotic prescriptions, and allergy. The fasting levels of plasma glucose, TC, TG, HDL, and LDL were measured in the clinical laboratory. Information of age, sex, height, and body weight was collected from the database in our hospital.

2.3. Sample Collection. All plasma samples were transferred to -80°C within one day. Blood samples of T2DM with AMI patients were collected following onset of AMI and before any treatment for AMI. Blood samples of T2DM patients and health subjects were obtained from overnight fasting individuals in the morning. All the blood samples were obtained by peripheral venous puncture and collected into tube coated with anticoagulant (EDTA). The stability of blood lipids during sample processing is a major issue. EDTA-coated tubes can not only prevent the platelets from activation and blood from clotting but also inhibit enzymatic activities involved in lipid metabolism [16]. The collected blood samples were centrifuged at 1,750 g for 15 minutes at room temperature. Then, the supernatants were immediately aliquoted into siliconized Eppendorf tubes and stored at -80°C until use.

Plasma quality control (QC) samples were employed to provide a representative "mean" sample containing all plasma samples. The QC-T2DM with AMI sample was prepared by mixing equal volumes of the plasma samples from each T2DM with AMI sample and the same to QC-T2DM sample and QC-health control sample. Meanwhile, a blank sample was set to identify the sample carryover.

2.4. Chemicals and Materials. Ultrahigh purity water was prepared by Millipore-Q Water Purification System. High-Performance Liquid Chromatography (HPLC) grade formic acid was ordered from Sigma-Aldrich. LC/MS-grade methanol, chloroform, isopropanol, nitrile, and acetonitrile were bought from Fisher Scientific. The standards, palmitic acid, stearic acid, arachidonic acid, phosphatidylcholine PC(18:2/18:0), PC(20:4/18:2), PC(18:2/18:2), sphingomyelin SM(d18:0/18:1), and LysoPC(18:0/0:0) were purchased from Avanti Polar Lipids Inc. The chromatographic columns (CSH T3 C18, 100×2.1 mm, 1.7 μm; HSS T3 C18, 100×2.1 mm, 1.7 μm) were purchased from Waters.

2.5. Analytical Design

2.5.1. LC-ESI-QTOF-MS Analysis. In the first/untargeted set, plasma samples were extracted by chloroform/methanol (3 : 1), followed by isopropanol/acetonitrile (1 : 1). LC-ESI-QTOF-MS (ACQUITY UPLC/Xevo G2 Q TOF, Waters) was applied. The chromatographic column was CSH T3 C18 and the mobile phase was 0.1% formic acid, 10 mM ammonium formate in "40% acetonitrile : 60% water" (A), and 0.1% formic acid, 10 mM ammonium formate in "90% acetonitrile : 10% isopropanol" (B). Positive and negative ion acquisition modes at a capillary voltage of 3.2 kV and a sampling cone voltage of 35 V were implemented. The scan range is 50-1200 M/Z. Desolvation temperature and desolvation gas flow were 400°C and 800 L/H, respectively. And the cone gas flow and source temperature were 30 L/H and 120°C, respectively. The original data was preprocessed by Progenesis QI.

2.5.2. LC/MS Analysis. In the second/targeted set, plasma samples were extracted by methanol, 10 μl standard was added into 90 μl plasma sample, and then LC/MS- (Ultimate 3000, Thermo Scientific; Q Exactive, Thermo Scientific) based metabolomic method was applied. The chromatographic column was HSS T3 C18 and the mobile phase was 0.1% formic acid, 2 mmol/L ammonium formate in water (A) and methanol (B). Negative polarity was implemented. The scan range is 100-1500 M/Z. Spray voltage and capillary temperature were -3.5 kV and 320°C, respectively.

2.6. Data Analysis. All subject characteristic data were presented as mean ± SD, and statistical analyses were performed in SPSS Statistics 21.0. Differences among 3 groups were presented according to Analysis of Variance (ANOVA). P value < 0.05 was defined as statistically significant.

For the first/untargeted set, peak intensity data were log-transformed and normalized on MetaboAnalyst; multivariate analyses, including partial least-squares discriminant analysis (PLS-DA) and ANOVA, were constructed to determine the distributions and find the metabolic difference among groups. The variable importance in the projection (VIP) was used to rank the contribution of each variable based on the PLS-DA model, and those variables with VIP > 1.0 are considered relevant for group discrimination. The preliminary identification of these differential features was conducted by searching metabolite databases, such as Human Metabolome Database, mzCloud, METLIN, and LIPID MAPS.

For the second/targeted set, metabolite concentrations were analyzed in SPSS Statistics 21.0. The diagnostic potential of the candidates was assessed using the ROC curve. The functions and related metabolic pathways of these metabolites were identified according to MetaboAnalyst and KEGG.

3. Results

3.1. Baseline Characteristics. The characteristics of two sets are shown in Table S1. *P* values below 0.05 were considered statistically significant. In the first set, patients in the T2DM with AMI group had higher body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), and HDL compared with those in the T2DM group. In the second set, patients in the T2DM with AMI group had higher BMI, SBP, DBP, HDL, TC, and LDL.

3.2. Screening and Defining of Lipidomics Profile Changes. In the first set, a total of 120 samples (40 T2DM with AMI patients, 40 T2DM patients, and 40 healthy subjects) were collected. Lipidomics profiling of plasma sample was acquired using LC-QTOF-MS in ESI+ and ESI− modes. Comparisons of the intensities of preprocessed ion peaks among three groups were performed on MetaboAnalyst. As shown in Figure 1(a), PLS-DA showed a clear inter-group separation in plasma metabolites from T2DM with AMI patients, T2DM patients, and health control group, indicating a significant alteration in plasma metabolic profiles. Differential metabolites contributing to the altered metabolic profiles were identified. A total of 8 lipid metabolites, palmitic acid (HMDB00220, C16H32O2), stearic acid (HMDB00827, C18H36O2), arachidonic acid (HMDB01043, C20H32O2), PC(18:2/18:0) (HMDB08135, C44H84NO8P), PC(20:4/18:2) (HMDB08467, C46H80NO8P), PC(18:2/18:2) (HMDB08138, C44H80NO8P), SM(d18:0/18:1) (HMDB12089, C41H83N2O6P), and LysoPC(18:0/0:0) (HMDB10384, C26H54NO7P), were selected as potential markers according to ANOVA (Figure 1(b)) and VIP scores (Figure 1(c)).

3.3. Validation and Evaluation of Potential Biomarkers. In the second set, LC/MS-based metabolomic method was applied. A total of 300 samples (100 T2DM with AMI patients, 100 T2DM patients, and 100 healthy subjects) were collected. Sample preparation method was completely unified; external/interior standard methods were established for quantitative analyses of all lipids. We quantitatively examined the levels of 8 lipid metabolites in plasma samples, including palmitic acid, stearic acid, arachidonic acid, PC(18:2/18:0), PC(20:4/18:2), PC(18:2/18:2), SM(d18:0/18:1), and LysoPC(18:0/0:0). The ability of biomarker to discriminate among groups was evaluated using receiver operator characteristic (ROC) curve analysis; the performance of each biomarker was presented as the area under the curve (AUC). At last, only one lipid metabolite, LysoPC(18:0/0:0), revealed satisfactory diagnostic values with AUC over 0.7 (Figure 2(a)). Box plots were provided in Figure 2(b), showing a decreasing trend in patients.

3.4. Metabolic Pathway Analysis. According to MetaboAnalyst, several metabolic pathways were altered in T2DM with AMI patients. The identified compounds were distributed in 8 pathways; the main metabolic pathways included glycerophospholipid metabolism, fatty acid biosynthesis, arachidonic acid metabolism, and linoleic acid metabolism, shown in Table S2 and Figure 3. The compound we validated and evaluated, LysoPC(18 : 0/0 : 0), was distributed in the pathway of glycerophospholipid metabolism.

4. Discussion

In the present study, we applied UHPLC-Q-orbitrap MS- and LC/MS/MS-based metabolomic approach to understand the lipid metabolic differences among T2DM patients with/-without AMI and healthy subjects in Chinese adults, in order to identify potential novel plasma biomarkers for T2DM with AMI.

There were two sets in our study, the untargeted set and the targeted set. In the first set, a total of 120 plasma samples were recruited; we applied a comprehensive workflow to identify novel biomarkers; 8 lipid metabolites showed a significant difference among three groups. To further validate these 8 lipid metabolites, another independent set was conducted; a total of 300 plasma samples were recruited. LysoPC(18:0/0:0) showed a clear decreasing trend in the T2DM with AMI group compared with the T2DM group and the control group.

LysoPC was involved in several possible pathways: (1) LCAT and oxidation of LDL production, (2) hepatocyte secretion, and (3) platelet activation and deletion of the LDL receptor [17]. Changed LysoPC concentrations have been found in cancers [18–24], inflammatory disorders [25], mitochondrial disease [26], Alzheimer's disease [27], diabetes [28–31], and acute coronary syndrome [17]. Nowadays, many researches showed that LysoPC18:0 concentration was associated with cancer risk [20–23, 32] and mitochondrial disease [26]; meanwhile, studies on the association between LysoPC18:0 and diabetes [29–31] or CVD/AMI/acute coronary syndrome [17] are still insufficient. In our study, LysoPC18:0 is significantly lower in the T2DM with AMI group. Consistent with the results from Kurano et al.'s research [17], almost all LysoPC species, LysoPC18:0 included, were significantly lower in samples obtained from

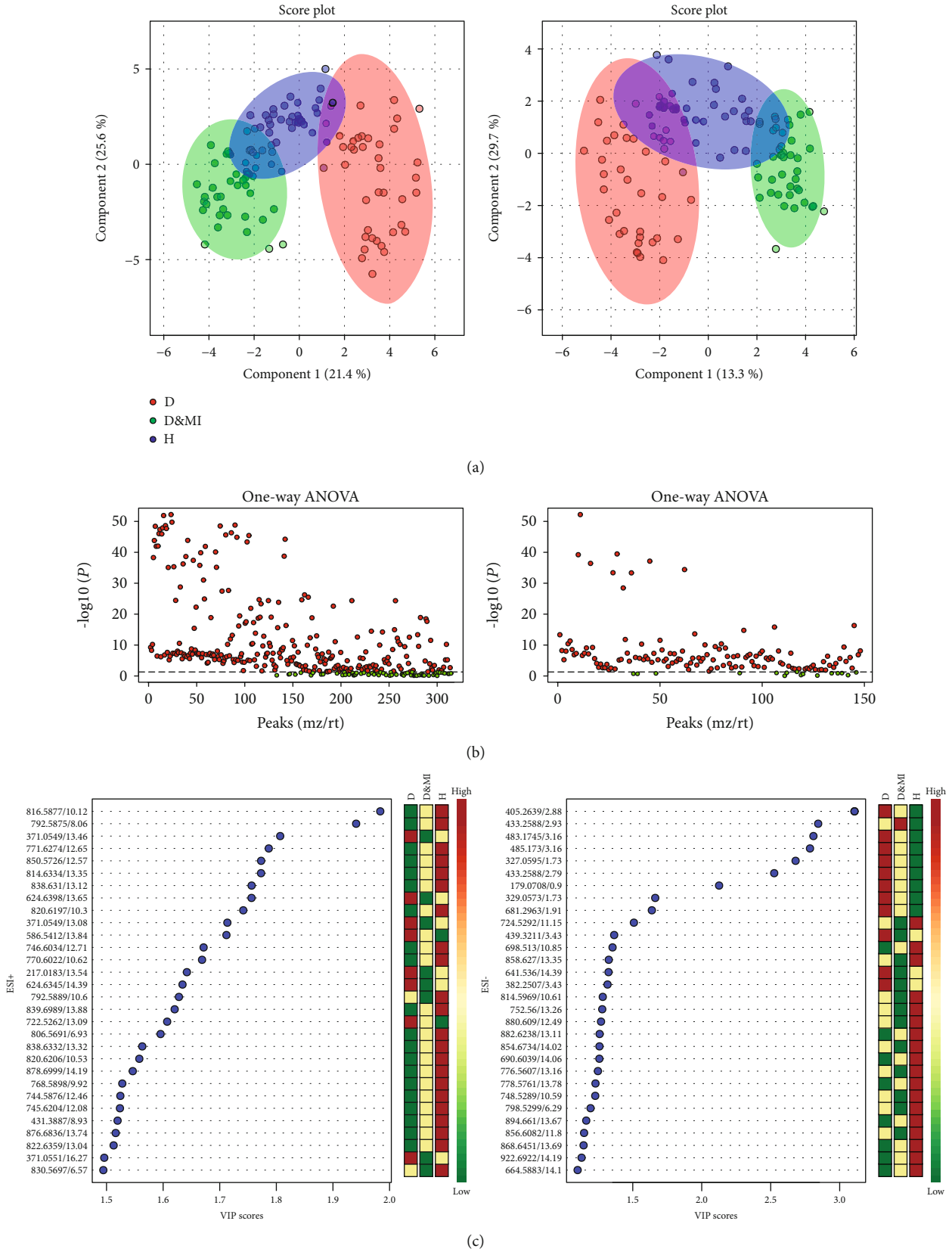
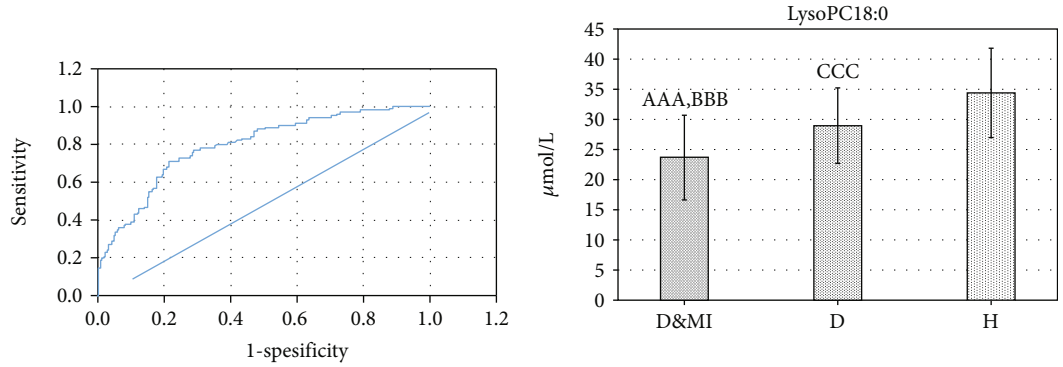


Figure 1: Statistical analysis for the data obtained from the first set. (a) PLS-DA of plasma samples of patients collected in positive ion mode (ESI+) and negative ion mode (ESI-). D: T2DM group; D&MI: T2DM with AMI group; H: health control group. (b) One-way ANOVA. (c) VIP scores in positive ion mode (ESI+) and negative ion mode (ESI-).



(a) (b)

Figure 2: (a) ROC curve of LysoPC 18:0. (b) Bar chart showed significant difference among three groups; there was a clear decreasing trend in T2DM with AMI trend compared with T2DM group and control group. The superscript letter (A, B, and C) indicates significant difference between groups at $P < 0.05$, respectively, according to ANOVA. a: T2DM with AMI in comparison with T2DM; b: T2DM with AMI in comparison with health control group; c: T2DM in comparison with health control group. If $P < 0.01$, the letter doubled. If $P < 0.001$, the letter tripled.

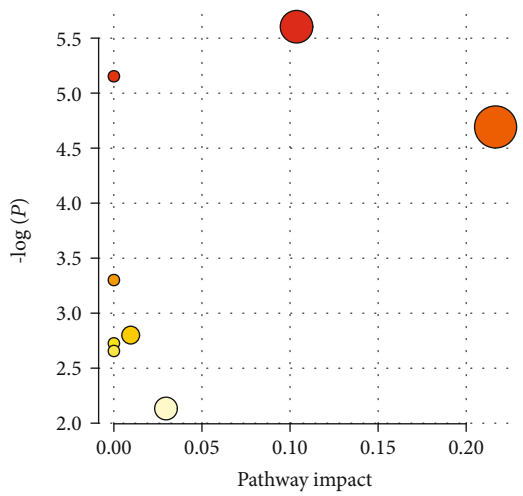


Figure 3: The metabolic pathway analysis conducted by MetaboAnalyst analysis. The node color is based on P value, and the node radius is determined by pathway impact value. Glycerophospholipid metabolism pathway showed the greatest value.

culprit coronary arteries of patients who underwent an emergency PCI and thrombectomy.

In this study, the samples of the T2DM with AMI group were collected immediately after the occurrence of AMI, before any AMI treatments, as the injection of heparin may increase the concentrations of LysoPA, LysoPG, and LysoPI among lysophospholipids [17]. And it avoided the dilution of lipids over time. The major limitation of this study is that, as this is an observational study, we cannot demonstrate how LysoPC18:0 is generated or how LysoPC18:0 is involved in the pathogenesis of T2DM with AMI. Another limitation of this study is that several other factors thought to be involved in regulating the production of LysoPC18:0 were not investigated in the present study. A recent study showed that LPC could bind to peroxisome proliferator-activated receptors gamma (PPARγ), which is a primary target of the effective drug to treat type II diabetes, and LPC18:0 could be the potential partial agonists [33]. The interaction between PPARγ and LPC18:0 was also reported in Qin et al.'s study [34]. Further study is needed to elucidate the role of LysoPC18:0 in the pathogenesis of T2DM with AMI.

In conclusion, using untargeted and targeted metabolomic approaches, we identified 8 plasma lipid metabolites reflecting multiple metabolic abnormalities, and we can show a robust correlation between LysoPC18:0 and the malignant development of T2DM. LysoPC18:0 could potentially serve as a marker to predict CVD/AMI occurrence in T2DM patients. The present study provides a basis for risk prediction and therapeutic development for T2DM patients. Further studies with larger sample sizes and patients are needed to confirm our findings.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

None of the authors has any conflict of interest to declare.

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Supplementary Materials

Table S1: baseline characteristics of subjects that participated in the study. Table S2: the identified compounds were distributed in 8 metabolic pathways. *(Supplementary Materials)*

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