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Diagnostic and clinical relevance of targeted metabolomic analysis of serum bile acid profiles in acute pancreatitis

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Abstract

Objective This study aims to identify specific bile acids with potential early diagnostic value for acute pancreatitis (AP) and to provide a foundation for improved early diagnosis and the development of future therapeutic targets.

Methods Targeted quantitative analysis of serum bile acids was performed using ultra-performance liquid chromatography coupled with high-resolution mass spectrometry in healthy individuals and individuals diagnosed with mild acute pancreatitis (MAP), moderate-to-severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP). Comparative analysis of bile acid profiles was conducted across these groups. The diagnostic performance of differential metabolic markers was evaluated using receiver operating characteristic curve analysis. Additionally, correlation heatmap analysis was employed to investigate associations between specific bile acids and clinical laboratory parameters.

Results Fourteen specific bile acids were identified. Taurocholic acid (TCA) was determined to be a distinguishing metabolite between the MSAP group and the healthy control group. Furthermore, taurochenodeoxycholic acid (TCDCA), glycocholic acid, taurodeoxycholic acid, and TCA were identified as differential metabolites between the SAP group and the healthy control group. Correlation analysis demonstrated that in the MSAP group, TCDCA exhibited a positive association with serum glucose, taurolithocholic acid (TLCA), serum triglycerides, cholic acid, and serum total cholesterol. In the SAP group, positive correlations were observed among TLCA, glycochenodeoxycholic acid, and serum calcium, between glycodeoxycholic acid (GDCA), chenodeoxycholic acid, and urine amylase, as well as between GDCA and serum lipase.

Conclusion Specific serum bile acids, particularly TCA and TCDCA, demonstrate potential as biomarkers for the early, non-invasive, and accurate diagnosis of MSAP and SAP. These findings contribute to the advancement of early diagnostic strategies for acute pancreatitis.

Keywords Acute pancreatitis, Bile acids, Early diagnosis, Mechanistic studies, Targeted metabolomics

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Introduction

Acute pancreatitis (AP) is a systemic condition characterized by localized pancreatic inflammation resulting from the activation of pancreatic enzymes due to various etiological factors. This condition may occur with or without dysfunction in other organ systems [1]. Early and accurate diagnosis of AP, along with the evaluation of disease severity, remains a significant focus of ongoing research [2]. However, existing early diagnostic markers and severity assessment criteria—including serum and urine amylase, serum lipase (LPS), serum calcium levels, the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, the Ranson score, and the Computed Tomography Severity Index (CTSI) scoring system—exhibit limitations in terms of accuracy, sensitivity, and specificity in the early stages of the disease [3].

For instance, although serum amylase is a key biomarker for AP diagnosis, its elevation is not exclusive to pancreatitis and may also be observed in conditions such as perforated peptic ulcer and cholelithiasis. Furthermore, amylase levels do not necessarily correlate with disease severity; individuals with severe pancreatitis may present with normal or even reduced amylase levels. Similarly, elevated fatty acid levels may also be associated with other metabolic disorders. Additionally, the APACHE-II, Ranson, and CTSI scoring systems rely on high-quality computed tomography imaging, and variations in radiological interpretation may lead to discrepancies in diagnostic assessments among clinicians.

Bile acids (BAs) are amphipathic molecules that serve as the primary products of cholesterol metabolism [4]. These molecules are predominantly found in bile and play a critical role in the digestion and absorption of lipids. However, disruptions in BA secretion or excretion can result in cholestasis, thereby increasing the risk of AP. Studies have demonstrated significant alterations in the levels of primary BAs, such as cholic acid (CA) and chenodeoxycholic acid (CDCA), as well as their derivatives in individuals with AP. Serum concentrations of these BAs fluctuate markedly between the acute and recovery phases of AP, with a notable decrease during the acute phase followed by a substantial increase during recovery. These variations are closely associated with disease severity, suggesting that BAs may play a pivotal role in the pathophysiological mechanisms underlying AP. Additionally, BAs such as CDCA and CA may contribute to AP pathogenesis by modulating intracellular calcium concentrations and mitochondrial function. Metabolites of CDCA and CA also exhibit distinct patterns in individuals with AP, potentially implicating their involvement in pancreatic acinar cell injury and pancreatic necrosis [5].

To date, no studies have investigated the correlation between targeted BA metabolomics and the early diagnosis of AP. The present study aims to analyze and compare the targeted metabolic profiles of serum BAs in individuals with AP and healthy controls using high-throughput metabolomics technology. By identifying differential metabolic markers, this study seeks to enhance understanding of their potential clinical applications in early diagnosis and their association with clinical indicators of AP.

Research methods

Between September 2019 and September 2021, individuals diagnosed with AP and admitted to Baotou Central Hospital were enrolled in this study. Disease severity was classified based on the Chinese Guidelines for the Diagnosis and Treatment of Acute Pancreatitis (2021) and the Revised Atlanta Classification. Participants were categorized into three groups: mild acute pancreatitis (MAP), moderate-to-severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP), with 25 cases included in each group.

Additionally, a control group consisting of 75 healthy individuals with matching demographic characteristics was recruited. A high-throughput metabolomics analysis platform was utilized to identify molecular markers for early AP diagnosis, and associations between clinical markers and specific BAs were evaluated. This approach aims to provide new insights into the pathophysiology of AP and contribute to the development of improved strategies for its early diagnosis, prevention, and treatment.

Clinical study enrollment protocol for patients with AP

Inclusion criteria

Participants were considered eligible for inclusion if they met the following criteria, as outlined in the Chinese Guidelines for the Diagnosis and Treatment of Acute Pancreatitis (2021):

(1) A diagnosis of AP was confirmed if at least two of the following conditions were met:

(i) Acute-onset, persistent epigastric pain, which may be accompanied by nausea and vomiting.
(ii) Serum amylase levels at or above three times the upper limit of normal.
(iii) Identification of pancreatic morphological abnormalities through imaging studies.

(2) No restrictions on gender; eligible participants were between 18 and 80 years of age.

(3) Provision of written informed consent.

Exclusion criteria

Participants were excluded from the study if any of the following conditions were present:

(1) Presence of malignancies, severe hepatic or renal dysfunction, hematologic disorders, hyperthyroidism, hypothyroidism, or severe mental health disorders.

(2) History of antibiotic or hormone use, exposure to significant psychological stress within the past two weeks, blood transfusions within the past six months, or current pregnancy or lactation.

(3) Inability to complete the full clinical trial observation period and associated examinations for any reason.

Experimental procedures and flowchart

Baseline demographic and clinical data of the enrolled participants were collected. Laboratory tests, including complete blood count, serum and urinary amylase, lipase, blood calcium, and blood lipid levels, were conducted. Peripheral blood samples (5 mL) were obtained, followed by centrifugation to isolate approximately 1 mL of serum. The serum samples were stored at -80 °C for future analysis (Fig. 1A).

Clinical study enrollment protocol for healthy control participants

Inclusion criteria

Healthy individuals were eligible for inclusion if they met the following criteria:

(1) No gender restrictions; individuals aged 18–80 years who had undergone a physical examination.

(2) Demographic characteristics matched those of the AP group.

(3) Written informed consent was provided, and voluntary participation in the study was confirmed.

Exclusion criteria

Individuals were excluded from the study if any of the following conditions were present:

(1) History of pancreatitis.

(2) Declined participation in the study.

Peripheral blood samples (5 mL) were collected from healthy controls, centrifuged, and approximately 1 mL of serum was separated and stored at -80 °C for future analysis. The remaining cellular components were pelleted and disposed of according to hospital protocols for infection control, disinfection, and medical waste management (Fig. 1B).

Clinical blood sample processing

Sample pretreatment

Collected blood samples were allowed to stand for one hour at room temperature before being centrifuged at 4 °C and 3000 rpm for 10 min using a low-temperature centrifuge. Following centrifugation, approximately 400 µL of serum was obtained. The remaining cell pellets were disposed of in accordance with the hospital's infection control, disinfection, and medical waste disposal protocols.

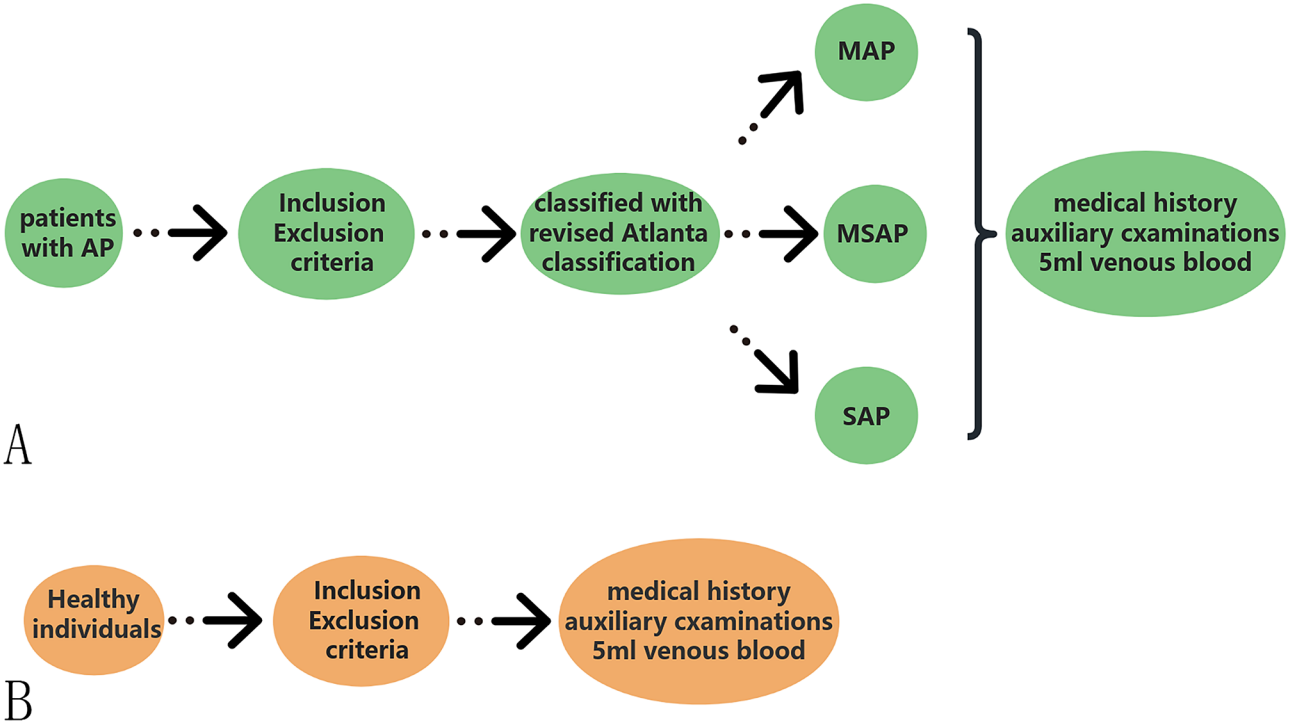

Fig. 1 Flowchart of study enrollment. (**A**) Flowchart of patient enrollment in the AP groups. (**B**) Flowchart of participant enrollment in the control group

Standard curve solution preparation

(1) A precise quantity of the reference standard was weighed, and a stock solution with a concentration of 1.0 mg/mL was prepared.

(2) The stock solution was systematically diluted to the required working concentration using the extraction solution, following a stepwise procedure.

Metabolome sample processing

Sample processing

Serum samples stored at -80 °C were retrieved and thawed at 4 °C. A precise volume of 50 µL was transferred to an EP tube, followed by the addition of 200 µL of a 1:1 methanol mixture containing a 50 ng/mL isotope-labeled internal standard for BAs. The mixture was vortexed for 5 min and subsequently centrifuged at 13,000 g for 10 min. A total of 200 µL of the supernatant was subjected to vacuum drying and then reconstituted in 100 µL of 50% methanol in water. Finally, 80 µL of the reconstituted supernatant was transferred to a 96-well plate for analysis using ultra-performance liquid chromatography coupled with high-resolution mass spectrometry (UPLC-HRMS).

(1) Liquid chromatography conditions:

Column: Acquity UPLC HSS C18 (1.8 µm, 2.1 × 100 mm).

Mobile phase: A: Water containing 5 mM ammonium bicarbonate and 0.01% ammonia; B: 50/50 Methanol/Acetonitrile containing 5 mM ammonium bicarbonate and 0.01% ammonia.

Gradient elution: 0 min: A 75%, B 25%; 0.5 min: A 75%, B 25%; 17.5 min: A 55%, B 45%.

Flow rate: 0.4 mL/min.

Injection volume: 5 µL.

(2) Mass spectrometry detection conditions:

Ionization source: Heated Electrospray Ionization; ionization mode: negative ionization; ionization voltage: 3.0 kV; capillary temperature: 320 °C; heating gas temperature: 350 °C; sheath gas flow rate: 50 arb; auxiliary gas flow rate: 15 arb; S-Lens radio frequency level: 50%; mass spectrometry resolution: 17,500 Full Width at Half Maximum; maximum ion accumulation time: 100 ms.

Statistical methods

All data collected in this study were analyzed using SPSS 25.0 software. Measurement data following a normal distribution were expressed as mean ± standard deviation (SD), with comparisons between groups evaluated using one-way analysis of variance (ANOVA). For non-normally distributed data, the rank-sum test was applied for within-group comparisons.

Multivariate statistical analyses included principal component analysis (PCA) to visualize clustering and grouping, and orthogonal partial least squares-discriminant analysis (OPLS-DA) to further distinguish variations between groups. A variable importance in projection (VIP) > 1 was used as the threshold for identifying characteristic differential BAs. Additionally, BAs that significantly contributed to intergroup differences were identified by integrating VIP values with $p < 0.05$ from univariate statistical analysis.

To assess the diagnostic performance of biomarkers, receiver operating characteristic (ROC) curves were generated, and the area under the ROC curve (AUC) was calculated. A correlation heatmap was used to evaluate the relationships between clinical indicators and specific BAs. Ten-fold cross-validation was performed to ensure the reliability of the study findings. A p-value < 0.05 was considered statistically significant.

Metabolomics analysis was conducted using liquid chromatography-mass spectrometry technology, enabling the detection of statistically significant BAs across the complete BA profile, including non-differential research analysis.

Results

General information

A total of 150 participants were enrolled in the study, comprising 25 individuals in each of the MAP, MSAP, and SAP groups, along with 75 healthy individuals in the control group. The cohort included 99 males (66%) and 51 females (34%), with ages ranging from 22 to 80 years. Despite variations in dietary habits and differences in the etiological factors of pancreatitis, no statistically significant differences were observed in the distribution of pancreatitis between male and female participants in the AP groups. Similarly, the broad age range of participants, which may reflect differing pathogenic factors, did not result in significant differences between the groups ($p > 0.05$, Fig. 2).

Targeted metabolomics analysis of serum BA profiles was conducted using UPLC-HRMS in the 75 individuals in the control group and 75 individuals in the three AP groups. A total of 14 specific BAs were detected, including: cholic acid (CA), taurolithocholic acid (TLCA), glycolithocholic acid (GLCA), glycocholic acid (GCA), taurocholic acid (TCA), deoxycholic acid (DCA), chenodeoxycholic acid (CDCA), ursodeoxycholic acid (UDCA), glycodeoxycholic acid (GDCA), glycochenodeoxycholic acid (GCDCA), glycoursodeoxycholic acid (GUDCA), taurodeoxycholic acid (TDCA), taurochenodeoxycholic acid (TCDCA), and tauroursodeoxycholic acid (TUDCA).

Statistical analyses were performed to compare these BAs based on their structural characteristics, and their variation patterns were further examined. Box plot analysis revealed increased expression levels of GLCA in the control group, UDCA in the MSAP group, and GDCA,

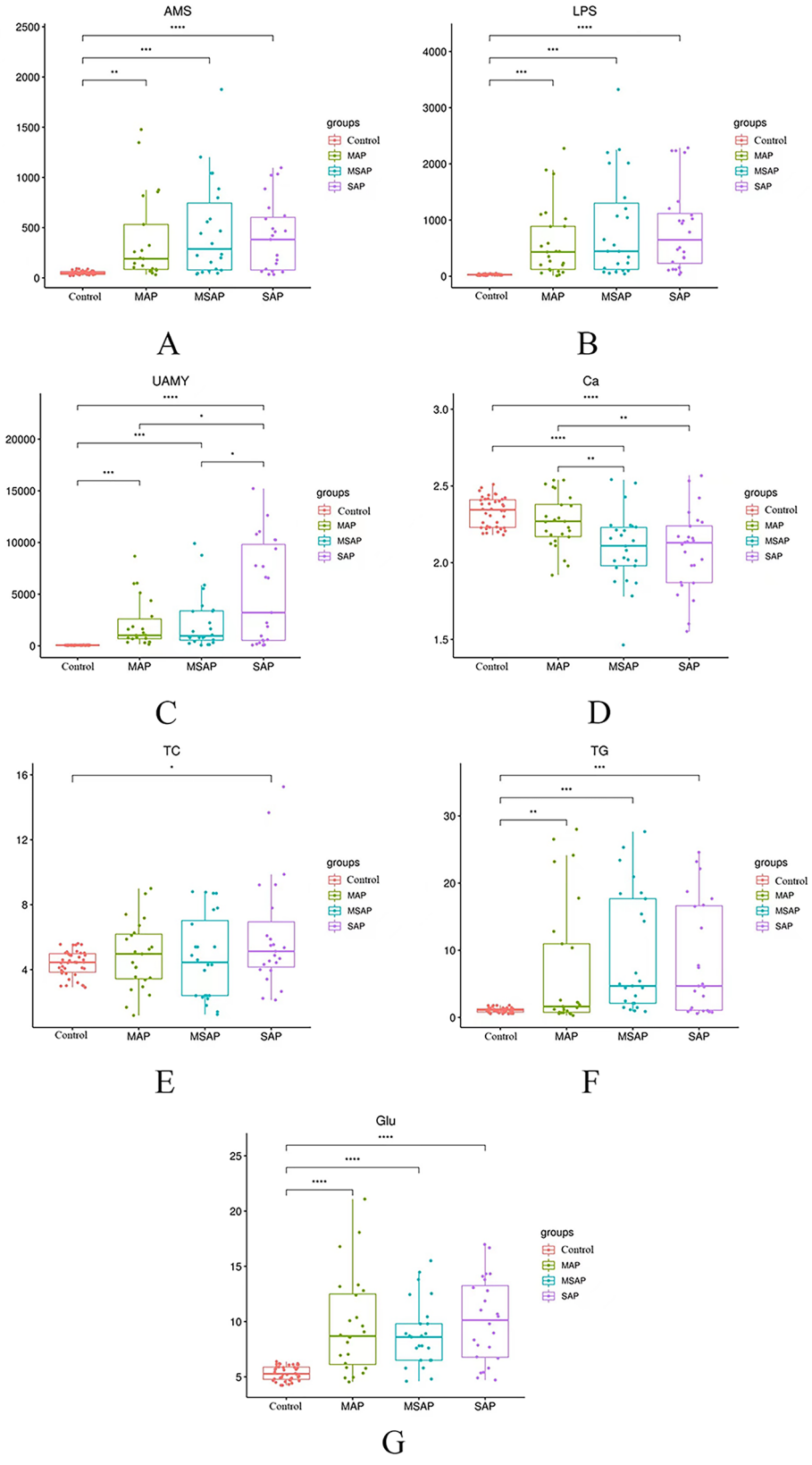

Fig. 2 Demographic and clinical characteristics of study participants across groups

TCDCA, TDCA, TUDCA, and GCA in the SAP group (Fig. 3).

Differentiating between AP groups and the control group using PCA

PCA was employed to compare the BA profiles of the control group with those of the MAP, MSAP, and SAP groups. Each point in the PCA plot represents a distinct BA.

The BA distributions in the control, MAP, and MSAP groups appeared highly concentrated, with substantial overlap, suggesting no statistically significant differences in BA profiles among these groups. However, a notable distinction was observed between the SAP and control groups, indicating significant alterations in the serum BA profile of patients with SAP. These findings suggest that monitoring BA fluctuations may aid in the identification of SAP (Fig. 4).

Identification of differential metabolites in various types of AP

Compared to PCA, OPLS-DA provides enhanced visualization and resolution for distinguishing metabolic differences among groups. As illustrated in the analysis, the

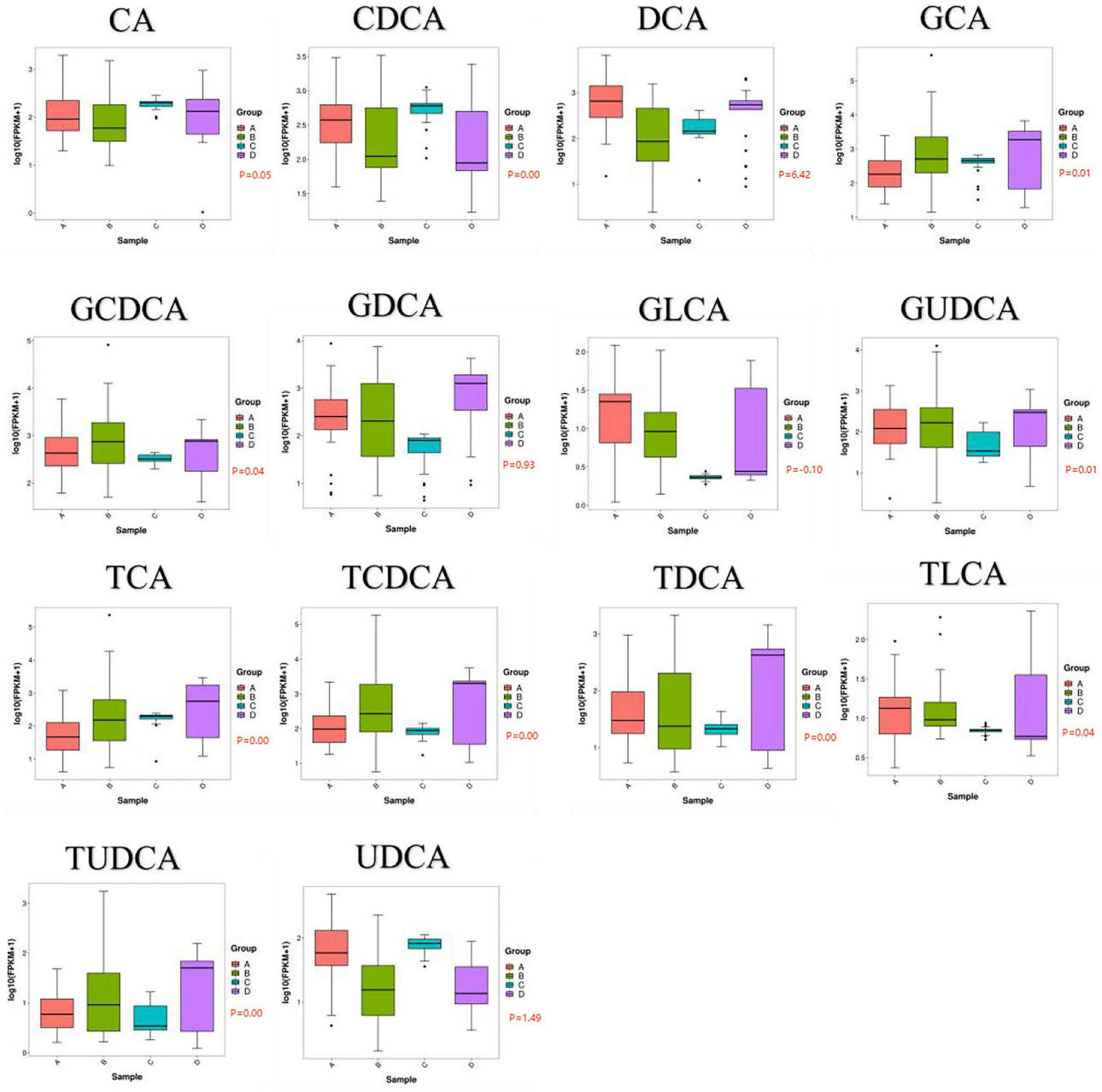

Fig. 3 Expression of 14 BAs in the control group (**A**), MAP group (**B**), MSAP group (**C**), and SAP group (**D**)

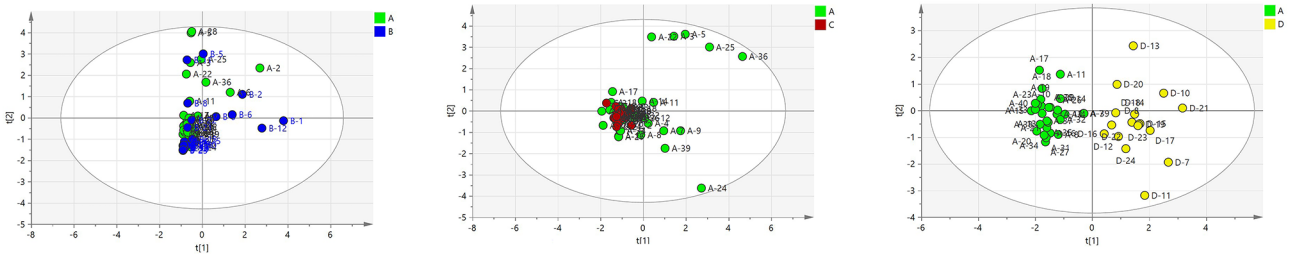

Fig. 4 PCA of BA profiles. (**A**) Control group; (**B**) MAP group; (**C**) MSAP group; (**D**) SAP group

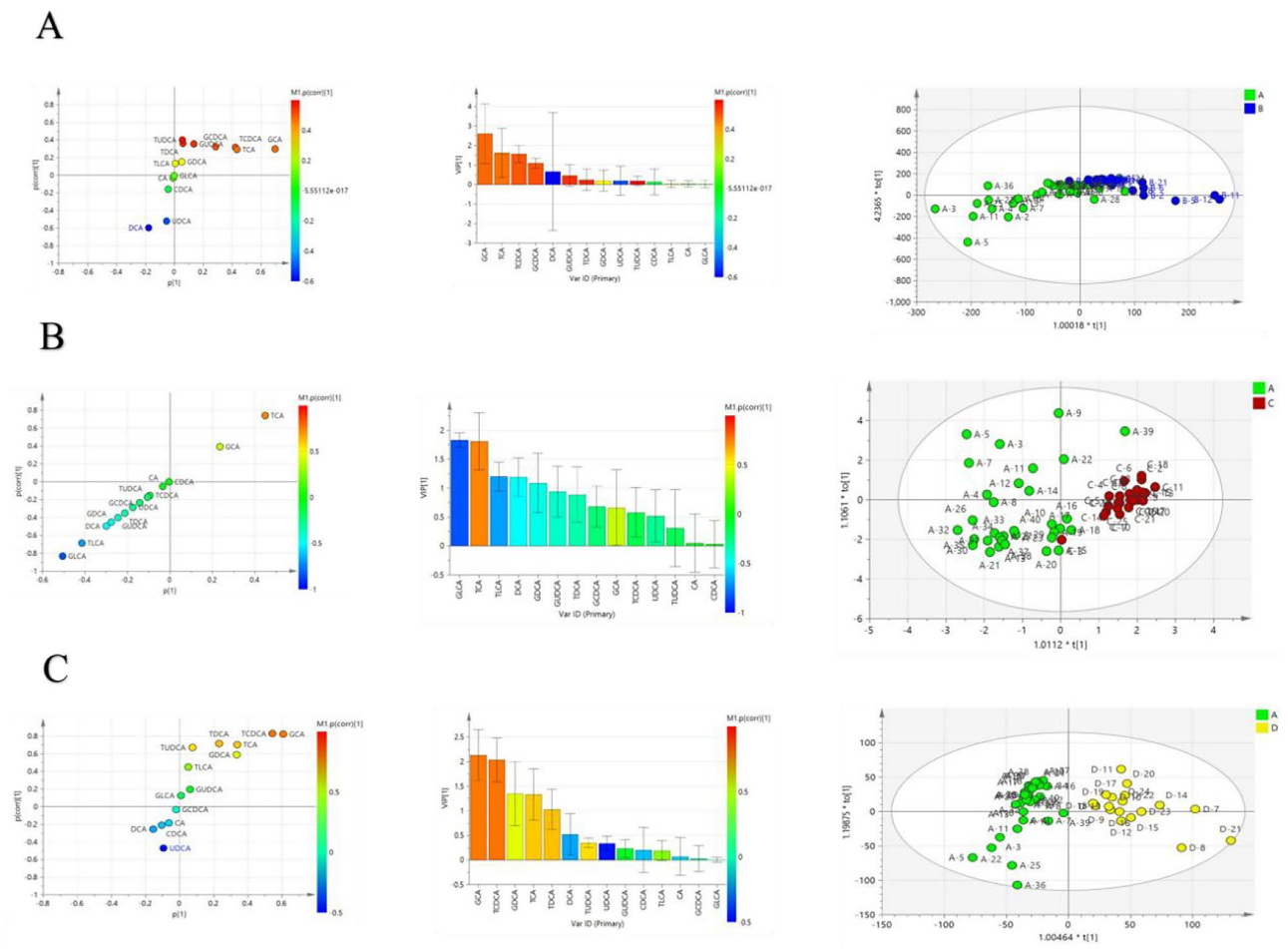

Fig. 5 OPLS-DA of BA profiles. (**A**) Comparison between the control group and the MAP group; (**B**) Comparison between the control group and the MSAP group; (**C**) Comparison between the control group and the SAP group

absolute values of all BAs in the MAP group were below 0.6 when compared to the control group, suggesting that specific BAs can be used to distinguish patients with MAP from healthy individuals.

In the MSAP group, TCA levels exhibited a significant elevation (VIP > 1), indicating that TCA may serve as a key biomarker for distinguishing patients with MSAP from healthy individuals.

For patients with SAP, four differential metabolites—TCDCA, GCA, TDCA, and TCA—were identified, all of which had VIP values > 1, suggesting that these BAs may be critical markers for differentiating patients with SAP from healthy individuals (Fig. 5).

ROC curve analysis of differential metabolites

ROC curves were plotted for the four identified differential metabolites—TCDCA, GCA, TDCA, and TCA—and their corresponding AUC values were calculated. As depicted in Fig. 6, TCDCA had the lowest AUC value (0.681), while TCA exhibited the highest AUC value (0.831), indicating that TCA possesses a higher diagnostic value compared to TDCA.

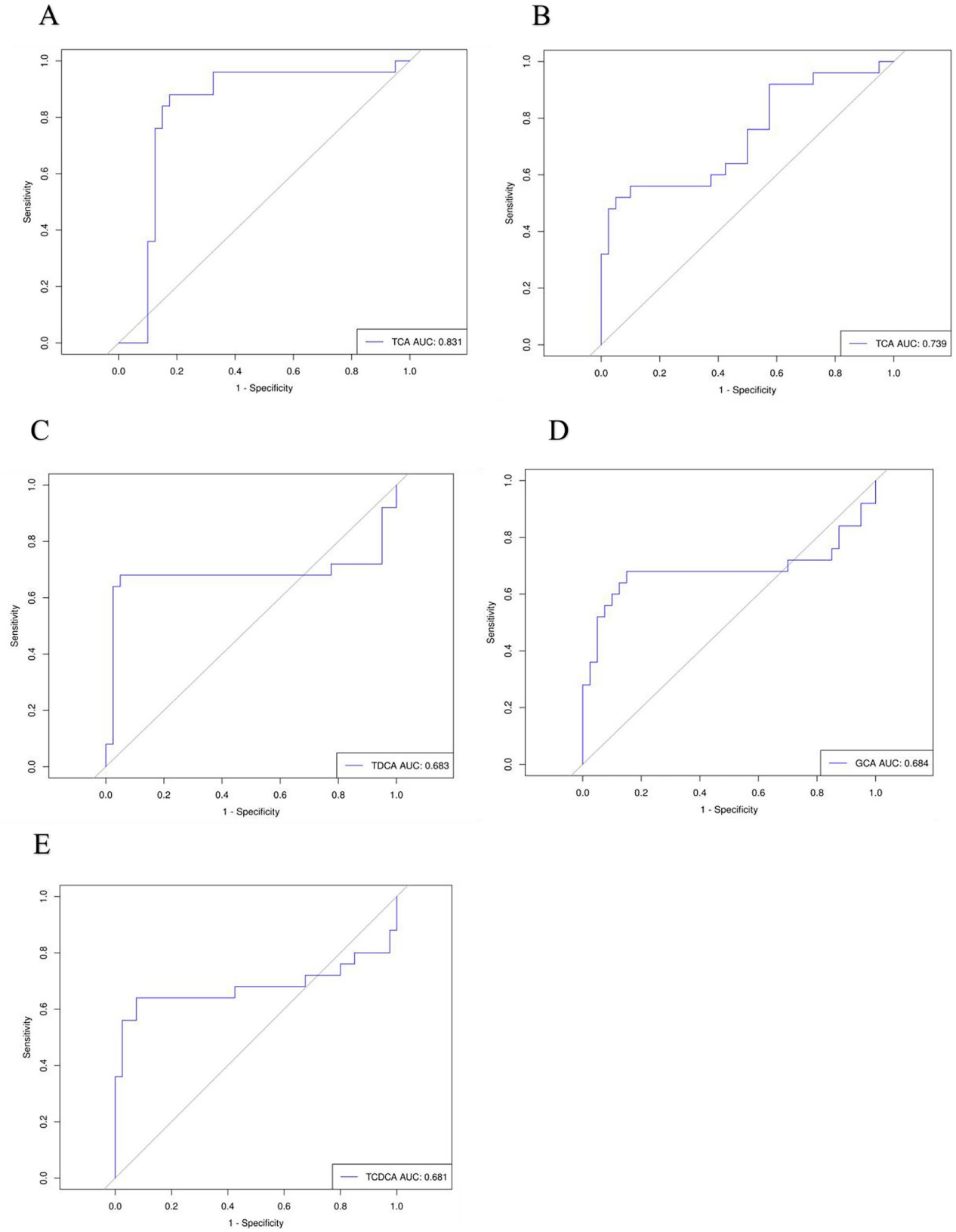

Fig. 6 ROC analysis of differential Bas. (**A**) ROC curve of TCA in the MSAP group; (**B**) ROC curve of TCA in the SAP group; (**C**) ROC curve of TDCA in the SAP group; (**D**) ROC curve of GCA in the SAP group; (**E**) ROC curve of TCDCA in the SAP group

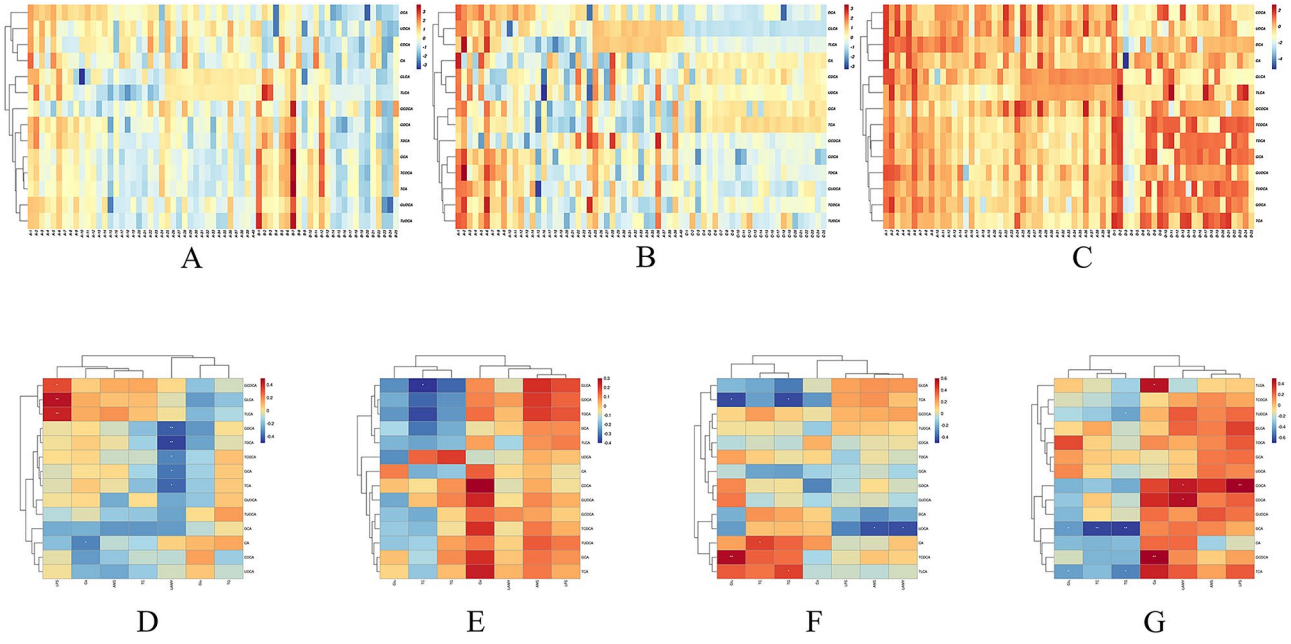

Fig. 7 Heatmap analyses of BA clustering and correlations with clinical indicators. (**A**) Clustering heatmap of control group vs. MAP group; (**B**) Clustering heatmap of control group vs. MSAP group; (**C**) Clustering heatmap of control group vs. SAP group; (**D**) Correlation heatmap of control group and clinical indicators; (**E**) Correlation heatmap of MAP group and clinical indicators; (**F**) Correlation heatmap of MSAP group and clinical indicators; (**G**) Correlation heatmap of SAP group and clinical indicators

Additionally, hierarchical clustering analysis was performed to examine the expression patterns of 14 BAs across different groups. The cluster heatmap analysis revealed no significant differences in BA expression between the control group and the MAP group. However, when compared to the MSAP group, TCA expression was higher in the control group. Furthermore, in the SAP group, the expression levels of TCDCA, GCA, TDCA, and TCA were notably elevated (Fig. 7A-C).

Correlation analysis between the laboratory indicators in the group

A correlation heatmap was used to visually assess the relationships between 7 laboratory indicators and 14 BAs across different study groups. Positive correlations are represented in red, while negative correlations are in blue, with color intensity and the number of asterisks indicating the strength of the correlation coefficient.

Control group

LPS exhibited a positive correlation with GCDCA, GLCA, and TLCA, with stronger correlations between LPS and GLCA or TLCA compared to LPS and GCDCA. Additionally, GDCA, TDCA, TCDCA, GCA, and TCA demonstrated negative correlations with urine amylase (UAMY), while CA exhibited a negative correlation with serum calcium levels.

Among patients with MAP, GLCA showed a negative correlation with total cholesterol (TC).

In patients with MSAP, TCDCA exhibited a positive correlation with serum glucose (Glu), TLCA revealed a positive correlation with serum triglycerides (TG), and CA was positively correlated with TC. Notably, TCDCA and Glu demonstrated a stronger correlation in this group compared to others. Additionally, TCA was negatively correlated with both Glu and TG, and UDCA demonstrated a negative correlation with amylase and UAMY.

In patients with SAP, TLCA and GCDCA were positively correlated with serum calcium levels, while GDCA and CDCA revealed positive correlations with UAMY. GDCA was positively correlated with LPS, with stronger correlations observed between GCDCA and serum calcium, as well as GDCA and LPS, in comparison to other groups. DCA exhibited negatively correlations with TC and TG, while TUDCA and TCA were negatively correlated with TG. Additionally, DCA and TCA exhibited negative correlations with Glu (Fig. 7D-G).

(Note: This section focuses on the positive correlations observed in the study)

Quality control measures

To ensure the reliability and validity of the study findings, the following quality control measures were implemented:

(1) Pre-Study Preparation: Prior to initiating the research, kick-off meetings and training sessions were conducted to ensure that all study personnel were

well-informed about the study objectives, methodologies, and expected outcomes.

(2) Representative Sample Selection: Efforts were made to ensure that the sample was representative of the target population, thereby enhancing the generalizability of the findings.

(3) Standardized Protocols: A detailed operations manual was provided to researchers, ensuring uniformity in experimental procedures and reducing methodological inconsistencies.

(4) Researcher Training: All study personnel received appropriate training to ensure adherence to the research protocol and accurate execution of research tasks.

(5) Standardized Data Collection: Validated data collection tools and standardized methodologies were employed to ensure data integrity and accuracy. A data management system was established to facilitate efficient data storage, management, and analysis.

(6) Robust Statistical Analysis: Appropriate statistical methods were utilized to analyze the data, with careful interpretation to avoid over-interpretation or misleading conclusions.

(7) Continuous Monitoring and Updates: Following study completion, ongoing monitoring of advancements in the field was conducted, with updates to methodologies and findings as necessary to maintain the study's relevance and scientific rigor.

Discussion

A review of the literature suggests that metabolomics holds significant potential in the early diagnosis, disease assessment, progression monitoring, and therapeutic guidance of AP. However, most prior studies in this field have been conducted either on animal models or have focused on comparisons between individuals with AP and those with healthy profiles, pancreatic cancer, or cholelithiasis. While these studies aimed to identify specific metabolic characteristics associated with pancreatitis, the application of metabolomics in the early diagnosis of AP remains underreported. Furthermore, limited research has been conducted on the metabolomic analysis of BA profiles in individuals with AP.

The present study addresses this research gap by conducting a targeted metabolomic analysis of serum samples from 150 participants, divided into four groups: MAP, MSAP, SAP, and a healthy control group. The analysis identified four key BAs—TCDCA, GCA, TDCA, and TCA—with TCA exhibiting a significant correlation with MSAP. These four metabolites demonstrated notable associations with SAP, suggesting their potential clinical relevance as biomarkers for assessing AP severity.

A more detailed discussion of the correlations between these four differential metabolites and different severities of AP is presented below.

There is a significant correlation between TCA and both MSAP and SAP. This result is consistent with the experimental work of Mengtao et al., who demonstrated that TCA concentration is closely associated with the extent of pancreatic injury [6, 7].

In the MAP group, GUDCA exhibited a negative correlation with TC. Based on previous studies, this relationship may be attributed to GUDCA's role in modulating intestinal microbiota composition, promoting the growth of beneficial bacteria and altering BA metabolism. Additionally, GUDCA has been reported to activate the TGR5 receptor in white adipose tissue, thereby enhancing lipid thermogenesis and improving glucose and lipid metabolism.

TCA is known to activate trypsinogen, which subsequently triggers the activation of various pancreatic enzymes, leading to pancreatic acinar cell damage and pathological changes such as hemorrhage and necrosis in pancreatic tissue. The observed correlation between TCA and both MSAP and SAP may be attributed to differences in pancreatic acinar cell death mechanisms and injury severity at varying TCA concentrations. Specifically, necrosis predominates in SAP, accompanied by severe inflammation, whereas apoptosis is more prevalent in MAP, which is associated with a milder inflammatory response [8].

Further insights into the role of TCA in AP were provided by gene expression profiling in a rat model of AP, where retrograde TCA injection into the pancreaticobiliary duct revealed that *F1lr* and *Cdh1* genes exhibited the highest frequency and significance. These genes are involved in calcium ion signaling and cell adhesion molecular pathways, both of which are critical in the progression of cellular apoptosis in SAP [9]. These pathways are critical in the progression of cellular apoptosis in SAP. Moreover, it has been reported that TCA stimulates the production of chemokine ligand 6 in hepatocytes under pathological conditions and induces the production of transforming growth factor-beta in Kupffer cells, which plays a significant role in promoting apoptosis in parenchymal cells [10, 11].

However, in this study, no significant correlation between TCA and MAP was identified. This result may be attributed to the limited sample size and the homogeneous nature of the study population, which could have influenced statistical power and variability in TCA levels.

The findings of this study indicate that TDCA, GCA, and TCDCA are significantly associated with SAP. This is consistent with the observations of Guixin et al., who reported that among seven BAs isolated from human bile, deoxycholic acid (DCA), TDCA, and TCA exhibited pronounced cytotoxic effects [12]. At lower concentrations, these BAs were found to induce apoptosis and necrosis, whereas at higher concentrations, they

primarily triggered necrosis, aligning with the pancreatic necrosis characteristic of SAP. However, in the present study, no significant differences in DCA and CDCA levels were observed between the groups, which may be attributed to the limited sample size.

TDCA has been reported to induce mitochondrial dysfunction by disrupting mitochondrial membranes, reducing mitochondrial membrane potential, and increasing the production of reactive oxygen species (ROS). These mechanisms contribute to enhanced inflammation and cellular apoptosis [13]. Furthermore, in a study by Rust et al., TDCA at a concentration of 50 μmol/L activated the phosphatidylinositol 3-kinase-dependent survival pathway in the McNtcp.24 hepatocyte cell line, leading to Bad phosphorylation, which ultimately transformed TDCA into a potential apoptosis inducer. Additional studies have demonstrated that TDCA can trigger apoptosis via activation of the caspase-9 pathway, initiating a caspase cascade, further supporting its role as a key promoter of pancreatic cell death [14].

GCA has also been identified as a key contributor to pancreatic necrosis. In a study by Xin et al., increased GCA concentrations were shown to promote spleen lymphocyte apoptosis both in vitro and in vivo by enhancing caspase-9 and caspase-3 activation [15]. These findings underscore the critical role of GCA in apoptosis induction.

Additionally, TCDCA has been demonstrated in previous studies to induce cellular apoptosis while also exerting anti-inflammatory effects by inhibiting the expression of pro-inflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor-alpha [16–18].

It is hypothesized that TDCA, GCA, TCDCA, and TCA mediate the production of various cytokines, which act through distinct apoptotic pathways to damage pancreatic acinar cells, contributing to the pathogenesis of SAP.

In contrast, TUDCA is generally regarded as a protective BA, known for its ability to inhibit apoptosis by stabilizing mitochondrial membranes [19]. TUDCA has also demonstrated a protective effect on pancreatic tissues. In in vivo rat models, TUDCA was shown to significantly reduce acinar cell damage and mitigate the toxic effects of CDCA on pancreatic ducts by preventing CDCA-induced mitochondrial dysfunction [20].

Recent findings suggest that TUDCA inhibits apoptosis through multiple mechanisms, including mitochondrial membrane stabilization, suppression of cytochrome-C release, and inhibition of caspase-9 activation [10]. Additionally, TUDCA has been reported to prevent Aβ-induced mitochondrial apoptosis by reducing ROS production, alleviating endoplasmic reticulum stress, and stabilizing the unfolded protein response [21].

Given these protective mechanisms, further research is warranted to investigate whether TUDCA could serve as a potential therapeutic agent for mitigating pancreatic cell damage and apoptosis in the context of SAP.

In this study, UPLC- was utilized to analyze serum samples from individuals with AP of varying severity, as well as healthy controls. The analysis revealed significant metabolic abnormalities in the AP groups, with TCDCA, GCA, TDCA, and TCA emerging as distinct metabolic biomarkers. These BAs demonstrated the potential to differentiate between patients with MSAP and SAP from those with MAP or healthy individuals. These findings suggest that TCDCA, GCA, TDCA, and TCA may serve as valuable indicators for the early diagnosis and severity assessment of AP.

Additionally, it is hypothesized that alterations in serum BA profiles may contribute to pancreatic tissue damage by influencing various apoptotic pathways in vivo. However, certain BAs, such as TUDCA, may counteract these effects by inhibiting apoptosis, potentially mitigating disease progression.

This study has several limitations that should be acknowledged. Firstly, its retrospective design introduces the possibility of selection bias, which may affect the generalizability of the findings. Secondly, the small sample size limits the statistical power of the study and may restrict the applicability of the results to a broader population. To further validate these findings and enhance their clinical relevance, prospective studies with larger sample sizes are necessary in future research.

Conclusion and future directions

The identification of specific serum BAs in individuals with AP presents a promising strategy for early, non-invasive, and accurate diagnosis. This approach not only offers a novel method for early detection but also provides a foundation for the development of future therapeutic targets in AP. Metabolomics has emerged as a valuable tool for identifying specific and sensitive biomarkers, which may aid in the early diagnosis and severity assessment of AP.

Additionally, targeting in vivo signaling pathways could modulate disease progression, prevent further deterioration, and improve patient outcomes. Future research is expected to utilize targeted metabolomics technology to analyze BA profile alterations, elucidate the molecular pathways involved in AP onset and progression, and establish a theoretical basis for improved diagnostic and therapeutic strategies. Ultimately, these advancements may contribute to better prognosis and clinical management for individuals affected by AP.

Abbreviations

MAP	Mild acute pancreatitis
MSAP	Moderate severe acute pancreatitis

SAP	Severe acute pancreatitis
AP	Acute pancreatitis
UPLC-HRMS	Ultra performance liquid chromatography-high resolution mass spectrometry
CA	Cholic acid
TLCA	Taurolithocholic acid
GLCA	Glycolithocholic acid
GCA	Glycocholic acid
TCA	Taurocholic acid
DCA	Deoxycholic acid
CDCA	Chenodeoxycholic acid
UDCA	Ursodeoxycholic acid
GDCA	Glycodeoxycholic acid
GCDCA	Glycochenodeoxycholic acid
GUDCA	Glycoursodeoxycholic acid
TDCA	Taurodeoxycholic acid
TCDCA	Taurochenodeoxycholic acid
TUDCA	Tauroursodeoxycholic acid
UAMY	Urine amylase
LPS	Serum lipase
PCA	Principal component analysis
OPLS-DA	Orthogonal partial least squares-discriminant analysis
VIP	Variable important in projection
AUC	Area under the curve

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Author contributions
Lu Liang and Bihui Yao conceived the idea and conceptualised the study. Chunliang Guo and Lei Song collected the data. Chunliang Guo and Lei Song analysed the data. Chunliang Guo and Bihui Yao did statistical analysis. Lu Liang obtaiined the funding. Chunliang Guo and Wen Yong drafted the manuscript, then Lu Liang and Wen Yong reviewed the manuscript. All authors read and approved the final draft.

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Data availability
All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
This study was conducted with approval from the Ethics Committee of Baotou Central Hospital (Approval number is KYLL2021-006). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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