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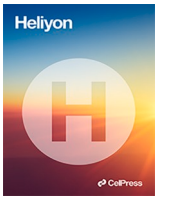

Research article

Dilated cardiomyopathy signature metabolic marker screening: Machine learning and multi-omics analysis

Xiao-Lei Li [a,b,c], Aibibanmu Aizezi [a,b], Yan-Peng Li [a,b], Yan-Hong Li [d], Fen Liu [a,b], Qian Zhao [a,b], Xiang Ma [a,b], Dilare Adi [a,b,**], Yi-Tong Ma [a,b,*]

[a] State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia, Department of Cardiology,First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, Xinjiang, China
[b] Xinjiang Key Laboratory of Cardiovascular Disease, Clinical Medical Research Institute, First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830054, Xinjiang, China
[c] Hubei University of Medicine, Sinopharm Dongfeng General Hospital (Hubei Clinical Research Center of Hypertension), Shiyan, Hubei, 442008, China
[d] Laboratory and Equipment Management, First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, Xinjiang, China

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ABSTRACT

Objects: Our aim was to identify changes in the metabolome in dilated cardiomyopathy (DCM) as well as to construct a metabolic diagnostic model for DCM.
Methods: We utilized non-targeted metabolomics with a cross-sectional cohort of age- and sex-matched DCM patients and controls. Metabolomics data were analyzed using orthogonal partial least squares-discriminant analysis (OPLS-DA) and pathway analysis. It was validated in combination with transcriptome sequencing data from public databases. Machine learning models were used for the diagnosis of DCM.
Results: Using multiple analytical techniques, 130 metabolite alterations were identified in DCM compared to healthy controls. Perturbations in glycerophospholipid metabolism (GPL) were identified and validated as a characteristic metabolic pathway in DCM. Through the least absolute shrinkage and selection operator (LASSO), we identified the 7 most important GPL metabolites, including LysoPA (16:0/0:0), LysoPA (18:1(9Z)/0:0), PC (20:3(8Z,11Z,14Z)/20:1(11Z)), PC (20:0/14:0), LysoPC (16:0), PS(15:0/18:0), and PE(16:0/20:4 (5Z,8Z,11Z,14Z)). The machine learning models based on the seven metabolites all had good accuracy in distinguishing DCM [All area under the curve (AUC) > 0.900], and the artificial neural network (ANN) model performed the most consistently (AUC: 0.919 ± 0.075).
Conclusions: This study demonstrates that GPL metabolism may play a contributing role in the pathophysiological mechanisms of DCM. The 7-GPL metabolite model may help for early diagnosis of DCM.

* Corresponding author. State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia,Department of Cardiology,First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, Xinjiang, China.
** Corresponding author. State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia,Department of Cardiology,First Affiliated Hospital of Xinjiang Medical University, Urumqi 830054, Xinjiang, China.
E-mail addresses: dil515@sina.com (D. Adi), myt-xj@163.com (Y.-T. Ma).

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1. Introduction

Dilated cardiomyopathy (DCM) is a commonly reported cardiomyopathy, often accompanied by severe heart failure, malignant arrhythmias, blood clots, and even sudden death [1]. DCM affects approximately 0.4 % of the global population [2,3] and is the leading cause of heart transplantation in adults [4]. Despite continuous optimization of drug and device therapy over the past decades, the overall prognosis of DCM remains poor, with a 5-year mortality rate of 19–39 % [5]. People of all ages, including adults and children, are affected by DCM [6]. Related studies had also shown that the length of disease was an independent risk factor for the prognosis of DCM [7]. Therefore, early diagnosis is particularly important to improve the prognosis of DCM.

A wide range of studies were dedicated to investigating the identification of blood biomarkers of DCM to improve diagnosis and facilitate individualized treatment [8]. Intensive studies have been conducted in terms of gene polymorphisms [9,10], miRNAs [11], and cytokines [12], but the current understanding of DCM is still deficient. The metabolomics technology that has emerged in recent years has given us a new way of thinking. Metabolomics is an important part of the biological function of the organism, which is an end reflection of the genome, transcriptome or proteome, and environmental factors [13]. There is growing evidence of altered metabolic profiles in the failing heart [14]. In previous studies, metabolomics was used to identify changes in serum metabolism in patients with ICM and DCM, and the results showed the potential of serum metabolites to discriminate between different types of cardiomyopathies [15]. Currently, there is still limited exploration of the value of systemic metabolic changes in DCM in its early diagnosis. Moreover, most of them are based on classical generalized linear regression methods. Modern machine learning approaches can handle high-latitude, nonlinear data and obtain better predictive performance. Nevertheless, to the best of our knowledge, no study has yet applied them to the diagnosis of DCM patients.

Hence, in this study, we evaluated systemic metabolic alterations in patients with DCM. The important metabolic perturbation pathways in DCM patients were analyzed and identified by combining metabolomics data and transcriptomics data. Finally, we developed the 7-glycerophospholipid model using a set of machine learning algorithms for the early diagnosis of DCM.

2. Materials and methods

2.1. Study population

We recruited 30 consecutive Uyghur patients with a first diagnosis of DCM who attended the Heart Center of the First Affiliated Hospital of Xinjiang Medical University. The diagnosis of DCM was referred to the Chinese Guidelines for the Diagnosis and Treatment of Dilated Cardiomyopathy 2018 [16]. Inclusion criteria were left ventricular end-diastolic dimension (LVEDd) > 5.0 cm in females or >5.5 cm in males and left ventricular ejection fraction (LVEF) < 45 %. Exclusion criteria were currently taking medication; combined with other diseases such as ischemic cardiomyopathy, diabetes, hypertension, congenital heart disease, thyroid disease, autoimmune disease, malignancy, and severe liver and kidney insufficiency; pregnancy and lactation; age less than 18 years; missing blood samples. Thirty healthy Uyghur participants were recruited as a control group. All participants were required to reside long-term in Xinjiang.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University and was in accordance with the Declaration of Helsinki. All participants were fully informed of the details of the study and signed an informed consent form.

2.2. Sample acquisition and preparation

First fasting venous blood was drawn from all subjects at the time of admission. Peripheral venous blood was collected in 4–5 ml using heparin anticoagulation tubes, gently inverted up and down 4–5 times and then centrifuged at 3000 r/min for 10 min at 4 °C. The plasma was immediately separated and stored in a −80 °C refrigerator for freezing. The samples were thawed on ice before preparation. 100 μL of sample was placed in an EP tube, 400 μL of extract (methanol: acetonitrile = 1:1 (V/V), containing the isotopically labeled internal standard mixture, vortexed for 30 s, sonicated for 10 min (ice-water bath), and allowed to stand at −40 °C for 1 h. Secondly, the samples were centrifuged at 12000 rpm for 15 min at 4 °C, and then the supernatant was taken in the injection vial and assayed on the machine. At the same time, all samples were mixed into Quality Control (QC) samples with equal amounts of supernatant.

2.3. Metabolomics data collection and analysis

Liquid Chromatography-Mass Spectrometry (LC-MS/MS) analyses were performed using an UHPLC system (Vanquish, Thermo Fisher Scientific) with a UPLC BEH Amide column (2.1 mm × 100 mm, 1.7 μm) coupled to Q Exactive HFX mass spectrometer (Orbitrap MS, Thermo). The mobile phase consisted of 25 mmol/L ammonium acetate and 25 ammonia hydroxide in water(pH = 9.75) (A) and acetonitrile (B). The auto-sampler temperature was 4 °C, and the injection volume was 2 μL.The Q Exactive HFX mass spectrometer was used for its ability to acquire MS/MS spectra on information-dependent acquisition (IDA) mode in the control of the acquisition software (Xcalibur, Thermo). In this mode, the acquisition software continuously evaluates the full scan MS spectrum. The electrospray ionization (ESI) source conditions were set as following: sheath gas flow rate as 30 Arb, Aux gas flow rate as 25 Arb, capillary temperature 350 °C, full MS resolution as 120000, MS/MS resolution as 7500, collision energy as 10/30/60 in NCE mode, spray Voltage as 3.6 kV (positive) or −3.2 kV (negative), respectively. Data preprocessing and annotation: The raw data were converted to the mzXML format using ProteoWizard and processed with an in-house program, which was developed using R and based on

XCMS, for peak detection, extraction, alignment, and integration. Then an in-house MS2 database (BiotreeDB) was applied in metabolite annotation. The cutoff for annotation was set at 0.3.

2.4. Data processing and statistical analysis

We first filtered the raw acquisition data by deviations (based on relative standard deviation), missing value filtering (retaining only peak area data with no more than 50 % null values in a single group or no more than 50 % null values in all groups), missing value filling (filling by numerical simulation with a minimum value of one-half), and data normalization (normalization using internal standard). The analysis was performed with log-transformed and auto scaled data.

The relative intensity of metabolites of in the case and control groups was tested by Students t-test. All normalized metabolomic data matrices were imported into SIMCA software (V16.0.2, Sartorius Stedim Data Analytics AB, Umea, Sweden). Principal component analysis (PCA) was used to observe the overall distribution trends and the degree of variation between groups in the metabolomics data. Orthogonal partial least squares-discriminant analysis (OPLS-DA) analysis was then performed to build models and use them to obtain more reliable differential metabolites between groups. Simultaneously, we validate the model using a 7-fold cross validation and 200 times response permutation testing. The cardinality criterion for differential metabolites was mainly based on the variable important in the projection (VIP) of the first principal component of the OPLS-DA model being greater than 1, while the p-value of Student's t-test was less than 0.05. To identify the top-ranked altered pathways and depict significant biomarkers altered in DCM, the metabolite set enrichment analysis and pathway analysis were conducted using Metaboanalyst 5.0 (https://www.metaboanalyst.ca/).

The LASSO method was used to select the best set of metabolic features from GPL-related differential metabolites for discriminating DCM. We integrated seven GPL metabolites and developed logistic regression (LR) models and four machine learning models. The four machine learning algorithms were random forest (RF), extreme gradient boosting (XGBoost), support vector machines (SVM), and artificial neural network (ANN). the models were evaluated by area under the curve (AUC), accuracy, precision, recall, and f1 scores. The net clinical benefit of the models was analyzed by clinical decision curves (DCA). Also, five internal cross-validations were performed to evaluate the models in order to prevent potential over-fitting of the models.

Categorical variables were expressed as frequencies (%) and continuous variables were expressed as mean ± standard deviation (SD) or median (range interquartile). The differences in baseline characteristics between the two groups were examined by Wilcoxon rank-sum tests for continuous variables and the Fisher exact test for categorical variables. All statistical analyses were performed with

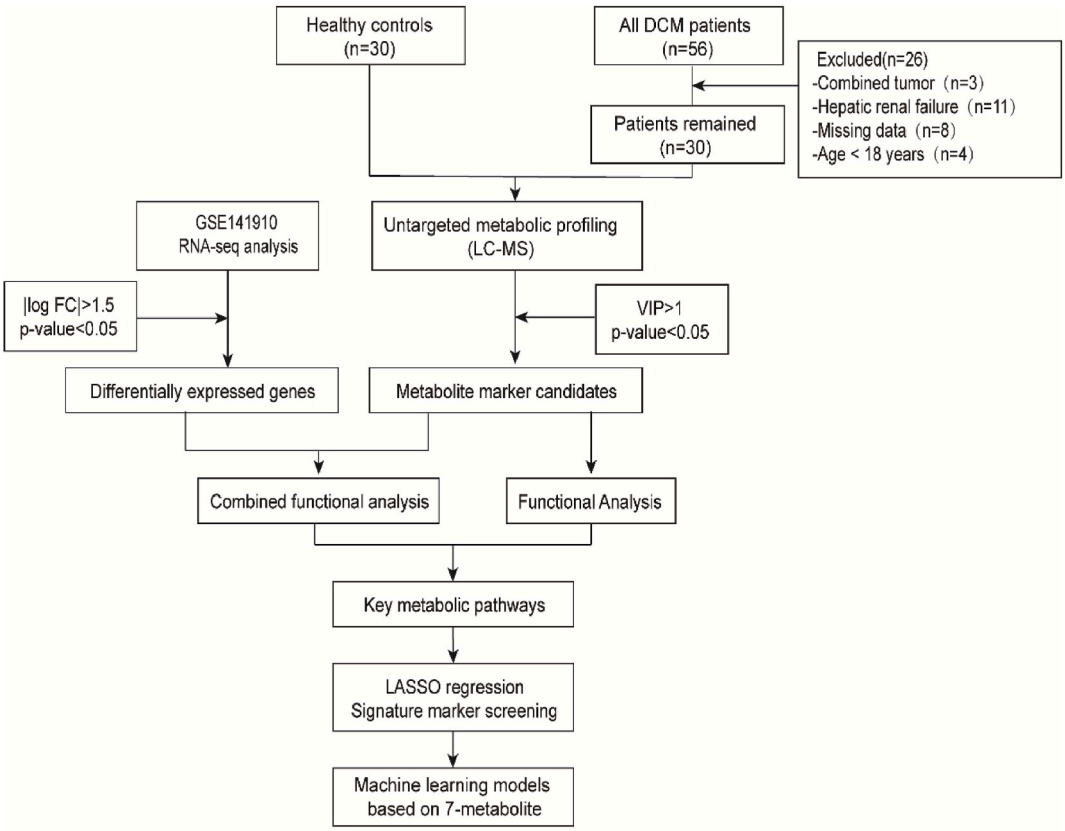

Fig. 1. Flow diagram of the study.

R 4.2.2, Python 3 and Social Package for the Social Sciences (SPSS) 26.0. All tests were 2-sided, and P value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of participant

The overall research design of this study was shown in Fig. 1. Detailed demographic and clinical characteristics are shown in Table S1. 30 patients with DCM and 30 healthy subjects were included in this study as previously described. There were no significant differences in age, sex, body mass index (BMI), or liver and kidney function between the DCM and healthy control groups (All $P > 0.05$). The LVEDd and left atrial diameter (LAd) were larger in the DCM group than in the healthy control group (All $P < 0.05$), and the LVEF were lower in the DCM patients($P < 0.05$).

3.2. Metabolomics profiling between DCM and healthy controls

3.2.1. Quality Control

In this study, a non-targeted LC-MS based metabolomics assay was used. After subtraction of isotopic peaks, 3292 ions were detected in positive ion mode (POS) and 4439 peaks were detected in negative ion mode (NEG). In both POS and NEG, PCA analysis suggested that QC sample veins were clustered together, suggesting the stability of the assay (Figs. S1A and S1B). We performed OPLS-DA analysis with R2Y and Q2 of 0.87,0.54 in POS (Fig. S2A) and 0.85,0.47 in NEG (Fig. S2A), respectively, and the validation plots obtained by 200 permutation tests showed that the R2Y and Q2 values of all rearrangements on the left side were lower than the origin on the right side, and the regression line intercept of Q2 values was in the negative half-axis, suggesting that OPLS-DA model has better stability and credibility and effectively prevents overfitting (Fig. S3).

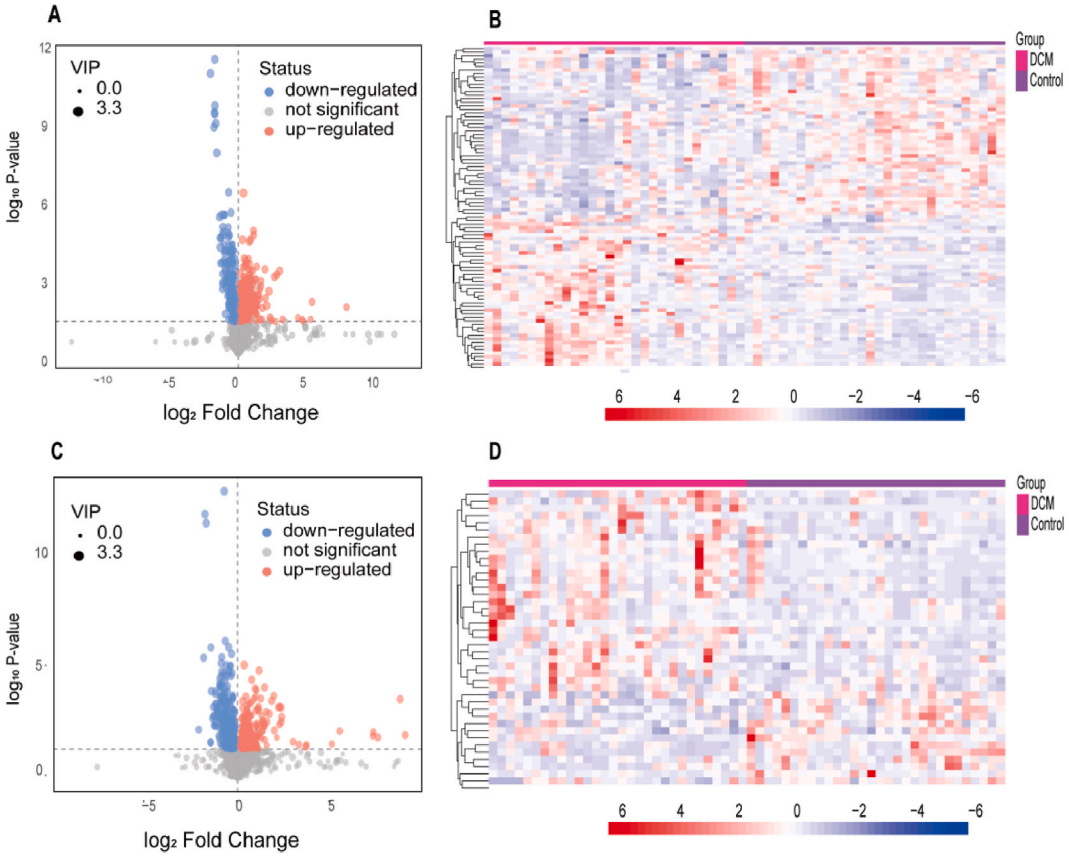

Fig. 2. Differential metabolites between dilated cardiomyopathy (DCM) and healthy individuals. A, Volcano plot under positive ion mode (POS) showed differences in metabolites between DCM and healthy individuals. B, the heatmap of metabolic characteristics under POS showed a good distinction between DCM and healthy controls. C, Volcano plot under negative ion mode (NEG) showed differences in metabolites between DCM and healthy individuals. B, the heatmap of metabolic characteristics under NEG showed a good distinction between DCM and healthy controls.

3.2.2. Metabolic profiling of DCM

Based on the criteria of VIP>1 and P < 0.05, 90 metabolites were identified in the POS model, of which 43 were up-regulated and 47 were down-regulated (Fig. 2A). 42 metabolites were identified in the NEG model, of which 28 were up-regulated and 14 were down-regulated (Fig. 2C). 130 differential metabolites in total (2 of which were duplicates) were identified. Plasma metabolic profiles of DCM patients were significantly different from those of healthy controls. To visualize the relationship between altered metabolites, hierarchical clustering of heatmaps were used to rank metabolites as shown in Fig. 2B (for POS) and Fig. 2D (for NEG). Overall, patients with DCM have significant metabolic alterations that can be diagnosed and identified by metabolomic analysis. We then classified the differential metabolites according to the Human Metabolome Database (https://hmdb.ca/), with the main distribution of all differential metabolites into seven major categories based on chemical classification, mainly Lipids and lipid-like molecules (39 %); amino acids (7 %); organic acids (6 %), Organ heterocyclic compounds (18 %), suggesting a dysfunctional lipid, amino acid and Organic compounds metabolism in DCM patients (Fig. S4).

3.2.3. Dysregulated pathways in DCM

MetaboAnalyst 5.0 was used to enrich 130 differential metabolites for a total of 32 metabolic pathways, of which 3 pathways were significantly enriched (P < 0.05, impact>0.1), mainly glycerophospholipid (GPL) metabolism, nicotinate and nicotinamide metabolism and glycolipid metabolism (Fig. 3A).

3.2.4. Multi-omics analysis

To expand our understanding of the association between DCM and plasma metabolites, we performed a combined multi-omics analysis using metabolomics and transcriptomics. We analyzed a publicly available dataset of 166 healthy control subjects, 166 DCM patients for RNA-seq analysis generated by Margulies et al. (NCBI GEO GSE141910) [17]. Detailed demographic information was provided in Table S3. A total of 266 genes were found to be significantly altered in DCM patients (P < 0.05, |log Fold-Change|>1.5) (Fig. S5). Combined analysis of differential metabolites with differential gene import into MetaboAnalyst 5.0 revealed that GPL was one of the most important pathways(Fig. 3B). Although the metabolomics and transcriptomics data in our study were from different populations and technical platforms, this result could further improve the credibility of our choice of metabolites as well as metabolic pathways.

3.2.5. GPL-related metabolic markers of DCM

GPL-related metabolites and enzymes were significantly altered in DCM patients. Therefore, we further analyzed the significant metabolite changes in the GPL pathway. Eighteen metabolites associated with GPL metabolism were identified in this study compared to normal subjects: LysoPA (16:0/0:0), LysoPA (18:1(9Z)/0:0), PC (20:3(8Z,11Z,14Z)/20:1(11Z)), PC (18:2(9Z,12Z)/P-18:1(11Z)), PC (20:0/14:0), PC (18:2(9Z,12Z)/18:0), PC (22:6(4Z,7Z,10Z,13Z,16Z,19Z)/20:2(11Z,14Z)), PC (22:2(13Z,16Z)/16:1(9Z)), LysoPC (16:0), PC (16:1(9Z)/16:1(9Z)), LysoPC (18:2(9Z,12Z)), LysoPC (20:3(5Z,8Z,11Z)), PE (16:0/20:4(5Z,8Z,11Z,14Z)), PS (15:0/18:0), PE (P-18:1(11Z)/18:3(6Z,9Z,12Z)), PC (15:0/20:2(11Z,14Z)), PC (15:0/18:2(9Z,12Z)), PE (P-18:1(9Z)/16:1(9Z)) (Table S2). We also used heatmap to show the relationship of 18 of the metabolites with LVEF, LVEDd, and NT-proBNP. As shown in Fig. S6, we observed that the expression of these metabolites converged with the trend of the relevant clinical indicators.

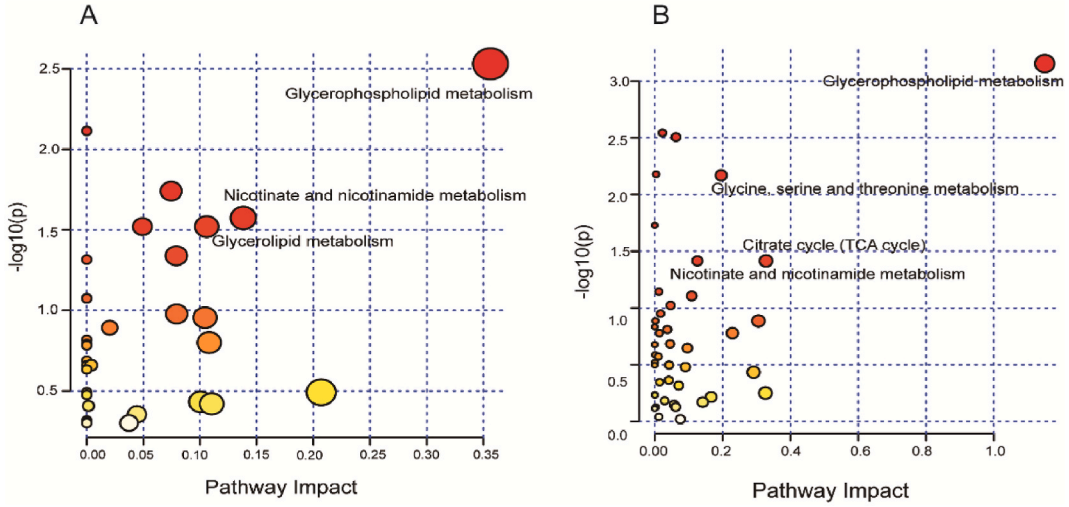

Fig. 3. Dysregulated pathways were observed in DCM. A, Enrichment of dysregulated pathways based on differential metabolites. B, Enriched pathways based on the combined analysis of differential metabolites and differentially expressed genes. Significant pathways were highlighted (p < 0.05, impact >0.1).

3.2.6. GPL metabolite prediction model

To screen for characteristic markers of diagnostic importance in GPL metabolites, we used LASSO regression and selected the optimal λ values at minimum criteria (Fig. 4A and B). Finally, from the 18 metabolites, 7 metabolites were screened as metabolic markers, namely: LysoPA (16:0/0:0), LysoPA(18:1(9Z)/0:0), PC (20:3(8Z,11Z,14Z)/20:1(11Z)), PC (20:0/14:0), LysoPC (16:0), PS (15:0/18:0), and PE (16:0/20:4(5Z,8Z,11Z,14Z)). In the univariate analysis, seven GPL metabolites were found to be significantly different between DCM patients and normal individuals. The ROC curve analysis suggested that all seven metabolites have acceptable diagnostic value (Fig. 4C–I).

We attempted to differentiate DCM patients using a combination of seven glycerophospholipid metabolites. We integrated the above data for the development of LR, RF, XGBoost, SVM and ANN models, as shown in Table 1. All models showed excellent diagnostic value. (Fig. 5A). A 5-fold internal cross-validation analysis showed that the ANN model performed most consistently (Fig. 5B).

Also, the DCA analysis showed that when the threshold probability of DCM was between 0 and 1, The diagnosis by using the models can correctly identify more patients with DCM (Fig. 5C).

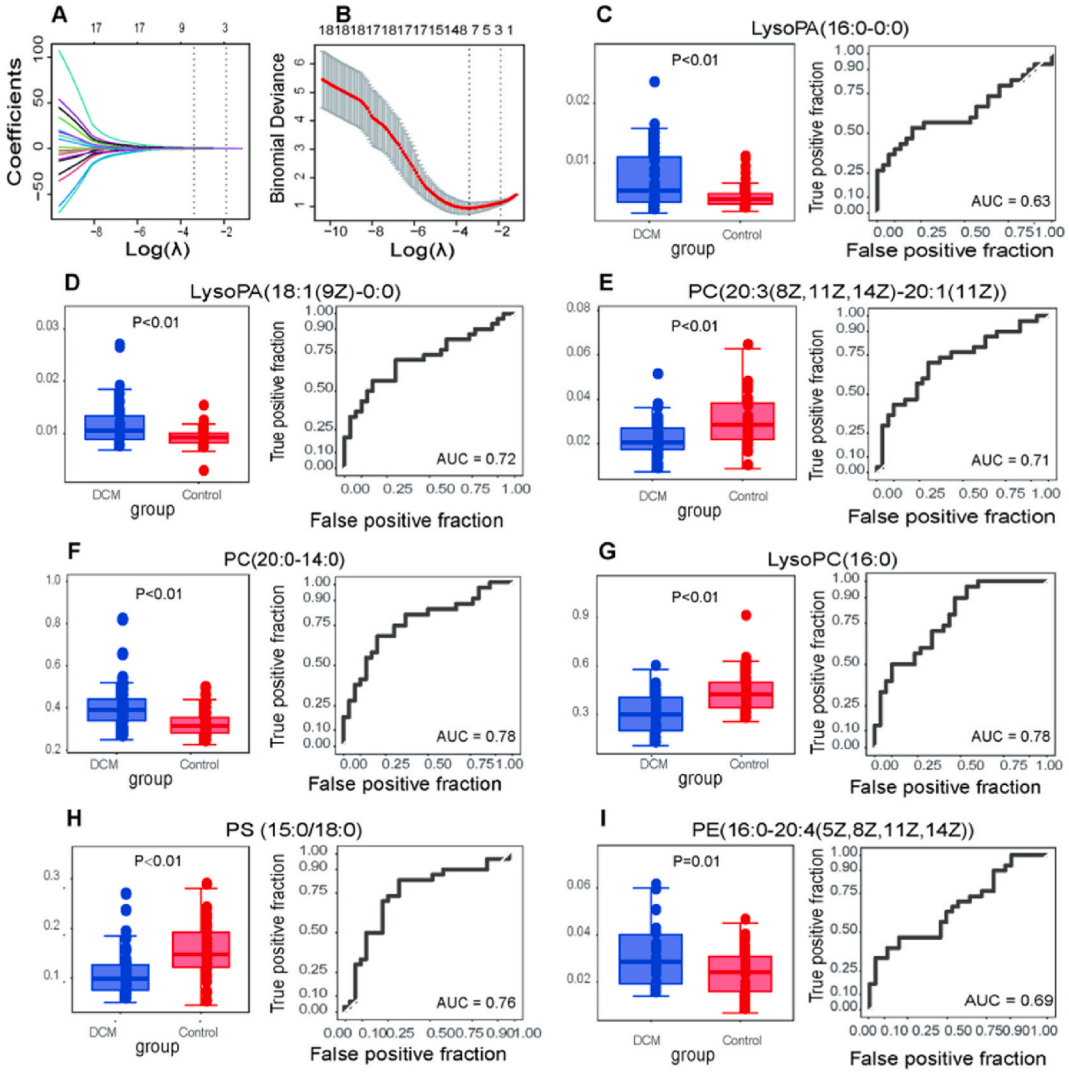

Fig. 4. The characteristic glycerophospholipid (GPL) metabolites of DCM. A, a plot of the coefficient profile against the log(λ) sequence was generated. The vertical dashed line was drawn at the optimal value of λ at the minimum criteria and1 standard error (1-SE criteria). The minimum criterion model was chosen as the final model with 7 nonzero coefficients. (B) The selection of the tuning parameter (λ) in the LASSO model used tenfold cross validation via minimum criteria. We plotted binomial deviance as a function of log (λ). C, D, E, F, G, G, and I were Boxplot (median and IQR) and the area under curve (AUC) of receive operating characteristics (ROC) testing of the 7 glycerophospholipid (GPL) metabolites. SE, standard error. IQR, interquartile range.

Table 1
Tables should be placed in the main text near to the first time they are cited.

Model	Discrimination statistics					Five-fold CV
	AUC	Accuracy	Precision	Recall	f1 score	AUC (mean ± SD)
LR	0.948	0.833	0.987	0.867	0.881	0.883 ± 0.067
RF	0.954	0.917	0.931	0.900	0.915	0.833 ± 0.053
XGBoost	0.988	0.967	0.967	0.967	0.967	0.783 ± 0.085
SVM	0.957	0.883	0.926	0.833	0.877	0.850 ± 0.082
ANN	0.949	0.917	0.963	0.867	0.912	0.917 ± 0.075

LR, logistic regression; RF, random forest; XGBoost, extreme gradient boosting tree; SVM, support vector machines; ANN, artificial neural network; AUC, area under the curve; SD, standard deviation.

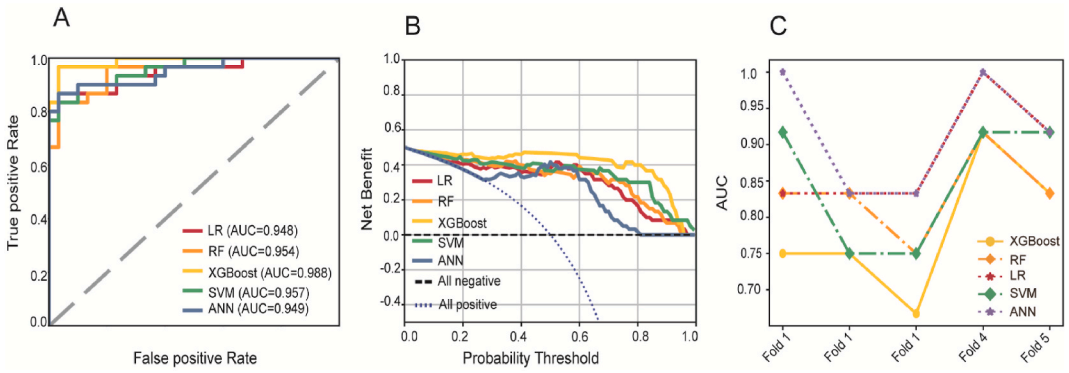

Fig. 5. The evaluation and internal validation for models. A, the AUC of different models in predicting DCM; B, the decision curve of different models; C, 5-fold cross-validation of different models. AUC, area under the curve; DCA, decision curve; LR, logistic regression; RF, random forest; XGBoost, extreme gradient boosting tree; SVM, support vector machines; ANN, artificial neural network.

4. Discussion

In this study, we used non-targeted metabolomics techniques to identify the metabolic fingerprints of Uyghur DCM patients for the first time. The presence of significant GPL metabolic disorders in DCM patients was identified by combined analysis with transcriptomic data. Subsequently, we developed machine learning models based on 7-GPL metabolic to diagnose DCM. Our study shows that the unique plasma GPL metabolic profile promises to be a valuable early diagnostic tool.

Early diagnosis is a critical factor in the success of DCM treatment and improved long-term prognosis. A comprehensive metabolomics could characterize the physiological status of disease cases and was widely used for the development of new diagnostic markers and potential therapeutic targets for disease. Cardiac metabolism had a unique metabolic capacity to adapt to different physiological environments and dietary requirements [18]. Several studies have characterized the metabolic profile of cardiovascular disease, and several studies have demonstrated the metabolomic profile of patients with DCM from different populations [19–21]. The main metabolic features of the enlarged, failing heart include disturbances in amino acids, lipids, and organic compounds. As previously reported, similar manifestations were observed in the present study from Uyghur DCM patients. The differential metabolites in DCM patients were mainly focused on lipids, organic acids and their analogs, and amino acids, with lipids accounting for the largest proportion of them. Lipids are important components of cell membranes and may influence a variety of biological activities in the pathological state of DCM. The association of lipid disorders with the risk of DCM-related heart failure has been demonstrated in relevant studies [22,23].

With further analysis we found that lipid metabolism, especially GPL metabolism, may play an important role in the pathogenesis of DCM. By categorizing and analyzing the differential metabolites, we found that GPL metabolites accounted for a large proportion (18 species, 35.29 %) of the differential lipid metabolites. Moreover, KEGG pathway enrichment analysis also revealed that the GPL pathway was one of the most important pathways, indicating the importance of GPL in the pathogenesis of DCM. Previous studies have also found disorders of fatty acid and GPL metabolism in patients with different phenotypes of DCM, which might have commonalities with the altered GPL metabolism observed in our results [21,24]. In conjunction with earlier reports, glycerophospholipid metabolism were identified to be significant in both Uyghur and Han DCM patients. However, alpha-linolenic acid metabolism was identified as most significant pathway in Han DCM patients [21]. We also found that the trends of 18 GPL metabolites converged with commonly used diagnostic and assessment indicators of DCM such as NT-proBNP, LVEF, and LVEDd, suggesting that dysfunction of glycerophospholipid metabolic pathways may be an important feature of DCM and that these metabolites may serve as potential markers for the diagnosis of DCM. To trace the upstream variation of the metabolome, we further validated our conjecture using RNA-seq data from public databases, and we were surprised to find that the GPL pathway was one of the most important pathways (with the smallest

p-value), further confirming the critical position of the GPL metabolic pathway in the pathogenesis of DCM. We also found that the expression and type of GPL metabolites identified in this study were not identical. Eight of the PC, three of the PE, one of the PS and two of the LysoPC we identified were downregulated. And both LysoPA were upregulated. The different metabolic patterns of these metabolites suggest that GPL homologous metabolites play different roles in the pathogenesis of DCM.

Considering the important role of GPL metabolism in DCM, we filtered seven key GPL metabolites using LASSO regression for model building. In order to better improve the accuracy of the models, we used a series of powerful machine learning methods, including RF, XGBoost, SVM, ANN, etc., to train the models. Encouragingly, all models shown excellent diagnostic ability. Among them, the ANN model performed most consistently. This also suggested that our 7-GPL metabolite model would potentially be a useful tool for early identification of DCM patients if our model could be confirmed in more data.

Glycerophospholipids are the most important phospholipids of eukaryotic cells and are the main lipid components of cell membranes. The specific molecular structure of glycerophospholipids also confers them close relevance to pathophysiological functions such as apoptosis, inflammation, oxidative stress, and energy metabolism [25]. Lysophosphatidic acid (LysoPA), the simplest glycerophospholipid, is a biosynthetic precursor of phosphatidic acid (PA) and has a wide range of biological activities. For example, LysoPA can promote inflammation by regulating the expression of cytokines and cytokine receptors [26], and can also act as an inflammatory mediator by acting on atypical receptors such as RAGE by acting on G protein-coupled receptors [27]. LysoPA was found to promote cell growth and differentiation through LPA receptor 1,3 and PPAR-γ, thereby promoting proliferation during mast cell inflammation. In mice knocked out of catabolic LysoPA lipid phosphatases such as LPP3, studies found higher systemic and cardiac inflammation and severely reduced cardiac function. Notably, LysoPA expression was also strongly associated with myocardial fibrosis and myocardial remodeling [28]. Elevated levels of LysoPA have been found not only in myocardial hypertrophy mice, but also in human studies, where LysoPA expression was found to be elevated in patients with acute myocardial infarction compared to normal subjects [29]. Recent studies have also confirmed that Autotaxin can mediate inflammation and fibrosis through LysoPA, leading to organ remodeling. By inhibiting ATX, the level of LysoPA was significantly reduced, and inhibition of myocardial fibrosis was accompanied by inhibition of myocardial structural remodeling as well as increased cardiac dysfunction [30]. Inflammation and myocardial fibrosis were important pathophysiological features of dilated cardiomyopathy, and our results also show that DCM patients are accompanied by higher levels of LysoPA. Based on the above studies, we hypothesize that LysoPA may be involved in the pathophysiology of dilated cardiomyopathy through inflammation and myocardial fibrosis and may be a potential therapeutic target to keep the inflammatory process and reverse ventricular remodeling in DCM.

Metabolites such as PC, PE, and LysoPC were also found to be abnormally metabolized in DCM patients in the present study. PC and PE are the most abundant glycerophospholipids in eukaryotic cell membranes, accounting for more than half of the total phospholipid species [31]. PC depletion may impair protein transport to the inner mitochondrial membrane and mitochondrial matrix and affect the energy metabolism of mitochondria [32]. Moreover, as a precursor molecule for a variety of signaling molecules and inflammatory mediators, PC is also involved in biological processes such as cell proliferation and apoptosis [33,34]. As in our findings, Zhao et al. [21]. found decreased PC levels in a Han Chinese DCM population, and combinations of metabolites such as PC can be used to distinguish DCM from ICM. Mueller-Hennesse et al. showed that PC-based lipid metabolite combinations combined with NT-proBNP could significantly improve the diagnostic performance of heart failure and can accurately assess the different stages [35]. LysoPC is mainly derived from the hydrolysis of PC by PLA. PC and LysoPC play important roles in the regulation of cellular lipid metabolism and homeostasis through the Lands cycle [36]. Xu et al. found that functional lipids such as PC, LysoPC, and PE were significantly reduced in mouse hearts by analyzing cardiomyocytes from mice with diabetic cardiomyopathy [37]. In the study by Yang et al., patients with ischemic cardiomyopathy also had similarly significant disturbances in the metabolism of glycerophospholipids such as PE, PC, and LysoPC [38].

However, we also need to recognize several limitations of our study. Our study only observed this metabolic phenomenon in a cross-sectional study, and the next step requires mechanistic studies to explore the specific biological processes as well as the specific effects of lipid species on the onset of DCM. To minimize confounding factors that may affect metabolomic differences, we included only a "pure" Uyghur population of DCM and normal controls, excluding co-morbidities and drug users from the subjects, and that caution is needed in generalizing them to all DCM patients. The transcriptomic data we used were not from the same cohort and the sample sources were inconsistent, which also limits its interpretability. We cannot avoid the disadvantage of small sample size due to sample scarcity, and we also need to note that metabolic profiling is derived from non-targeted metabolomics, and our next step will be to expand the subject population and use targeted lipidomic to further validate and assess the role of GPL metabolism in the pathogenesis of DCM. Large-scale and long-term follow-up studies are also needed to validate the diagnostic and predictive functions of GPL metabolites on disease phenotypes. Although the metabolic markers we identified have some diagnostic value for DCM, the impact of the overall state of the organism on metabolism, such as chronic or acute stress and inflammation, should be considered. At the same time, we should also be aware of the influence of confounding factors such as medications, comorbidities, and the environment on experimental results, which will also limit the generalization of our results. Therefore, in follow-up studies, other diseases involving chronic and acute stress and inflammation need to be investigated to validate the potential use of these markers in the diagnosis of DCM.

5. Conclusions

Our study identified that DCM was associated with altered metabolomic profiles. GPL metabolic perturbations were identified for the first time as a potential warning sign of DCM. A combinatorial model including seven GPL metabolites performed well in discriminating DCM and showed promise as a tool for early DCM diagnosis.

CRediT authorship contribution statement

Xiao-Lei Li: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Aibibanmu Aizezi:** Data curation. **Yan-Peng Li:** Resources. **Yan-Hong Li:** Resources. **Fen Liu:** Resources. **Qian Zhao:** Data curation. **Xiang Ma:** Writing – review & editing, Validation. **Dilare Adi:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Yi-Tong Ma:** Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

The research protocol for this study was approved by the Ethics Committees of the First Affiliated Hospital of Xinjiang Medical University (Approved No. of Ethics Committee: 20190505-01)

Consent for publication

Not applicable.

Availability of data and material

The metabolic profiling data and clinical data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.The RNA-seq dataset of this article are available in the Gene Expression Omnibus database (GEO; https://www.ncbi.nlm.nih.gov/geo/; GSE141910).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e41927.

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