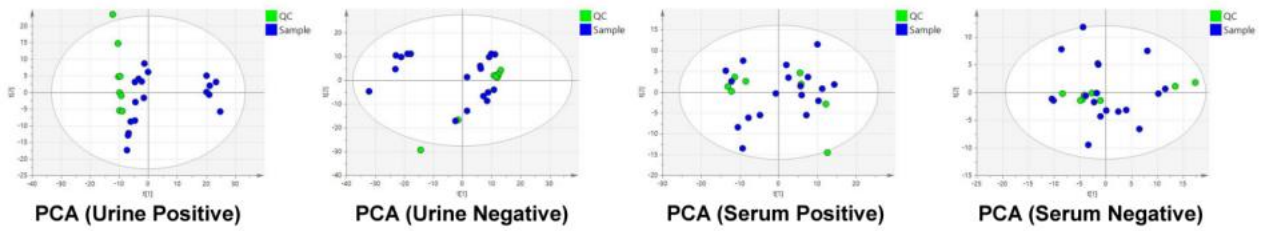
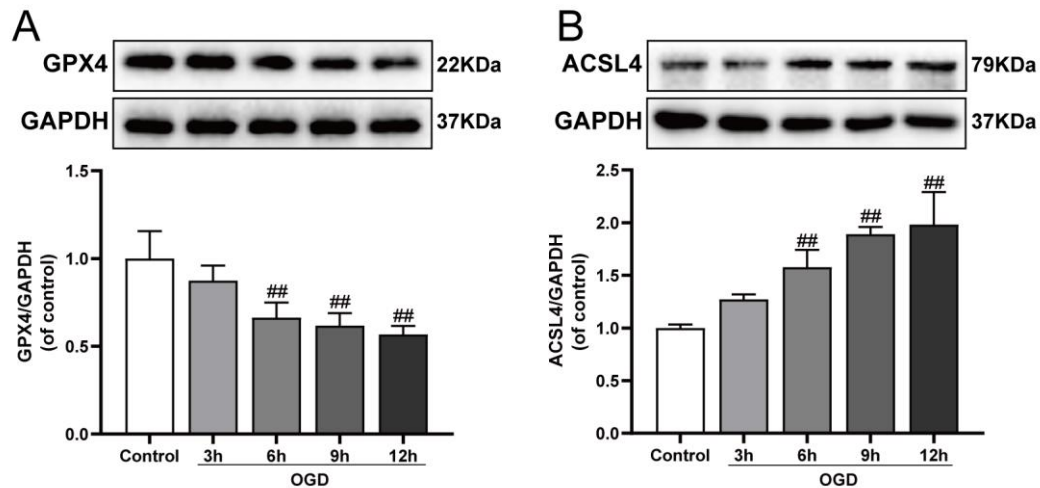


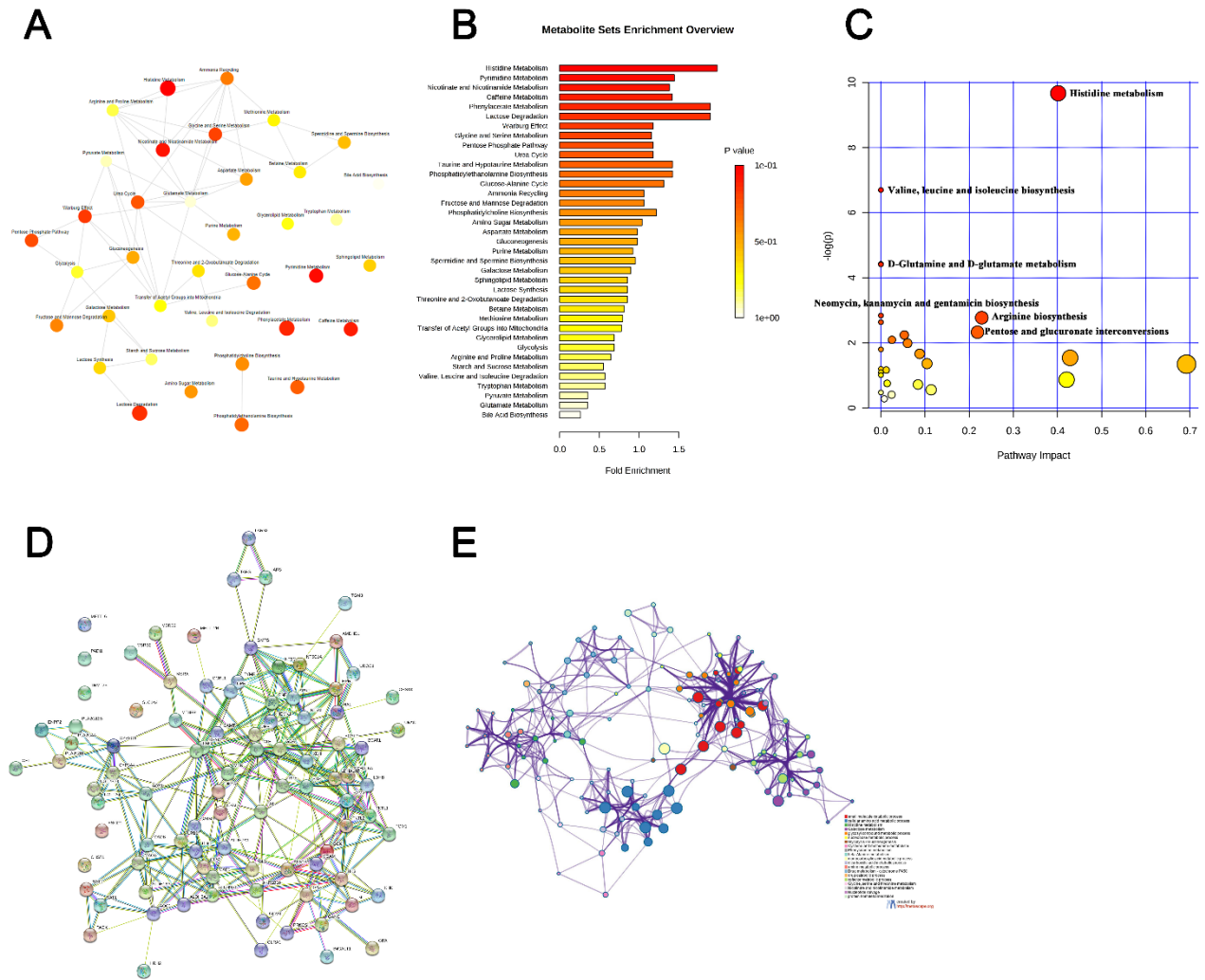
Supplementary Information



Supplementary Figure S1. PCA score plots obtained from the analysis of the QC group (green dots) and other groups (Sham, MI, and MI treated with 0.75 mg/kg RUS: blue dots), based on Q-TOF system (n=6).

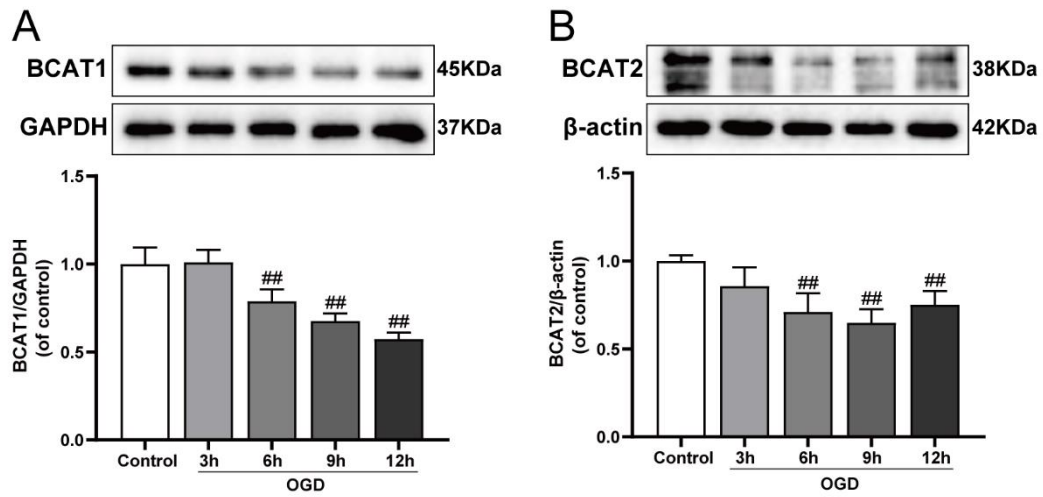


Supplementary Figure S2. Changes of the expression of (A) GPX4 and (B) ACSL4 with the prolongation of OGD-injured time in H9c2 cardiomyocytes (n=3-4). Results were expressed as mean \pm SD. ^{##} $p < 0.01$ vs. the control group.

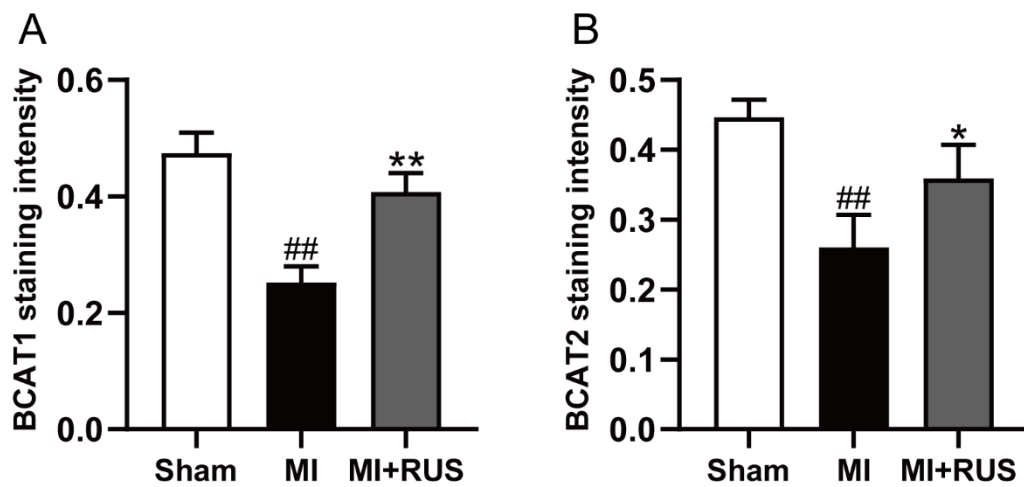


Supplementary Figure S3. Enrichment analysis of metabolic pathway and regulatory enzymes.

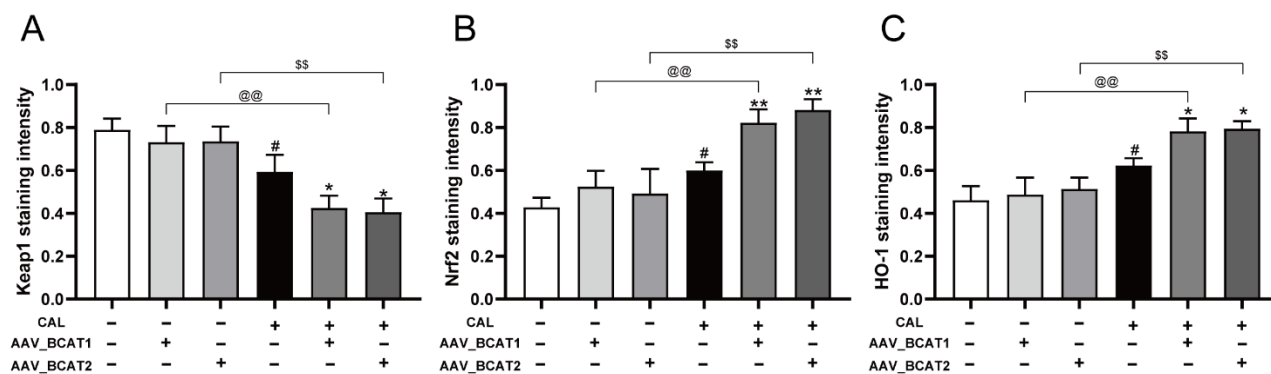
(A) Network map of metabolic pathway. (B) Overview of pathways related to the differential endogenous metabolites. (C) A summary of pathway analysis by MetPA. (D) Network map of regulatory proteins. (E) GO enrichment analysis of regulatory enzymes.



Supplementary Figure S4. Changes of the expression of (A) BCAT1 and (B) BCAT2 with the prolongation of OGD-injured time in H9c2 cardiomyocytes (n=3-4). Results were expressed as mean \pm SD. $^{##}p < 0.01$ vs. the control group.



Supplementary Figure S5. (A) The relevant statistical results of immunohistochemistry analysis of BCAT1 in Figure 4A (n=3). (B) The relevant statistical results of immunohistochemistry analysis of BCAT2 in Figure 4B (n=3). Results were expressed as mean \pm SD. $^{##}p < 0.01$ vs. the sham group, $^{\#}p < 0.05$, $^{**}p < 0.01$ vs. the MI group.



Supplementary Figure S6. The relevant statistical results of immunohistochemistry analysis of (A) Keap1, (B) Nrf2 and (C) HO-1 in Figure 6C (n=3). Results were expressed as mean \pm SD. # $p < 0.05$ vs. the sham group, * $p < 0.05$, ** $p < 0.01$ vs. the MI group, @@ $p < 0.01$ vs. the group treated with AAV-BCAT1, \$\$ $p < 0.01$ vs. the group treated with AAV-BCAT2.

Supplementary Table S1. The RSD of retention time and peak area in QC samples

Sample-mode	RSD of retention time (%)	RSD of peak area (%)
Urine-positive	0.67	3.71
Urine-negative	0.45	3.94
Serum-positive	0.36	4.21
Serum-negative	0.33	4.74

Supplementary Table S2. Sequences of siRNAs

Gene name	Accession number	siRNA sequence (5' to 3')
BCAT1	NM_017253.3	Forward: GGCUGCAACUAUGGAUCUU
		Reverse: AAGAUCCAUAGUUGCAGCC
BCAT2	NM_022400.2	Forward: GGAGUGGAACAGCAAGACA
		Reverse: UGUCUUGCUGUUCCACUCC

Supplementary Table S3. The parameters for assessing the model quality of OPLS-DA

Sample-mode	R ² X (cum)	R ² Y (cum)	Q ²
Urine-positive	0.698	0.997	0.984
Urine-negative	0.669	0.955	0.964
Serum-positive	0.786	0.998	0.875
Serum-negative	0.736	0.995	0.905

Supplementary Table S4. Identification of 58 differential metabolites in urine

Ion Mode	Identification	m/z	Rt (min)	VIP	p-value	FC ^b	Metabolic pathways	Enzymes	Genes
Positive	N-butrylrglycine	748.53	2.37	1.07	3.82E-04	1.22	Histidine Metabolism	Glycine N-acyltransferase; Glycine N-acyltransferase-like protein 1; Glycine N-acyltransferase-like protein 2	GLYAT; GLYAT1; GLYAT2
	(3-Arylcarbonyl)-alanine	226.14	2.36	1.41	3.93E-07	0.60			
	Methylimidazoleacetic acid	261.18	14.89	1.08	1.09E-03	1.48		Aldehyde dehydrogenase, dimeric NADP-preferring; Aldehyde dehydrogenase family 1 member A3	ALDH3A1;ALDH1A3
	2-Deoxysepiapterin	204.09	13.90	1.21	8.52E-04	0.70		Glycine N-acyltransferase; Glycine N-acyltransferase-like protein 1; Glycine N-acyltransferase-like protein 2	GLYAT; GLYAT1; GLYAT2
	2-Methylbutyrylrglycine	256.15	2.27	1.15	1.16E-02	0.94			
	2-Methylguanosine	112.05	10.69	1.42	4.69E-11	1.75			
	3-Methylguanine	369.15	10.57	1.31	3.06E-06	1.54			
	3'-O-Methylguanosine	277.12	10.93	1.31	2.53E-05	1.34			
	4-Guanidinobutanoic acid	204.13	4.03	1.20	1.95E-06	1.17			
	Allantoin	60.08	5.21	1.03	4.40E-04	1.21		Putative 2-oxo-4-hydroxy-4-carboxy-5-ureidoimidazoline decarboxylase	PRHOXNB
	L-Arginine	189.09	16.35	1.31	2.39E-04	0.88			
	Cellotriose	344.13	16.47	1.20	1.58E-02	0.91		Glucosidase 2 subunit beta;Glucosylceramidase; Cytosolic beta-glucosidase	PRKCSH; GBA
	Creatine	250.16	15.09	1.37	2.74E-06	1.85	Glycine and Serine Metabolism; Arginine and Proline Metabolism	Guanidinoacetate N-methyltransferase; Glycine amidinotransferase, mitochondrial	GAMT; GATM;

Glycylprolylhydroxyproline	323.14	16.82	1.26	3.51E-04	0.88			
Guanine	451.16	14.01	1.42	3.88E-08	0.70	Purine Metabolism	Adenine phosphoribosyltransferase; Hypoxanthine-guanine phosphoribosyltransferase; Guanine deaminase	APRT; HPRT1; GDA
Hexanoylglycine	233.09	2.39	1.12	8.50E-06	1.17		Glycine N-acyltransferase; Glycine N-acyltransferase-like protein 1; Glycine N-acyltransferase-like protein 2	GLYAT; GLYAT1; GLYAT2
Histamine	150.06	14.32	1.43	7.45E-11	0.59	Histidine Metabolism	Aromatic-L-amino-acid decarboxylase; Amiloride-sensitive amine oxidase; Retina-specific copper amine oxidase; Histamine H2 receptor	DDC; ABP1; HRH2
Imidazoleacetic acid	307.12	6.81	1.02	2.08E-02	0.81	Histidine Metabolism	Alpha-aminoadipic semialdehyde dehydrogenase; Aldehyde dehydrogenase family 1 member A3	ALDH9A1; ALDH1A3
Isobutyrylglycine	818.61	2.39	1.38	4.96E-08	1.83		Glycine N-acyltransferase; Glycine N-acyltransferase-like protein 1; Glycine N-acyltransferase-like protein 2	GLYAT; GLYAT1; GLYAT2
L-Alloisoleucine	149.11	4.66	1.35	3.28E-04	0.75			
Ureidoisobutyric acid	173.09	15.85	1.39	7.21E-08	1.42	Pyrimidine Metabolism	Dihydropyrimidinase; Beta-ureidopropionase	DPYS; UPB1
L-Glutamine	147.08	15.96	1.40	6.39E-08	0.77	Pyrimidine Metabolism; Glutamate Metabolism; Purine Metabolism	Kynurenine--oxoglutarate transaminase 1; GMP synthase; Protein-glutamine gamma-glutamyltransferase E Branched-chain-amino-acid aminotransferase, cytosolic; Branched-chain-amino-acid aminotransferase, mitochondrial; Isoleucine--tRNA ligase, cytoplasmic	CCBL1; GMPS; TGM3
L-Isoleucine	396.16	4.26	1.31	2.88E-04	0.70	Valine, Leucine and Isoleucine Degradation	Branched-chain-amino-acid aminotransferase, cytosolic; Branched-chain-amino-acid aminotransferase, mitochondrial; Probable leucine--tRNA ligase, mitochondrial	BCAT1; BCAT2; IARS;
L-Leucine	226.08	14.02	1.23	7.33E-03	0.87	Valine, Leucine and Isoleucine Degradation		BCAT1; BCAT2; LARS2

	L-Norleucine	76.08	4.58	1.22	6.97E-05	1.18			
	Methionine	162.11	6.23	1.34	4.17E-07	3.57	Betaine Metabolism; Methionine Metabolism	Methionine synthase; Methylene-tetrahydrofolate reductase; Tyrosine aminotransferase Diamine acetyltransferase 2; Diamine acetyltransferase 1; Peroxisomal N(1)-acetyl-spermine/spermidine oxidase Carbohydrate sulfotransferase 3; Carbohydrate sulfotransferase 1; Beta-1,4-galactosyltransferase 1	MTR; MTHFR; TAT SAT2; SAT1; PAOX CHST3; CHST1; B4GALT1;
	N1-Acetylspermidine	398.03	14.51	1.07	3.99E-03	1.79			
	N-Acetylglucosamine	365.11	15.72	1.04	7.11E-05	1.16			
	N-Methyl-4-pyridone-3-carboxamide	240.16	3.28	1.12	6.94E-05	1.24	Nicotinate and Nicotinamide Metabolism	Aldehyde oxidase	AOX1
	Phenylacetylglutamine	820.62	2.43	1.33	2.35E-06	1.59		Glycine N-acyltransferase; Glycine N-acyltransferase-like protein 1; N-acetyltransferase ESCO1	GLYAT; GLYAT1; ESCO1
	Ribothymidine	399.20	15.31	1.27	5.96E-05	1.73		tRNA (uracil(54)-C(5))-methyltransferase homolog	TRMT2B
	Thymine	127.05	6.72	1.30	2.28E-03	2.16	Pyrimidine Metabolism	Dihydropyrimidine dehydrogenase; Thymidine phosphorylase	DPYD; TYMP
	Tryptophan	223.09	10.73	1.44	5.45E-13	2.57			
	Tyramine glucuronide	336.11	16.56	1.43	1.57E-12	1.89		UDP-glucuronosyltransferase 2B28; UDP-glucuronosyltransferase 2B4; UDP-glucuronosyltransferase 1-4	UGT2B28; UGT2B24; UGT1A4
	Urocanic acid	155.13	5.21	1.13	9.73E-05	1.26	Histidine Metabolism; Ammonia Recycling	Histidine ammonia-lyase; Urocanate hydratase	HAL; UROC1
	Xanthurenic acid	414.30	3.07	1.36	3.49E-07	1.70	Tryptophan Metabolism	HemK methyltransferase family member 1; Methyltransferase-like protein 2B; Methyltransferase-like protein 6	HEMK1; METTL2B; METTL6
Negative	2-Hydroxyethanesulfonate	325.11	12.40	1.43	8.51E-05	0.52			

4-Imidazolone-5-propionic acid	74.02	15.36	1.33	2.48E-03	0.83	Histidine Metabolism	Urocanate hydratase; Probable imidazolonepropionase	UROC1; AMDHD1
5-Acetylamino-6-amino-3-methyluracil	151.06	13.66	1.03	1.07E-04	1.21	Caffeine Metabolism		
Aminoacetone	251.05	15.62	1.40	3.91E-07	1.76	Glycine and Serine Metabolism	Amine oxidase [flavin-containing] B; Amine oxidase [flavin-containing] A; Bile salt-activated lipase	MAOB; MAOA; CEL
D-Glutamine	487.19	16.00	1.39	2.82E-05	0.68		Glutaminase liver isoform, mitochondrial; Glutaminase kidney isoform, mitochondrial	GLS2; GLS
Fructose	397.07	13.25	1.03	3.81E-03	1.55	Amino Sugar Metabolism; Fructose and Mannose Degradation; Galactose Metabolism	Ketohexokinase; Lysosomal alpha-glucosidase; Maltase-glucoamylase, intestinal; Neutral alpha-glucosidase C	KHK; GAA; MGAM; GANC
Homocysteinesulfinic acid	324.96	3.07	1.53	5.29E-15	13.07			
Aspartate-4-phosphate	363.02	1.79	1.38	6.19E-04	0.88			
L-Galactose	357.03	14.08	1.44	1.32E-07	2.02			
Glucose	179.06	14.20	1.24	1.61E-03	0.69	Glycolysis; Galactose Metabolism; Gluconeogenesis	Glucokinase; Hexokinase-3; Sucrase-isomaltase, intestinal	GCK; HK3; SI
L-Threonine	118.05	15.63	1.26	1.10E-02	0.84	Glycine and Serine Metabolism	Threonine--tRNA ligase, cytoplasmic; L-serine dehydratase/L-threonine deaminase; Neutral amino acid transporter A	TARS; SDS; SLC1A4
Methionine sulfoxide	302.10	16.05	1.22	1.60E-05	1.35	Methionine Metabolism	Mitochondrial peptide methionine sulfoxide reductase; Methionine-R-sulfoxide reductase B2, mitochondrial; Methionine-R-sulfoxide reductase B3	MSRA; MSRB2; MSRB3
Paraxanthine	183.00	12.91	1.23	5.50E-03	0.83	Caffeine Metabolism	Xanthine dehydrogenase/oxidase; Cytochrome P450 3A4; Cytochrome P450 2C9	XDH; CYP3A4; CYP2C9

p-Cresol sulfate	349.00	1.69	1.41	4.71E-08	1.64			
Quinolinic acid	277.04	3.11	1.28	1.41E-02	0.90	Nicotinate and Nicotinamide Metabolism	Nicotinate-nucleotide pyrophosphorylase; Kynurenine 3-monooxygenase	QPRT; KMO
Ribose 1-phosphate	165.04	3.06	1.49	2.70E-05	0.41	Pentose Phosphate Pathway; Purine Metabolism	Phosphoglucomutase-1; Phosphoglucomutase-2; Purine nucleoside phosphorylase; Uridine phosphorylase 1	PGM1; PGM2; PNP; UPP1
Taurine	288.98	14.69	1.43	9.56E-06	0.80	Taurine and Hypotaurine Metabolism; Bile Acid Biosynthesis	Glutamate decarboxylase 1; Cysteine sulfinic acid decarboxylase; Glycine receptor subunit alpha-1 Cystathionine gamma-lyase	GAD1; CSAD; GLRA1 CTH
Thiocysteine	126.91	2.44	1.34	9.94E-06	1.83			
Threonic acid	116.03	6.13	1.42	6.34E-06	0.80			
Uridine	367.07	13.67	0.00	1.46E+00	4.26	Pyrimidine Metabolism	Cytosolic 5'-nucleotidase 1A; 5'(3')-deoxyribonucleotidase, cytosolic type; 5'(3')-deoxyribonucleotidase, mitochondrial Xanthine dehydrogenase/oxidase;	NT5C1A; NT5C; NT5M
Xanthine	151.02	4.64	1.51	3.62E-08	1.66	Purine Metabolism	Hypoxanthine-guanine phosphoribosyltransferase; Purine nucleoside phosphorylase	XDH; HPRT1; PNP
Xylulose 5-phosphate	245.02	3.07	1.43	2.05E-05	0.71	Pentose Phosphate Pathway	Transketolase-like protein 1; Ribulose-phosphate 3-epimerase; Transketolase-like prote 2	TKTL1; RPE; TKTL2

RT(min)^a: retention time; **FC^b**: fold change, as calculated by average relative quantitation acquired from MI group/RUS group, and a value more than 1 indicates an increased level in the metabolites of MI group.

Supplementary Table S5. Identification of 4 differential metabolites in serum

Ion Mode	Identification	m/z	Rt (min)	VIP	p-value	FC ^b	Metabolic pathways	Enzymes	Genes
Positive	LysoPE(0:0/16:1(9Z))	279.23	13.25	2.14	1.48E-03	0.78		Ectonucleotide pyrophosphatase/phosphodiesterase family member 2	ENPP2
Negative	Glyceraldehyde	711.34	6.9869	1.99	2.23E-07	1.62	Glycerolipid Metabolism; Fructose and Mannose Degradation; Glycerolipid Metabolism	Aldose reductase; 4-trimethylaminobutyraldehyde dehydrogenase; Alpha-aminoadipic semialdehyde dehydrogenase	AKR1B1; ALDH9A1; ALDH7A1
	L-Lactic acid	160.90	2.14	1.45	4.20E-03	1.91	Gluconeogenesis; Pyruvate Metabolism	L-lactate dehydrogenase A-like 6A; L-lactate dehydrogenase B chain; M-L-lactate dehydrogenase A-like 6B	LDHAL6A; LDHB; LDHAL6B
	PE(22: 2(13Z, 16Z)/ 15: 0)	343.24	13.67	1.26	1.54E-03	0.86		Cytosolic phospholipase A2; Phospholipase A2; Group XIIB secretory phospholipase A2-like protein	PLA2G4A; PLA2G1B; PLA2G12B

RT(min)^a: retention time; **FC^b:** fold change, as calculated by average relative quantitation acquired from MI group/RUS group, and a value more than 1 indicates an increased level in the metabolites of MI group.