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Retrospective Cohort Study

Analysis of metabolic characteristics of metabolic syndrome in elderly patients with gastric cancer by non-targeted metabolomics

Huan Zhang, Wen-Bing Shen, Lin Chen

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Abstract

BACKGROUND

The relationship between metabolic syndrome (MetS) and gastric cancer (GC), which is a common metabolic disease, has attracted much attention. However, the specific metabolic characteristics of MetS in elderly patients with GC remain unclear.

AIM

To investigate the differentially abundant metabolites and metabolic pathways between preoperative frailty and MetS in elderly patients with GC based on non-targeted metabolomics techniques.

METHODS

In this study, 125 patients with nonfrail nonmeal GC were selected as the control group, and 50 patients with GC in the frail group were selected as the frail group. Sixty-five patients with GC combined with MetS alone were included in the MetS group, and 50 patients with GC combined with MetS were included in the MetS group. Nontargeted metabolomics techniques were used to measure plasma metabolite levels by ultrahigh-performance liquid chromatography-mass spectrometry. Multivariate statistical analysis was performed by principal component analysis, orthogonal partial least squares, pattern recognition analysis, cluster analysis, and metabolic pathway annotation.

RESULTS

A total of 125 different metabolites, including amino acids, glycerophospholipids,

sphingolipids, fatty acids, sugars, nucleosides and nucleotides, and acidic compounds, were identified *via* nontargeted metabolomics techniques. Compared with those in the control group, there were 41, 32, and 52 different metabolites in the MetS group, the debilitated group, and the combined group, respectively. Lipid metabolites were significantly increased in the MetS group. In the weak group, amino acids and most glycerol phospholipid metabolites decreased significantly, and fatty acids and sphingosine increased significantly. The combined group was characterized by significantly increased levels of nucleotide metabolites and acidic compounds. The alanine, aspartic acid, and glutamate metabolic pathways were obviously enriched in the asthenic group, and the glycerol and phospholipid metabolic pathways were obviously enriched in the combined group.

CONCLUSION

Elderly GC patients with simple frailty, simple combined MetS, and frailty combined with MetS have different metabolic characteristics, among which amino acid and glycerophospholipid metabolite levels are significantly lower in frail elderly GC patients, and comprehensive supplementation of fat and protein should be considered. Many kinds of metabolites, such as amino acids, lipids, nucleotides, and acidic compounds, are abnormally abundant in patients with MetS combined with fthenia, which may be related to tumor-related metabolic disorders.

Key Words: Nervous breakdown; Metabolic syndrome; Elderly individuals; Gastric cancer; Nontargeted metabolomics

Core Tip: Nontargeted metabolomics techniques were used to systematically analyze the metabolic characteristics of metabolic syndrome (MetS) in elderly patients with gastric cancer (GC). By comparing metabolomic data, we explored the unique metabolic characteristics of MetS in patients with GC and identified potential biomarkers and metabolic pathways. This study combined metabolomics technology with the study of MetS in elderly patients with GC, providing a new perspective and theoretical support for the diagnosis and treatment of elderly patients with GC.

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INTRODUCTION

Frailty and metabolic syndrome (MetS) are common health problems in elderly individuals and can contribute to poor prognosis in cancer patients as a result of disease burden[1]. Previous studies have shown that the two may be closely related at the level of pathogenesis, but the mechanism of stage decline is still unclear[2-4]. Research shows that the pathogenesis of frailty may involve the pathogenesis of endocrine disorders, inflammatory reaction enhancement, immune dysfunction, metabolic imbalance, oxidative stress damage, and other systems, and each system is interrelated[5, 6]. In addition, because cancer itself is a metabolic disease, tumor cells can change metabolic pathways, resulting in metabolic reprogramming, a unique metabolic state, and the formation of cells different from those of normal cells and the surrounding tissue microenvironment[7]. In this setting, the associations between Deicht's sign and diabetes and between elderly MetS patients with gastric cancer (GC) are unclear[8]. Metabolomics can be used to conduct a comprehensive analysis of the body's small-molecule metabolites to determine the final results of interactions between the genome and the environment at the individual level and has important value in the health management of cancer patients [9-11].

Therefore, this study analyzed the metabolic characteristics of individuals with frailty and MetS, as well as potential pathways of action, based on nontargeted metabolomics detection techniques and elucidated their significance in monitoring preoperative nutritional metabolism, determining intervention targets, and formulating precise frailty management programs.

MATERIALS AND METHODS

Clinical data analysis

A total of 290 elderly patients with GC admitted to the Department of General Surgery of our hospital from August 2022 to August 2023 were selected as the study subjects. Inclusion criteria: (1) Aged 65-80 years old, GC was diagnosed by gastroscopy and computed tomography; (2) Radical gastrectomy was performed for the first time; and (3) Clear mind, able to carry out simple written and verbal communication. Exclusion criteria: (1) Unable to complete the study due to a serious physical illness, cognitive impairment, or mental illness; (2) Suffering from serious infectious diseases; (3)

Combined with other sites of tumor; (4) Serious cardiovascular and cerebrovascular diseases: Liver, kidney, and lung insufficiency; (5) Metal medical devices are installed in the body; (6) Taking drugs that affect the measurement of body composition; and (7) Received neoadjuvant therapy before the operation.

According to the diagnosis, 125 patients with nonfrail and non-MetS GC were selected as the control group, and 50 patients with frailty alone were selected as the frailty group. Sixty-five patients with GC combined with MetS alone were included in the MetS group, and 50 patients with GC combined with MetS were included in the combined group. The Fried Frailty Phenotype Scale was used to measure frailty, and the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2023 Edition) were used as the diagnostic criteria for MetS. All the subjects volunteered to participate in this study and signed informed consent forms. The Ethics Review Committee of Shanghai Sixth People's Hospital reviewed and approved this study (No: GYZL-048).

Instrument and test agent

The main instruments used included a high-resolution mass spectrometer (QExactiveHFX), an ultrahigh-pressure liquid chromatograph (Vanquish, Thermo Fisher Scientific), a centrifuge (Heraeus Fresco17, Thermo Fisher Scientific), a balance (BSA124S-CW, Sartorius), and an ultrasonic instrument (PS-60AL, Red Bang, Shenzhen). The main reagents included methanol, acetonitrile, ammonium acetate, ammonia water, and ultrapure water.

Data collection

Age, sex, body mass index (BMI), comorbidities, number of drugs taken (multiple drug use was defined as taking ≥ 4 drugs at the same time), risk screening table 2002 (NRS2002), smoking history, alcohol consumption history, and tumor-node-metastasis tumor data were collected, as were stage, waist circumference, and other clinical data.

Sample collection and pretreatment

After fasting for 12 h, the patient was asked to collect 5 mL of peripheral blood from the median cubit vein in the early morning on an empty stomach. The blood and the anticoagulant EDTA were placed in the collection vessel, the blood and the anticoagulant were mixed, the serum was centrifuged at 4 °C at 1300 × *g* for 10 min to separate the serum, and the specimens were frozen at -80 °C. During the test, 100 μL of each specimen was frozen at room temperature, and the sample was transferred to an EP tube. Then, 400 μL of extraction liquid [methanol:acetonitrile = 1:1 (v/v), containing an internal standard mixture of isotope labels] was added, and the sample was centrifuged at 4 °C (12000 r/min, 15 min). The supernatant was transferred to a sample bottle for testing by a machine. The same amount of supernatant was mixed into the QC samples for testing.

Conditions for the analysis of plasma samples

The target compounds were separated by ultrahigh-performance liquid chromatography using a Waters ACQUITY UPLC BEH Amide (2.1 mm × 100 mm, 1.7 μm) liquid chromatographic column. The liquid phase color spectrum phase A was the water phase, containing 25 mmol/L ammonium acetate and 25 mmol/L ammonia water; phase B was acetonitrile. The sample plate temperature was 4 °C, and the injection volume was 2 μL. The high-resolution mass spectrometer can be controlled by the control software (Xcalibur, Thermo) for first- and second-stage mass spectrum data acquisition. The detailed parameters are as follows: Sheath gas flow rate of 30 Arb, auxiliary air flow rate of 25 Arb, capillary temperature of 350 °C, total ms resolution rate of 120000, ms/ms resolution rate of 7500, impact energy NCE mode of 10/30/60, and spray voltage of 3.6 kV (+) or -3.2 kV (-).

Principal component analysis

Principal component analysis (PCA) and orthogonal partial least squares pattern recognition analysis (OPLS-DA) were performed using SIMCA software (version 16.0.2, Sartorius Ste-Dim Data Analysis Company, Sweden). A projected importance of variables (VIP) > 1.0 and $P < 0.05$ were used as criteria to screen for differentially abundant metabolites, and the pathways where the differentially abundant metabolites were located were comprehensively analyzed to further identify the key pathways with the highest correlation with the metabolites.

Statistical management and analysis

SPSS 26.0 statistical software was used for data processing and analysis. Normally distributed data are expressed as mean ± SD, and ANOVA was used for comparisons among groups. Count data are expressed as frequencies or percentages, and the χ^2 test was used for comparisons between groups. A difference for which $P < 0.05$ was considered statistically significant. After the original test data were converted into mzXML format by Pro-teoWizard software, the R program package (whose kernel is XCMS) was used for peak identification, peak extraction, peak alignment, and integration. Then, the data were matched with the BiotreeDB (V2.1) self-built two-stage mass spectrometry data library for material annotation, and the original data were preprocessed by deviation filtering, missing value filtering, missing value filling, and data standardization.

RESULTS

Comparison of baseline data in each group

The age of the frail group was significantly greater than that of the control group ($P < 0.05$). The BMI and incidence of

comorbidities in the MetS group and comorbidity group were significantly greater than those in the control group ($P < 0.05$). There was no significant difference in other baseline data among all groups ($P > 0.05$) (Table 1).

Results of multivariate statistical analysis

The results of PCA showed that the interpretative values (R2X) of x variation in the MetS group and control group, the Fadroit group and control group, and the combined group and control group were 0.501, 0.526, and 0.520, respectively, indicating that the prediction rate of each group could reach 50.1%, 52.6%, and 52.0%, respectively. In addition, the number of principal components among the three groups was 6, and there were significant differences in biological metabolism among all groups, as shown in Figure 1. On this basis, OPLS-DA was performed, and the results showed that the separation between the two samples in the three groups was good, and there were obvious differences in metabolite profiles, as shown in Figure 2. The fit (R2Y) and prediction (Q2) of the MetS group and control group, the Faddy group and control group, and the combined group and control group were 0.953 and 0.109, 0.922 and 0.193, 0.891 and 0.185, respectively.

Intergroup differentially abundant metabolite screening

In this study, the card value criterion was $P < 0.05$ for the T test and VIP > 1.0 for the first principal component of the OPLS-DA model. We chose the compounds based on the secondary mass spectrum fragment information of the metabolites and then looked for the total differential heterometabolites in both the positive and negative dissociative submodes. Compared with those in the control group, a total of 41 metabolites with significant differences were detected in the MetS group, mainly involving amino acids ($n = 7$), lipids (9 glycerolipids, 1 sphingolipid, 6 fatty acids), and sugars ($n = 6$). Most lipid metabolites were significantly upregulated, while most other metabolites were significantly downregulated.

A total of 32 metabolites with significant differences were detected in the asthenic group, mainly involving amino acids ($n = 5$) and lipids (10 glycerophospholipids, 1 sphingolipid, and 6 fatty acids). Among them, sphingolipid metabolites such as sphingosine and arachidonic acid, succinic semialdehyde, myristic acid, α-linoleic acid, 10E, 12Z-linoleic acid, and five fatty acid metabolites were significantly upregulated. There was a large decrease in five amino acids, namely, arginine, n-acetylvaline, D-citrulline, L-valine, L-aspartamide, and most phospholipid metabolites.

A total of 52 metabolites with significant differences were detected in the combined group, including amino acids ($n = 9$), lipids (5 glycerolipids, 3 sphingolipids, and 5 fatty acids), nucleosides and nucleotides ($n = 7$), sugars ($n = 2$), and acidic compounds ($n = 6$). Among these metabolites, 5 nucleotides, such as pseudouridine, n-acetylcytosine nucleoside, orioside, and 4 acidic compounds, such as dopamine-3-o-sulfate, were significantly upregulated. Sphingosine was a common feature in both the weak group and the combined group. According to the VIP values, the top 10 metabolites in each group are shown in Tables 2-4.

Analysis of metabolic pathways for differentially abundant metabolites

The chosen different metabolites were put into the Kyoto Encyclopedia of Genes and Genomes metabolic pathway database so that metabolic pathway enrichment analysis could be performed. With an impact > 0.1 and $P < 0.05$ as the criteria, three groups of differentially abundant metabolites were selected. Compared with those in the control group, there were no obvious metabolic pathways in the MetS group, and the differentially abundant metabolites in the fthenic group were mainly related to the alanine, aspartate, and glutamate metabolic pathways, while the differentially abundant metabolites in the combined group were mainly related to glycerophospholipid metabolic pathways, as shown in Table 5.

DISCUSSION

In this study, we investigated the differentially abundant metabolites and metabolic pathways in the debilitated, MetS, and combined groups based on nontargeted ultrahigh-performance liquid chromatography and mass spectrometry in nondebilitated, non-MetS patients[12]. Compared with those in the control group, the levels of lipid metabolites such as glycerophospholipids were significantly greater in the MetS group. In the weak group, amino acid metabolites such as D-citrullinic acid, L-valine, L-asparagine, and most glycerol phospholipids decreased significantly, and fatty acids such as myristic acid, α-linolenic acid, and phytosphingosine increased significantly[13-15]. In the combined group, the levels of pseudouridine, n-acetylcytidine, whoridin, and other nucleotide metabolites and acidic compounds were significantly increased. The alanine, aspartic acid, and glutamate metabolic pathways were obviously enriched in the asthenic group, and the glycerol phospholipid pathway was obviously enriched in the combined group[16].

Amino acid metabolism is the central component of protein decomposition and plays an important role in the activation and function of immune cells in the tumor microenvironment[17]. Compared with those in the control group, the five amino acids arginylalanine, n-acetylvaline, D-citrulline, L-valic acid, and L-aspartamide in the frail group decreased significantly, which was related to the decrease in muscle mass or strength during the frailty process[18-20]. Based on the MetaboFrail project in Europe, 37 kinds of amino acids were measured in patients with asthenic diabetes and in the asthenic control population, and the specific amino acid metabolism characteristics of elderly patients with asthenic diabetes were revealed[21]. Amino acids such as glutamine, glutathione, n-acetyl-l-alonic acid, n-valeric acid, and (S)-β-aminoisobutyric acid, which produced significant metabolic changes in the combined group, have been found to be related to tumor initiation, development, treatment, and predensitization[22]. Previous studies have focused on tumor-related metabolic differences in patients with frailty and MetS to reveal their amino acid metabolic patterns[23-25]. Reprogramming lipid metabolism is one of the important characteristics of tumor metabolism. Tumor cells can

Table 1 Comparison of baseline data among groups, mean ± SD or *n* (%)

Group	Control group	Frailty group	MetS group	Merging group
N	125	50	65	50
Age (yr)	66.76 ± 5.16	73.30 ± 5.94[a]	67.08 ± 4.89	68.90 ± 6.33
BMI (kg/m^2)	22.88 ± 2.10	22.48 ± 2.00	25.15 ± 3.15[a]	26.33 ± 3.33[a]
Female	7 (28.0)	4 (40.0)	4 (30.8)	5 (50.0)
Complication	10 (40.0)	7 (70.0)	13 (100.0)[a]	9 (90.0)[a]
Polypharmacy	1 (4.0)	0 (0.0)	3 (23.1)	1 (10.0)
NRS2002 ≥ 3	7 (28.0)	2 (20.0)	3 (23.1)	2 (20.0)
TNM III	9 (36.0)	5 (50.0)	4 (30.8)	7 (70.0)

[a]$P < 0.05$.

MetS: Metabolic syndrome; BMI: Body mass index; TNM: Tumor-node-metastasis.

Table 2 Differentially abundant metabolite information between metabolic syndrome group and control group

MS2	MS2	Ingredient	VIP	Difference multiple	*P* value
Ribothymidine	0.977184462	5-liter urine test	2.875235598	0.853099352	0.001
LysoPC[20:3(5Z,8Z,11Z)]	0.431478462	Glycerophospholipids	2.617379975	1.316226543	0.003
Sucrose	0.587560154	Sucrose	2.505082856	0.294077555	0.009
2-methylglutaric acid	0.868639769	2-methylglutaric acid	2.492929728	0.880090096	0.007
PC 22:5(4Z,7Z,10Z,13Z,16Z)	0.761099923	Glycerophospholipids	2.430802959	1.197463285	0.010
PC 22:2(13Z,16Z)/16:1(9Z)	0.814371846	Glycerophospholipids	2.419402577	1.372234468	0.003
B-alanine	1.000000000	β monoalanine	2.387846925	1.191057245	0.011
Orotidine	0.755108923	Orotidine	2.385776400	1.285397754	0.004
PC[P-18.1(11Z)/14:0]	0.724108077	Glycerophospholipids	2.37334905	0.672678582	0.009
2-benzylbutanediaic acid	0.671941538	A-benzylsuccinic acid	2.309647568	0.601709013	0.021

VIP: Projected importance of variables.

increase the intake and oxidation of fatty acids to produce energy and lipid accumulation, and abnormal fatty acid metabolism can affect tumor occurrence and development[26]. Most glycerol phospholipid metabolites were significantly downregulated in the asthenic group, but sphingosine, a sphingolipid metabolite, was significantly increased[27]. This was also true for the combined group and the asthenic group. The results of animal experiments showed that sphingosine was positively correlated with aging in rats, suggesting a metabolic correlation between the weak group and the combined group at the aging level. The results of the Dixie pathway analysis showed that the Dixie pathway in the Hehe group was obviously enriched[28]. Although the Dixie pathway in the Hehe group had the characteristics of weakness and MetS at the same time as the clinical diagnosis or evaluation index level, its fat metabolism characteristics were different from those in the other two groups[29]. Researchers need to note the status of lipid depletion in this population to confirm the prognosis based on prospective studies.

Nucleotide metabolism is considered to be the most critical link between tumorigenesis and tumor cell replication. Studies have shown that the polymerase activity of DNA and RNA synthesis in tumor tissues is greater than that in normal tissue, nucleotide synthesis is increased, and decomposition is reduced[30-32]. As a result, nucleotide metabolites are upregulated in the cancer state to meet the uncontrolled and rapid self-growth needs of tumor cells. The changes in nucleotide metabolites in the combined group in which pseudouridine and n-acetyl cytoridinucleate were upregulated and 5-methylcytosine was downregulated have been found to be closely related to cancer diagnosis, tumor invasion and metastasis, treatment, and prognosis[33]. This finding indicates that the metabolic abnormalities in the combination group are often more affected by the tumor cells themselves, and further attention should be given to tumor-related clinical indicators and treatment prognosis[34]. In addition, an imbalance in the acid-base balance in the body is also an important factor causing metabolic differences. For example, an acidic environment enhances the pantothenic acid-mediated albumin degradation pathway, weakens the signaling pathway related to muscle biosynthesis, and eventually leads to an increase in muscle protein dissociation[35]. Acidosis is one of the basic characteristics of the tumor tissue

Table 3 Differentially abundant metabolite information between the frail group and the control group

MS2	MS2	Ingredient	VIP	Difference multiple	*P* value
Phytosphingosine	0.454496692	Phytosphingosine	3.657534241	1.294323976	4.96942×10^{-5}
Ethylbenzene	0.999986538	Ethyl benzene	2.933313807	0.779138228	3.49882×10^{-5}
Arginyl-Aanin	0.538666308	Arginine monoalanine	2.637262363	0.670807534	9.32837×10^{-5}
Beta-D-glucosamine	0.479228462	3-D-glucosamine	2.523529662	1.706788545	0.040552211
2.3-dimethy1-2-cydohexen-1	0.583867615	Ketones	2.426992074	0.745005971	0.003652162
N-Acetylvaline	0.523245077	N-acetyl-DL-valine	2.425756767	0.548096577	6.01189×10^{-5}
Alpha-dimorphecolic acid	0.979338000	Fatty acids	2.422824991	0.591828042	0.01624548
Arachidonic acid	0.626860308	Arachidonic acid	2.41783857	1.448871331	0.006223154
D-citrulline	0.996183538	D-citrulline	2.354091235	0.738050459	0.014028588
Succinic acid semialdehyde	0.973268385	Succinic acid	2.310730757	1.414979613	0.045517081

VIP: Projected importance of variables.

Table 4 Differentially abundant metabolite information between the merged group and the control group

MS2	MS2	Ingredient	VIP	Difference multiple	*P* value
2-aminoacetophenone	1.000000000	Aromatic compounds	2.961804513	2.196907422	0.015884556
Alpha-N-phenylacetyl	0.999461308	A-N-phenylacetyl	2.922737465	2.928594266	0.015713599
Arginyl-alaninr	0.538666308	Argininylalanine	2.870719541	0.577806767	0.000093284
Pseudouridine	0.761171308	pseudouridine	2.654758398	1.209468419	0.010376873
N-methylnicotinamide	0.695534769	N-methylnicotinamide	2.596565350	0.436187388	0.023415222
Dopamine 3-O	0.583639154	Dopamine 3-O-monosulfate	2.508348482	1.474559460	0.045180328
Choline	1.000000000	Choline	2.485758030	0.874659513	0.004134701
N4-acetylcytidine	0.990193846	N-acetylcytosine nucleoside	2.485751726	1.458921122	0.001565543
N-acetyl-L-alanine	0.907531231	N-acetyl-L-alanine	2.462896266	1.145011518	0.020139388
Bliverdin	0.981282462	Biliverdin	2.445197302	0.489904504	0.003203639

VIP: Projected importance of variables.

degradation environment and is manifested by acidic, alkaline intracellular and extracellular microenvironments. One metabolic trait that differed between the combined group and the other groups was a significant increase in several acidic compounds[36]. This may be because the tumors in the combined group were in a later stage. An acidic extracellular environment can increase the expression of cholesterol synthase, which is conducive to the growth of tumor cells and reduces the survival rate of tumor patients. Therefore, improving the prognosis of patients with tumors by regulating the tumor microenvironment is also an important way to regulate metabolism.

The results of this study showed that, compared with those in the control group, the alanine, aspartate, and glutamate metabolic pathways were significantly enriched in the asthenic group, and the glycerophosphoripid depletion pathway in the combined group was significantly enriched. Liu *et al*[37] performed a secondary analysis using MAPT research data. They found differences between age-related frailty and disease-related frailty in terms of clinical features. They then suggested that different strategies for preventing and managing frailty should be used based on these differences. This suggests that although the existing assessment tools can clearly distinguish between asthenia and nonasthenia, they can only identify the clinical manifestations that have occurred and cannot reflect the pathological and biological processes related to weak decay, and the same phenotype corresponds to different etiologies and disease development mechanisms. Even if the same intervention is given, the results will vary. In the future, it will be possible to explore the age-related decline in amino acids or fatty dioxins. For the development of disease-related debilitation populations, specific metabolic regulation measures should be formulated.

Table 5 Key metabolic pathways and metabolites in each group

Group	Route	Hits	Impact	*P* value
MetS group	Fructose and mannose metabolism	Sorbitol, mannitol	0.00887	0.0076735
	Galactose metabolism	Sorbitol	0.000.00	0.113450.0
	Metabolism of glyoxylates and dicarboxylates	Glycollic acid	0.00686	0.1368100
	Arachidonic acid metabolism	Arachidonic acid	0.21669	0.1671500
Frailty group	Metabolism of alanine, aspartic acid, and glutamic acid	L-aspartic acid and succinic acid semialdehyde	0.10256	0.0069520
	Vitamin B metabolism	Pyridomide, succinic acid semialdehyde	0.00000	0.0121920
	Biotin metabolism	Biotin	0.20325	0.0579490
	Metabolism of methyl butyrate	Succinic acid semialdehyde	0.03343	0.1962000
	Arachidonic acid metabolic pathway	Succinic acid semialdehyde	0.21669	0.2883000
Merging group	Glycerophospholipid metabolism	Choline, ethanolamine phosphate, glycerophosphatidylcholine	0.10234	0.0037066
	Sphingolipid metabolism	Plant sphingosine and ethanolamine phosphate	0.01288	0.0175530
	Glutathione metabolism	Glutathione	0.23743	0.2735200
	Starch and sucrose metabolism	Trehalose	0.00944	0.3439500
	Porphyrin and chlorophyll metabolism	Biliverdin	0.01844	0.5880900

MetS: Metabolic syndrome.

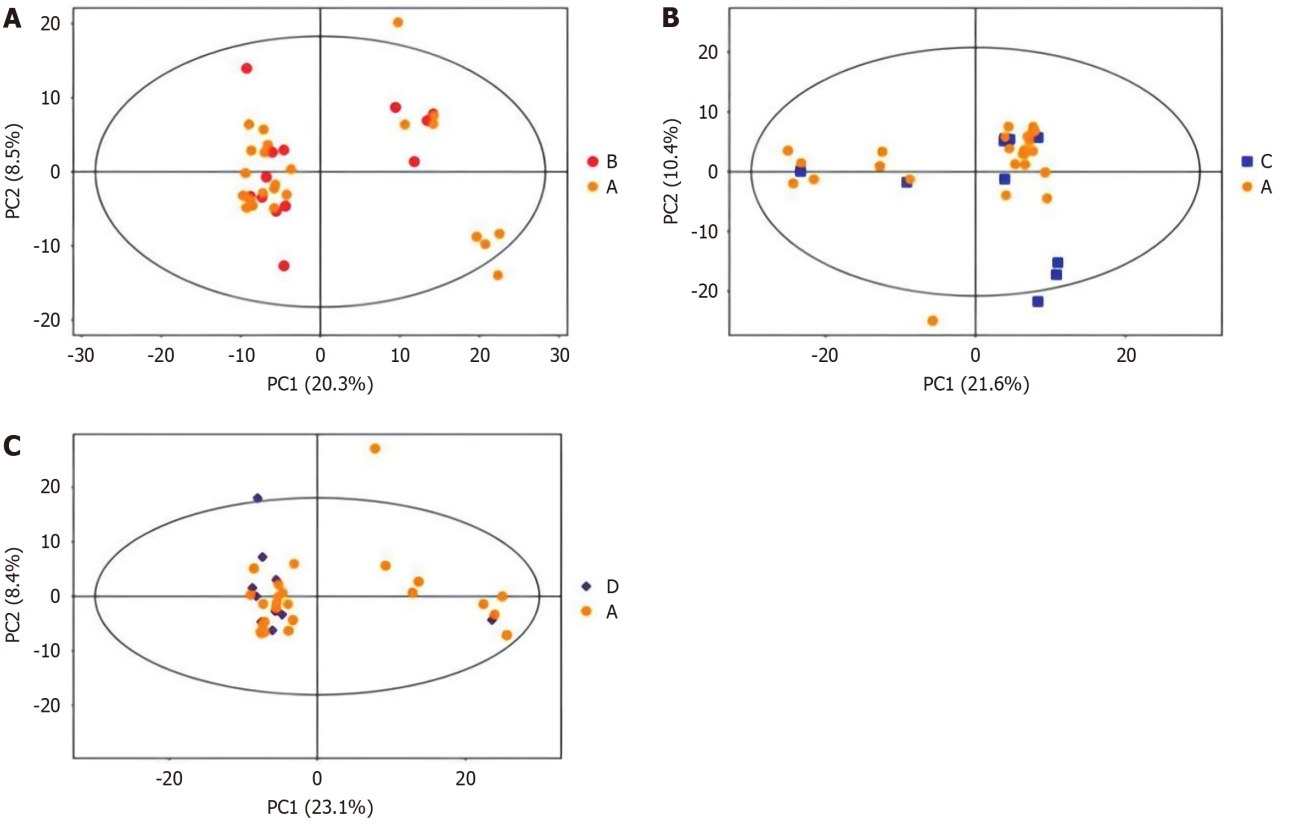

Figure 1 Principal component analysis graph analysis. A: Metabolic test sample-1; B: Metabolic test sample-2; C: Metabolic test sample-3.

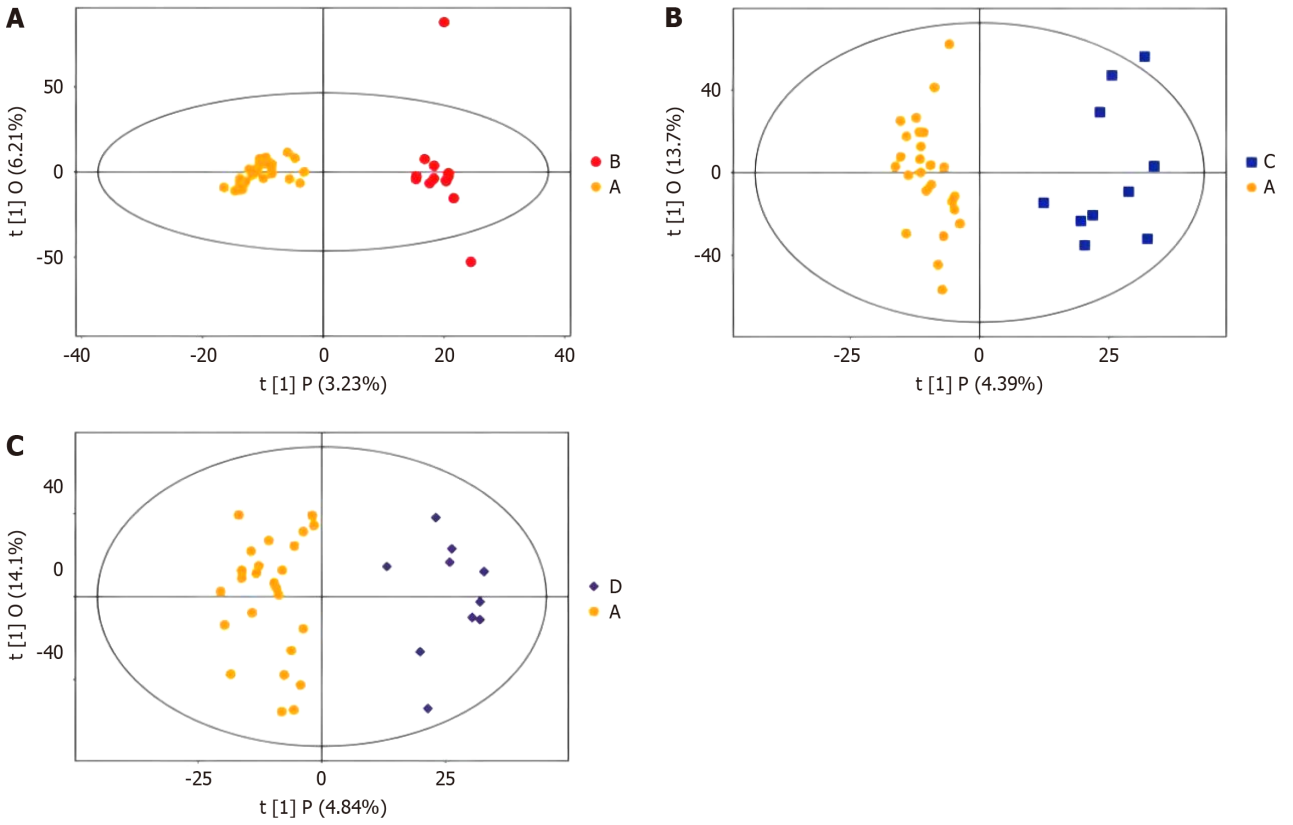

Figure 2 Orthogonal partial least squares pattern recognition analysis score scatter plot. A: Metabolic test sample-1; B: Metabolic test sample-2; C: Metabolic test sample-3.

CONCLUSION

Elderly patients with weakened GC have significantly upregulated fatty acid metabolites and significantly downregulated amino acid and glycerophospholipid metabolites, whereas elderly patients with MetS have significantly upregulated lipid metabolites. Many metabolites, such as amino acids, lipids, nucleotides, and acidic compounds, are abnormal in patients with fthenia complicated with MetS, which may be related to tumor-related metabolic disorders. Those who do not come to study need to note the different etiologies and disease development mechanisms corresponding to the same weak phenotype and provide targeted and targeted debilitating interventions. However, the sample included in this study was small, the data were not predictive enough, and the generalizability of the findings was limited. In the future, it will still be necessary to verify the results of this study based on large samples of blood test data.

FOOTNOTES

Author contributions: Zhang H wrote the manuscript; Shen WB collected the data; Chen L guided the study; and all authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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REFERENCES

1 **Sun C**, Wang A, Zhou Y, Chen P, Wang X, Huang J, Gao J, Shu L, Lu J, Dai W, Bu Z, Ji J, He J. Spatially resolved multi-omics highlights cell-specific metabolic remodeling and interactions in gastric cancer. *Nat Commun* 2023; **14**: 2692 [PMID: 37164975 DOI: 10.1038/s41467-023-38360-5]

2 **Zhang B**, Wang CM, Wu HX, Wang F, Chai YY, Hu Y, Wang BJ, Yu Z, Xia RH, Xu RH, Cao XT. MFSD2A potentiates gastric cancer response to anti-PD-1 immunotherapy by reprogramming the tumor microenvironment to activate T cell response. *Cancer Commun (Lond)* 2023; **43**: 1097-1116 [PMID: 37539769 DOI: 10.1002/cac2.12476]

3 **Huang S**, Guo Y, Li ZW, Shui G, Tian H, Li BW, Kadeerhan G, Li ZX, Li X, Zhang Y, Zhou T, You WC, Pan KF, Li WQ. Identification and Validation of Plasma Metabolomic Signatures in Precancerous Gastric Lesions That Progress to Cancer. *JAMA Netw Open* 2021; **4**: e2114186 [PMID: 34156450 DOI: 10.1001/jamanetworkopen.2021.14186]

4 **Wang J**, Kunzke T, Prade VM, Shen J, Buck A, Feuchtinger A, Haffner I, Luber B, Liu DHW, Langer R, Lordick F, Sun N, Walch A. Spatial Metabolomics Identifies Distinct Tumor-Specific Subtypes in Gastric Cancer Patients. *Clin Cancer Res* 2022; **28**: 2865-2877 [PMID: 35395077 DOI: 10.1158/1078-0432.CCR-21-4383]

5 **Dai D**, Yang Y, Yu J, Dang T, Qin W, Teng L, Ye J, Jiang H. Interactions between gastric microbiota and metabolites in gastric cancer. *Cell Death Dis* 2021; **12**: 1104 [PMID: 34819503 DOI: 10.1038/s41419-021-04396-y]

6 **Wu L**, Zheng Y, Liu J, Luo R, Wu D, Xu P, Li X. Comprehensive evaluation of the efficacy and safety of LPV/r drugs in the treatment of SARS and MERS to provide potential treatment options for COVID-19. *Aging (Albany NY)* 2021; **13**: 10833-10852 [PMID: 33879634 DOI: 10.18632/aging.202860]

7 **Yuan Q**, Deng D, Pan C, Ren J, Wei T, Wu Z, Zhang B, Li S, Yin P, Shang D. Integration of transcriptomics, proteomics, and metabolomics data to reveal HER2-associated metabolic heterogeneity in gastric cancer with response to immunotherapy and neoadjuvant chemotherapy. *Front Immunol* 2022; **13**: 951137 [PMID: 35990657 DOI: 10.3389/fimmu.2022.951137]

8 **Shi WB**, Wang ZX, Liu HB, Jia YJ, Wang YP, Xu X, Zhang Y, Qi XD, Hu FD. Study on the mechanism of Fufang E'jiao Jiang on precancerous lesions of gastric cancer based on network pharmacology and metabolomics. *J Ethnopharmacol* 2023; **304**: 116030 [PMID: 36563889 DOI: 10.1016/j.jep.2022.116030]

9 **Ursu Ş**, Ciocan A, Ursu CP, Gherman CD, Ciocan RA, Pop RS, Spârchez Z, Zaharie F, Al Hajjar N. Role of Metabolomics in Pathogenesis and Prompt Diagnosis of Gastric Cancer Metastasis-A Systematic Review. *Diagnostics (Basel)* 2023; **13** [PMID: 37998537 DOI: 10.3390/diagnostics13223401]

10 **Wu L**, Zhong Y, Wu D, Xu P, Ruan X, Yan J, Liu J, Li X. Immunomodulatory Factor TIM3 of Cytolytic Active Genes Affected the Survival and Prognosis of Lung Adenocarcinoma Patients by Multi-Omics Analysis. *Biomedicines* 2022; **10** [PMID: 36140350 DOI: 10.3390/biomedicines10092248]

11 **Nabavi-Rad A**, Yadegar A, Sadeghi A, Aghdaei HA, Zali MR, Klionsky DJ, Yamaoka Y. The interaction between autophagy, Helicobacter pylori, and gut microbiota in gastric carcinogenesis. *Trends Microbiol* 2023; **31**: 1024-1043 [PMID: 37120362 DOI: 10.1016/j.tim.2023.04.001]

12 **Noto JM**, Piazuelo MB, Shah SC, Romero-Gallo J, Hart JL, Di C, Carmichael JD, Delgado AG, Halvorson AE, Greevy RA, Wroblewski LE, Sharma A, Newton AB, Allaman MM, Wilson KT, Washington MK, Calcutt MW, Schey KL, Cummings BP, Flynn CR, Zackular JP, Peek RM Jr. Iron deficiency linked to altered bile acid metabolism promotes Helicobacter pylori-induced inflammation-driven gastric carcinogenesis. *J Clin Invest* 2022; **132** [PMID: 35316215 DOI: 10.1172/JCI147822]

13 **Yang Y**, Dai D, Jin W, Huang Y, Zhang Y, Chen Y, Wang W, Lin W, Chen X, Zhang J, Wang H, Zhang H, Teng L. Microbiota and metabolites alterations in proximal and distal gastric cancer patients. *J Transl Med* 2022; **20**: 439 [PMID: 36180919 DOI: 10.1186/s12967-022-03650-x]

14 **Yu L**, Lai Q, Feng Q, Li Y, Feng J, Xu B. Serum Metabolic Profiling Analysis of Chronic Gastritis and Gastric Cancer by Untargeted Metabolomics. *Front Oncol* 2021; **11**: 636917 [PMID: 33777793 DOI: 10.3389/fonc.2021.636917]

15 **Wu L**, Liu Q, Ruan X, Luan X, Zhong Y, Liu J, Yan J, Li X. Multiple Omics Analysis of the Role of RBM10 Gene Instability in Immune Regulation and Drug Sensitivity in Patients with Lung Adenocarcinoma (LUAD). *Biomedicines* 2023; **11** [PMID: 37509501 DOI: 10.3390/biomedicines11071861]

16 **Lei C**, Gong D, Zhuang B, Zhang Z. Alterations in the gastric microbiota and metabolites in gastric cancer: An update review. *Front Oncol* 2022; **12**: 960281 [PMID: 36081564 DOI: 10.3389/fonc.2022.960281]

17 **Chiu HF**, Venkatakrishnan K, Golovinskaia O, Wang CK. Gastroprotective Effects of Polyphenols against Various Gastro-Intestinal Disorders: A Mini-Review with Special Focus on Clinical Evidence. *Molecules* 2021; **26** [PMID: 33917379 DOI: 10.3390/molecules26072090]

18 **Wang Y**, Chen W, Li K, Wu G, Zhang W, Ma P, Feng S. Tissue-based metabolomics reveals metabolic signatures and major metabolic pathways of gastric cancer with help of transcriptomic data from TCGA. *Biosci Rep* 2021; **41** [PMID: 34549263 DOI: 10.1042/BSR20211476]

19 **Drew DA**, Klempner SJ, Chan AT. Metabolomics as a Tool for Biomarker Discovery in Gastric Cancer. *Cancer Epidemiol Biomarkers Prev*

2021; **30**: 1601-1603 [PMID: 34475120 DOI: 10.1158/1055-9965.EPI-21-0457]

20 **Wu L**, Zheng Y, Ruan X, Wu D, Xu P, Liu J, Li X. Long-chain noncoding ribonucleic acids affect the survival and prognosis of patients with esophageal adenocarcinoma through the autophagy pathway: construction of a prognostic model. *Anticancer Drugs* 2022; **33**: e590-e603 [PMID: 34338240 DOI: 10.1097/CAD.0000000000001189]

21 **Yin S**, Liu H, Zhou Z, Xu X, Wang P, Chen W, Deng G, Wang H, Yu H, Gu L, Huo M, Li M, Zeng L, He Y, Zhang C. PUM1 Promotes Tumor Progression by Activating DEPTOR-Meditated Glycolysis in Gastric Cancer. *Adv Sci (Weinh)* 2023; **10**: e2301190 [PMID: 37469018 DOI: 10.1002/advs.202301190]

22 **Wu L**, Zhong Y, Yu X, Wu D, Xu P, Lv L, Ruan X, Liu Q, Feng Y, Liu J, Li X. Selective poly adenylation predicts the efficacy of immunotherapy in patients with lung adenocarcinoma by multiple omics research. *Anticancer Drugs* 2022; **33**: 943-959 [PMID: 35946526 DOI: 10.1097/CAD.0000000000001319]

23 **Zhao P**, Yuan F, Xu L, Jin Z, Liu Y, Su J, Yuan L, Peng L, Wang C, Zhang G. HKDC1 reprograms lipid metabolism to enhance gastric cancer metastasis and cisplatin resistance *via* forming a ribonucleoprotein complex. *Cancer Lett* 2023; **569**: 216305 [PMID: 37423558 DOI: 10.1016/j.canlet.2023.216305]

24 **Cao W**, Zheng C, Xu X, Jin R, Huang F, Shi M, He Z, Luo Y, Liu L, Liu Z, Wei J, Deng X, Chen T. Clostridium butyricum potentially improves inflammation and immunity through alteration of the microbiota and metabolism of gastric cancer patients after gastrectomy. *Front Immunol* 2022; **13**: 1076245 [PMID: 36466862 DOI: 10.3389/fimmu.2022.1076245]

25 **Shang F**, Cao Y, Wan L, Ren Z, Wang X, Huang M, Guo Y. Comparison of Helicobacter pylori positive and negative gastric cancer *via* multi-omics analysis. *mBio* 2023; **14**: e0153123 [PMID: 37846989 DOI: 10.1128/mbio.01531-23]

26 **He R**, Ma R, Jin Z, Zhu Y, Yang F, Hu F, Dai J. Proteomics and Metabolomics Unveil Codonopsis pilosula (Franch.) Nannf. Ameliorates Gastric Precancerous Lesions *via* Regulating Energy Metabolism. *Front Pharmacol* 2022; **13**: 933096 [PMID: 35928258 DOI: 10.3389/fphar.2022.933096]

27 **Ren Z**, Rajani C, Jia W. The Distinctive Serum Metabolomes of Gastric, Esophageal and Colorectal Cancers. *Cancers (Basel)* 2021; **13** [PMID: 33578739 DOI: 10.3390/cancers13040720]

28 **Yu J**, Zhao J, Yang T, Feng R, Liu L. Metabolomics Reveals Novel Serum Metabolic Signatures in Gastric Cancer by a Mass Spectrometry Platform. *J Proteome Res* 2023; **22**: 706-717 [PMID: 36722497 DOI: 10.1021/acs.jproteome.2c00295]

29 **Wu L**, Li X, Qian X, Wang S, Liu J, Yan J. Lipid Nanoparticle (LNP) Delivery Carrier-Assisted Targeted Controlled Release mRNA Vaccines in Tumor Immunity. *Vaccines (Basel)* 2024; **12** [PMID: 38400169 DOI: 10.3390/vaccines12020186]

30 **Qu T**, Zhang S, Yang S, Li S, Wang D. Utilizing serum metabolomics for assessing postoperative efficacy and monitoring recurrence in gastric cancer patients. *BMC Cancer* 2024; **24**: 27 [PMID: 38166693 DOI: 10.1186/s12885-023-11786-2]

31 **Wang D**, Li D, Zhang Y, Chen J, Liao C, Qin S, Tian Y, Zhang Z, Xu F. Functional metabolomics reveal the role of AHR/GPR35 mediated kynurenic acid gradient sensing in chemotherapy-induced intestinal damage. *Acta Pharm Sin B* 2021; **11**: 763-780 [PMID: 33777681 DOI: 10.1016/j.apsb.2020.07.017]

32 **Wu L**, Chen X, Zeng Q, Lai Z, Fan Z, Ruan X, Li X, Yan J. NR5A2 gene affects the overall survival of LUAD patients by regulating the activity of CSCs through SNP pathway by OCLR algorithm and immune score. *Heliyon* 2024; **10**: e28282 [PMID: 38601554 DOI: 10.1016/j.heliyon.2024.e28282]

33 **Bednarz-Misa I**, Fleszar MG, Fortuna P, Lewandowski Ł, Mierzchała-Pasierb M, Diakowska D, Krzystek-Korpacka M. Altered L-Arginine Metabolic Pathways in Gastric Cancer: Potential Therapeutic Targets and Biomarkers. *Biomolecules* 2021; **11** [PMID: 34439753 DOI: 10.3390/biom11081086]

34 **Pan C**, Deng D, Wei T, Wu Z, Zhang B, Yuan Q, Liang G, Liu Y, Yin P. Metabolomics study identified bile acids as potential biomarkers for gastric cancer: A case control study. *Front Endocrinol (Lausanne)* 2022; **13**: 1039786 [PMID: 36465663 DOI: 10.3389/fendo.2022.1039786]

35 **Wu L**, Li H, Liu Y, Fan Z, Xu J, Li N, Qian X, Lin Z, Li X, Yan J. Research progress of 3D-bioprinted functional pancreas and in vitro tumor models. *IJB* 2024; **10**: 1256 [DOI: 10.36922/ijb.1256]

36 **Li B**, Shu X, Jiang H, Shi C, Qi L, Zhu L, Zhou J, Tang M, Hu A. Plasma metabolome identifies potential biomarkers of gastric precancerous lesions and gastric cancer risk. *Metabolomics* 2023; **19**: 73 [PMID: 37561286 DOI: 10.1007/s11306-023-02037-3]

37 **Liu D**, Zhu J, Ma X, Zhang L, Wu Y, Zhu W, Xing Y, Jia Y, Wang Y. Transcriptomic and Metabolomic Profiling in Helicobacter pylori-Induced Gastric Cancer Identified Prognosis- and Immunotherapy-Relevant Gene Signatures. *Front Cell Dev Biol* 2021; **9**: 769409 [PMID: 35004676 DOI: 10.3389/fcell.2021.769409]

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