Supplementary Material

1. Supplementary Materials and Methods

Serum assays

We performed serum assays of interleukin (IL)-18, a disintegrin and metalloproteinase with thrombospondin type 1 motif member 13 (ADAMTS13), vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-α, and intercellular adhesion molecule (ICAM)-1 using enzyme-linked immunosorbent assay (ELISA) kits for human serum and plasma (Quantikine, R&D Systems, MN, USA). Samples and standards of recombinant human IL-18, ADAMTS13, VEGF, TNF-α, or ICAM-1 protein were added to microtiter plate wells precoated with IL-18, ADAMTS13, VEGF, TNF-α, or ICAM-1 antibody and incubated for two hours at room temperature. Each well was washed and then incubated with IL-18, ADAMTS13, VEGF, TNF-α, or ICAM-1 conjugate for two hours at room temperature. Wells were washed, and substrate solution was added. After incubation for 20-30 min at room temperature according to each assay instruction, the enzyme reactions were stopped, and then the optical density of each well was determined with a microplate reader set to 450 nm. The data were subtracted by the readings at 540 nm. IL-18, ADAMTS13, VEGF, TNF-α, and ICAM-1 concentrations were determined by comparison to the standard curve. The intra-assay coefficients of variation for IL-18, ADAMTS13, VEGF, TNF-α, and ICAM-1 were 6.72%, 7.8%, 13.9%, 4.51%, and 3.31%, respectively.

Fecal microbiome analysis

Genomic DNA from fecal samples was extracted using NucleoSpin® DNA Stool (Macherey-Nagel, Duren, Germany) according to the manufacturer's instructions and quantified using a Qubit 4 Fluorometer (Promega, Madison, WI, USA). 16S rRNA gene sequencing PCR and data processing were based on a previously described method (1). Taxonomy classification for the microbiome was calculated by comparing all amplicon sequence variants with SILVA 138.1 using the q2-feature-classifier (2). α-diversity and β-diversity were calculated using QIIME2 (3). Principal coordinate analysis (PCoA) was applied to the distance matrices to create a two-dimensional plot. We used the linear discriminant analysis (LDA) effect size approach to identify bacterial taxa that differed significantly between the critical group and noncritical group (4). Taxa groups with > 3 log 10 LDA scores were considered significantly enriched at a *P* value < 0.05.

Fecal metabolome analysis

Fecal metabolome analysis was performed by Human Metabolome Technologies, Inc. (HMT). Approximately 30-50 mg of feces were mixed with 500 µL of Milli-Q water containing internal standards (H3304-1002, HMT, Tsuruoka, Yamagata, Japan). The mixture was centrifuged at 2,300 ×g and 4 ℃ for five min, after which 80 µL of the supernatant was centrifugally filtered through a Millipore 5-kDa cutoff filter (ULTRAFREE MC PLHCC, HMT) at 9,100 ×g and 4 ℃ for 120 min to remove macromolecules. Subsequently, the filtrate was evaporated to dryness under vacuum and reconstituted in 20 µL of Milli-Q water for metabolome analysis. Metabolome analysis was conducted according to HMT's Basic Scan package using capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS) based on methods

described previously (5,6). Briefly, CE-TOFMS analysis was carried out using an Agilent CE capillary electrophoresis system equipped with an Agilent 6210 time-of-flight mass spectrometer (Agilent Technologies, Inc., Santa Clara, CA, USA). The systems were controlled by Agilent G2201AA ChemStation software version B.03.01 (Agilent Technologies) and connected by a fused silica capillary (50 μm i.d. × 80 cm total length) with commercial electrophoresis buffer (H3301-1001 and I3302-1023 for cation and anion analyses, respectively, HMT) as the electrolyte. The spectrometer was scanned from m/z 50 to 1,000, and peaks were extracted using MasterHands automatic integration software (Keio University, Tsuruoka, Yamagata, Japan) to obtain peak information, including m/z, peak area, and migration time (7). Signal peaks corresponding to isotopomers, adduct ions, and other product ions of known metabolites were excluded, and the remaining peaks were annotated according to HMT's metabolite database based on their m/z values and migration times. Areas of the annotated peaks were then normalized to internal standards and sample amount to obtain relative levels of each metabolite. Hierarchical cluster analysis (HCA) and principal component analysis (PCA) (8) were performed by HMT's proprietary MATLAB and R programs, respectively.

Mucosal gene expression analysis

All samples obtained from the patients were quickly put into RNAprotect Tissue Reagent (QIAGEN, Hilden, Germany) after biopsy and stored at -80 °C until analysis.

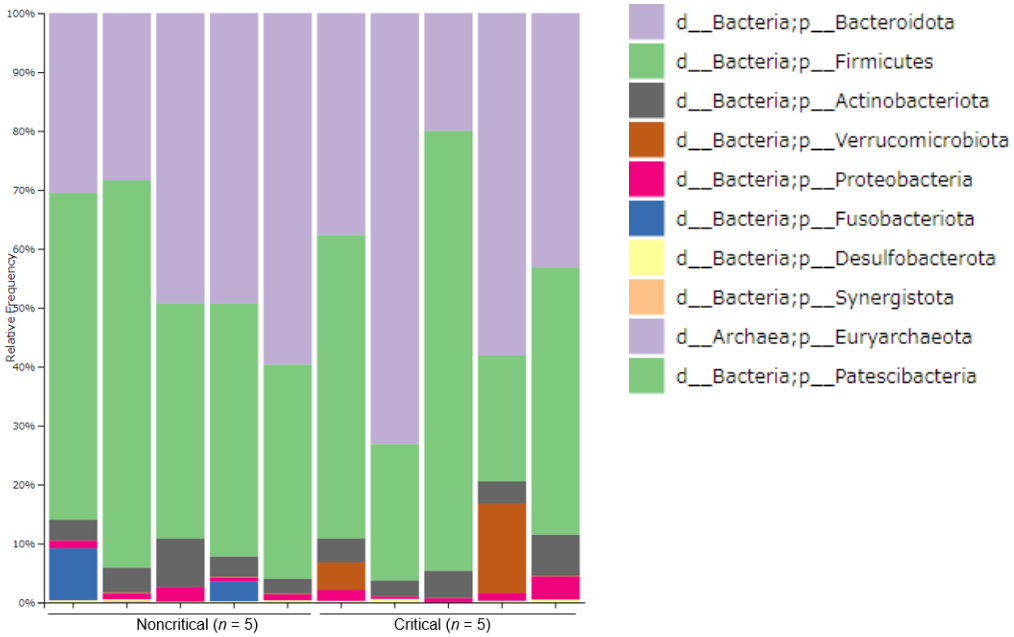
Total RNA was extracted from the biopsy tissues using TRIzol reagents (Invitrogen, Carlsbad, CA, USA), and RNA concentrations were measured at 260/280 nm using UV

spectrophotometry. RNA from each sample was reverse transcribed using SuperScript IV VILO Master Mix (Invitrogen, Carlsbad, CA, USA). Synthesized complementary DNA equivalent to 1000 ng of RNA was mixed with Applied Biosystems™ PowerUp™ SYBR™ Green Master Mix (Applied Biosystems, Foster City, CA, USA) in wells up to a volume of 20 µl. The reaction conditions used for quantitative real-time PCR were as follows: 95 °C for 10 min followed by 40 cycles of 95 °C for 15 s and 60 °C for 60 s. The primers used for real-time PCR are shown in Table S6.

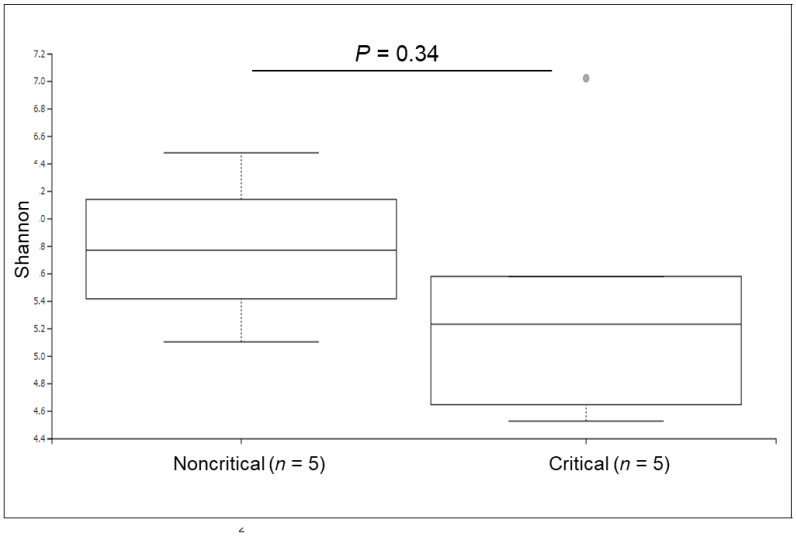
2. Supplementary Figures

Supplementary Figure 1

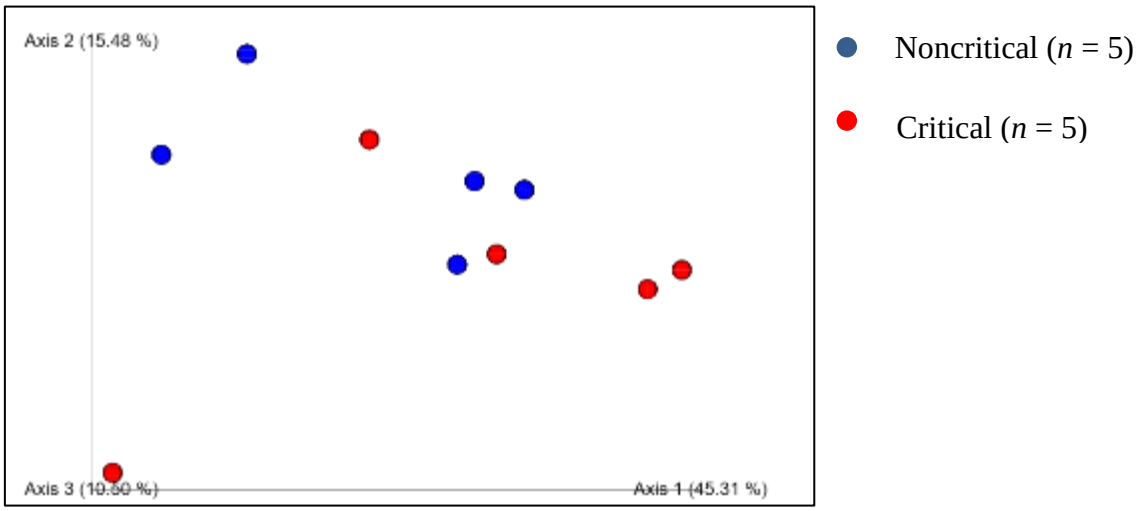
A



B



C

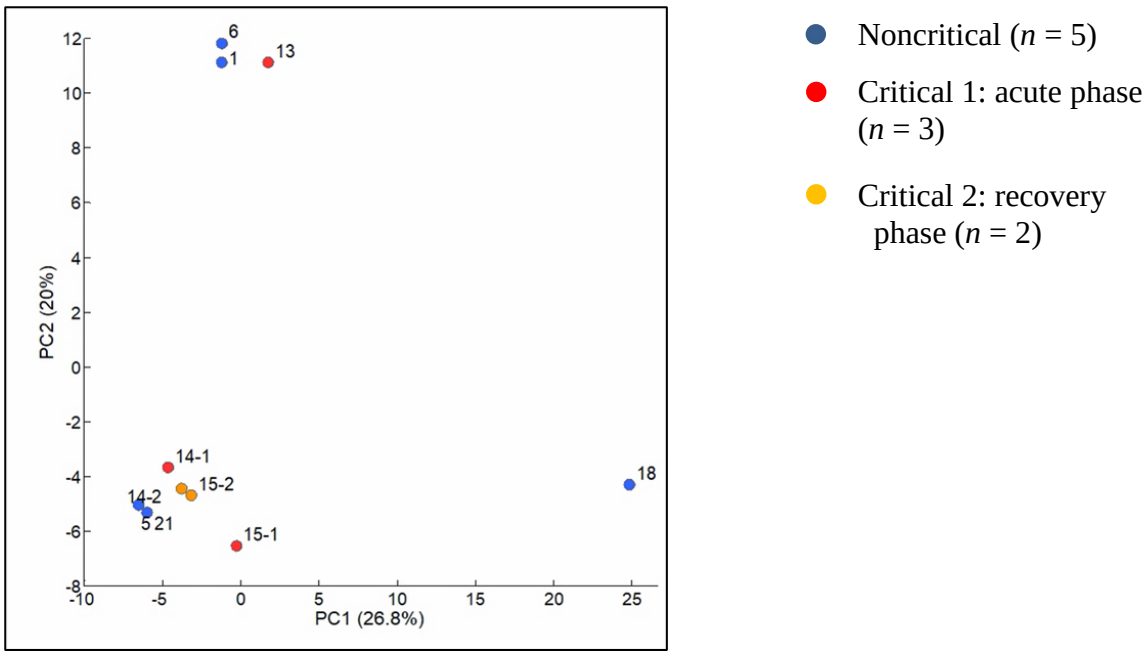


(A) Gut microbiota at the phylum level in two groups of COVID-19 patients. p_ means phylum.

(B) α-diversity represented by the Shannon index. The vertical axis shows the Shannon index. Box-and-whisker plots show the median, 25th, and 75th percentiles, with whiskers extending to the minimum and maximum values. Data were analyzed using the Mann-Whitney U test. Statistical significance was accepted as $P < 0.05$. The Shannon index was slightly lower in the critical group than in the noncritical group, but the difference was not statistically significant ($P = 0.34$).

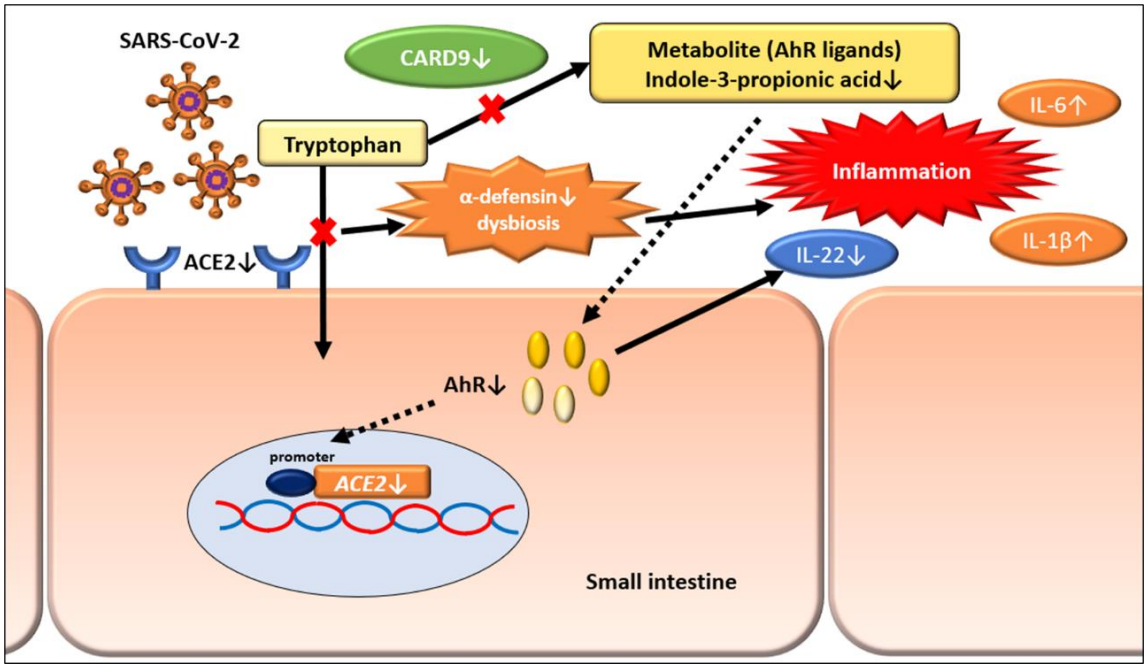
(C) Principal coordinates analysis (PCoA) derived from unweighted UniFrac distances. Statistical analysis was performed by using permutational analysis of variance (PERMANOVA). Statistical significance was accepted as $P < 0.05$. Comparison between the noncritical and critical groups showed no significant difference *(P* = 0.28).

Supplementary Figure 2



Principal component analysis (PCA) of metabolomic data from noncritical and critical COVID-19 patients. There were no significant changes in fecal metabolite levels among the three groups.

Supplementary Figure 3



Possible mechanisms of gastrointestinal inflammation in patients with critical COVID-19.

3. Supplementary Tables

Supplementary Table 1. Characteristics of 10 patients with COVID-19 from whom stool samples were obtained			
	All (*n* = 10)	**Noncritical (*n* = 5)**	**Critical (*n* = 5)**
GENERAL CHARACTERISTICS			
Age, yo	50.9 ±11.1	44.4 ± 12.3	57.4 ± 4.34
Male, %	6 (60)	2 (40)	4 (80)
BMI	28.5 ±5.38	28.8 ± 7.34	28.3 ± 3.34
Current smoking, %	2 (20)	1 (20)	1 (20)
DISEASE SEVERITY CATEGORY			
Mild, %	0 (0)		
Moderate, %	3 (30)	3 (60)	
Severe, %	2 (20)	2 (40)	
Critical, %	5 (50)		6 (100)
DURATION FROM INFECTION TO SAMPLE COLLECTION			
Days	10.5 (5.5-12.8)	8 (5-11)	12 (10.5-18)
COMORBIDITY			
Hypertension, %	4 (40)	1 (20)	3 (60)
Diabetes Mellitus, %	2 (20)	0 (0)	2 (40)

Hyperlipidemia, %	3 (30)	1 (20)	2 (40)
COPD, %	1 (10)	1 (20)	0 (0)
Ischemic Heart Disease, %	1 (10)	1 (20)	0 (0)
Ulcerative Colitis, %	1 (10)	1 (20)	0 (0)
SYMPTOMS AT HOSPITALIZATION			
High Fever >37.5 °C, %	10 (100)	5 (100)	5 (100)
General Fatigue, %	6 (60)	4 (80)	2 (40)
Cough, %	4 (40)	2 (40)	2 (40)
Diarrhea, %	1 (10)	1 (20)	0 (0)
Appetite Loss, %	1 (10)	1 (20)	0 (0)
Abdominal Pain, %	1 (10)	0 (0)	1 (20)
Nausea, %	2 (10)	2 (40)	0 (0)
THERAPEUTICS AFTER ADMISSION			
Steroids, %	10 (100)	5 (100)	5 (100)
Anti-virus Antibodies, %	6 (60)	2 (40)	4 (80)
Anti-inflammatory Drugs, %	7 (70)	3 (60)	4 (80)
Anti-SARS-CoV-2 Ab Cocktail, %	1 (10)	1 (20)	0 (0)
Data are expressed as the mean ± SD for normally distributed data or median (IQR) for nonnormally distributed data.			

Supplementary Table 2. Characteristics of three patients from whom mucosal biopsies were obtained

No	Age	Gender	BMI	Comorbidity*	GI symptoms	Duration from infection to the onset of GI symptoms (days)	Duration from infection to biopsy (days)	Biopsy site	Severity	Prognosis
1	68	Male	26.1	HT, DM	watery diarrhea	25	33	rectum	critical	dead
2*****	63	Male	33.7	HT, DM, asthma	watery diarrhea	30	38	ileum/rectum	critical	dead
3	71	Male	19.9	Prostate cancer	watery diarrhea	16	19	ileum/rectum	critical	dead

Abbreviations; HT: Hypertension, DM: Diabetes mellitus, GI: Gastrointestinal tract.

*****Number 2 is a case that has already been published (3).

Supplementary Table 3. Laboratory data on admission				
	All （*n* = 19）	**Noncritical (*n* = 13)**	**Critical (*n* = 6)**	***P* value**
White blood cells,/uL	5000 (4100, 11900)	4800 (4100, 9100)	11250 (5125, 14075)	0.19
Neutrocytes,/uL	3619 (2513, 10282)	3395 (2464.5, 7227)	9821 (4272, 12683.5)	0.13
Lymphocytes,/uL	**869 (666, 1160)**	**949 (748.5, 1372.5)**	**663 (517.8, 764)**	**0.01**
Hemoglobin, g/dL	14.6 ± 1.73	14.9 ± 1.67	13.9 ± 1.84	0.28
Platelets, $x10^4$/uL	22.0 ± 9.30	20 ± 8.44	26.5 ± 10.3	0.16
Total Protein, g/dL	**6.41 ± 0.81**	**7.7 ± 0.65**	**5.77 ± 0.80**	**0.01**
Albumin, g/dL	**3.28 ± 0.74**	**3.83 ± 0.51**	**2.65 ± 0.13**	**<0.001**
Total Bilirubin, mg/dL	0.6 (0.4, 0.7)	0.7 (0.4, 0.75)	0.5 (0.3, 0.63)	0.15
Creatine Kinase, U/L	94 (45.5, 170.3)	135.5 (70.3, 178.8)	54.5 (18.8, 194.5)	0.24
AST, U/L	30 (23, 53)	27 (21.5, 44)	33.5 (25.8, 82.3)	0.43
ALT, U/L	46 (23, 92)	41 (19, 144.4)	74 (28.3, 105)	0.24
LD, U/L	**270 (217, 415)**	**239 (208.5, 300)**	**490 (268.8, 650.8)**	**0.01**
ALP (IFCC), U/L	66.0 ± 15.95	65.9 ± 16.26	66 ±16.79	0.99
Creatinine, mg/dL	0.8 (0.7, 0.97)	0.8 (0.7, 0.96)	0.83 (0.67, 0.99)	0.69

BUN, mg/dL	**17 (12, 22)**	**14 (10.5, 27.4)**	**29 (16.8, 40.5)**	**0.05**
Uric Acid, mg/dL	4.41 ± 1.85	4.68 ± 2.03	3.7 ± 1.17	0.33
Na, mmol/L	138 (136, 140)	138 (137, 140)	136 (132.3, 143.3)	0.12
Cl, mmol/L	101 (99, 104)	101 (98.5, 103)	103 (100.3, 106.8)	0.17
K, mmol/L	4.12 ± 0.47	4.0 ± 0.43	4.37 ± 0.48	0.12
Ca, mg/L	**8.45 ± 0.55**	**8.73 ± 0.56**	**8.13 ± 0.14**	**0.04**
CRP, mg/dL	0.64 (0.19, 3.05)	0.64 (0.23, 2.93)	1.27 (0.11, 5.15)	0.86
HbA1c, %	5.9 (5.6, 6.1)	5.8 (5.6, 5.98)	6.3 (5.75, 8.3)	0.07
PT-INR	0.97 (0.93, 1.02)	0.99 (0.95, 1.03)	0.95 (0.91, 1.00)	0.20
APTT, sec	34.5 (27.9, 37.5)	33.3 (27.5, 37.9)	36.1 (29.6, 37.8)	0.69
Fibrinogen, mg/dL	397.9 ± 115.0	385.5 ± 92.1	424.8 ± 161.3	0.50
D-dimer, ug/mL	**0.6 (0, 0.9)**	**0.4 (0, 0.75)**	**0.9 (0.7, 8.58)**	**0.02**

Data are expressed as the mean ± SD for normally distributed data or median (IQR) for nonnormally distributed data. Statistical analysis was performed by using unpaired Student t-test and Wilcoxon rank-sum test. Noncritical and Critical groups were included in this comparison. Statistical significance was accepted as $P < 0.05$. Data in bold are statistically significant.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; LD, lactate dehydrogenase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Na, serum sodium; Cl, serum chloride; K, serum potassium; Ca, serum calcium; CRP: C-reactive protein; HbA1c, hemoglobin A1c; PT-INR, prothrombin time- international normalized ratio; APTT, activated partial thromboplastin time

Supplementary Table 4. Comparison of serum biomarkers between healthy control and COVID-19 patients

	Healthy control (*n* = 6)	**COVID-19 (*n* = 19)**	***P* value**
IL-18, pg/ml	**174.6 ± 74.30**	**402.0 ± 133.5**	**<0.001**
TNF-α, pg/ml	**1.68 (0.072, 6.24)**	**9.37 (7.93, 11.53)**	**<0.001**
VEGF, pg/ml	**70.1 (13.5, 787.0)**	**402.9 (266.7, 787.0)**	**<0.001**
ADAMTS13, ng/ml	800.2 ± 114.13	749.7 ± 135.9	0.49
ICAM-1, ng/ml	172.2 ± 29.02	224.3 ± 84.3	0.18

Data are expressed as the mean ± SD for normally distributed data or median (IQR) for nonnormally distributed data. Statistical analysis was performed by using unpaired Student t-test and Wilcoxon rank-sum test. Statistical significance was accepted as $P < 0.05$. Data in bold are statistically significant.

Supplementary Table 5. Metabolites identified as targets by metabolomic analysis

ID	HMT DB†		Relative area						Comparative Analysis		
	Compound name	Pathway Label	Noncritical (n=5)		Critical 1 acute phase (n=3)		Critical 2 recovery phase (n=2)		Noncritical (n=5) vs Critical 1 (acute phase, n=3)		
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Ratio ¶	p-value‖	
A_0082	Indole-3-propionic acid	Indole-3-propionic acid	1.0E-04	7.8E-06	4.1E-05	1.6E-05	2.6E-05	N.A.	2.5	0.013	*
C_0068	Asn	Asn	3.1E-04	2.2E-04	1.9E-03	2.9E-04	7.2E-04	N.A.	0.2	0.029	*
C_0081	1-Methyl-4-imidazoleacetic acid	MIA	1.3E-03	8.3E-04	1.6E-04	6.3E-05	5.9E-04	N.A.	7.9	0.039	*
A_0011	Glyceric acid	Glyceric acid	7.6E-04	2.8E-04	3.5E-04	1.3E-04	2.1E-04	N.A.	2.2	0.055	

A_0073	Homovanillic acid Hydroxyphenyllactic acid	HVA Hydroxyphenyllactic acid	7.4E-05	1.7E-05	2.6E-04	1.1E-04	1.7E-03	N.A.	0.3	0.097	
C_0056	*N*-Methylproline	N-Methylproline	3.0E-04	9.3E-05	1.6E-04	6.6E-05	2.2E-04	N.A.	1.9	0.106	
C_0135	Gly-Asp	Gly-Asp	4.5E-05	1.7E-05	9.3E-05	7.9E-06	N.A.	N.A.	0.5	0.117	
A_0118	*N*-Acetylneuraminic acid	NeuNAc	9.6E-04	7.0E-04	2.3E-04	2.7E-04	9.1E-05	8.2E-05	4.1	0.126	
A_0019	2-Hydroxyvaleric acid	2-Hydroxyvaleric acid	2.2E-04	1.2E-04	5.8E-04	2.7E-04	2.9E-04	3.2E-04	0.4	0.136	

C_0041	Homoserine	Homoserine	2.8E-04	1.9E-04	9.2E-05	4.6E-05	6.2E-05	1.2E-05	3.0	0.143	
C_0083	XC0029 Stachydrine	XC0029 Stachydrine	3.5E-04	2.9E-04	1.2E-04	7.1E-05	8.3E-05	N.A.	2.9	0.159	
A_0006	Lactic acid	Lactic acid	9.0E-04	5.9E-04	3.5E-04	2.3E-05	4.3E-04	3.0E-04	2.6	0.161	
C_0002	Ethanolamine	Ethanolamine	1.7E-03	1.4E-03	4.4E-04	4.0E-04	1.8E-04	1.7E-04	3.9	0.176	
A_0043	3-Phenylpropionic acid	3-Phenylpropionic acid	5.0E-04	5.2E-04	1.3E-04	8.3E-05	2.6E-04	2.0E-04	4.0	0.180	
C_0109	7-Methylguanine	7-Methylguanine	3.5E-04	1.5E-04	2.1E-04	8.5E-05	2.6E-04	2.7E-05	1.6	0.200	
C_0073	Adenine	Adenine	1.6E-04	1.0E-04	5.9E-05	4.0E-05	5.2E-05	N.A.	2.8	0.206	
C_0151	*N*-Acetylgalactosamine *N*-Acetylglucosamine *N*-Acetylmannosamine	N-Acetylgalactosamine GlcNAc ManNAc	3.7E-03	3.4E-03	1.0E-03	6.8E-04	4.9E-04	3.8E-04	3.7	0.212	
C_0059	*N*-Acetylputrescine	N-Acetylputrescine	6.6E-03	5.7E-03	8.1E-04	6.9E-04	4.4E-03	N.A.	8.2	0.216	

A_0050	*m*-Ethoxybenzoic acid 3-Phenyllactic acid *p*-Methoxyphenylacetic acid	m-Ethoxybenzoic acid 3-Phenyllactic acid p-Methoxyphenylacetic acid	7.4E-05	6.5E-05	2.7E-04	1.9E-04	3.2E-04	N.A.	0.3	0.222	
C_0133	N^6,N^6,N^6-Trimethyllysine	Trimethyllysine	1.3E-04	6.4E-05	4.3E-04	3.2E-04	2.7E-04	3.3E-04	0.3	0.239	
C_0134	Homocitrulline	Homocitrulline	1.2E-04	1.1E-05	9.2E-05	1.9E-05	1.4E-04	N.A.	1.3	0.244	
C_0079	Tyramine	Tyramine	1.6E-04	9.0E-05	3.5E-03	3.7E-03	1.5E-03	1.9E-03	0.05	0.257	
C_0054	4-Oxopyrrolidine-2-carboxylic acid	4-Oxopyrrolidine-2-carboxylic acid	5.0E-04	4.5E-04	1.9E-04	1.2E-04	1.9E-04	2.8E-05	2.6	0.264	
C_0103	N^6-Methyllysine	N6-Methyllysine	6.7E-05	2.7E-05	1.8E-04	7.7E-05	N.A.	N.A.	0.4	0.264	
C_0162	Cytidine	Cytidine	3.2E-04	2.6E-04	9.1E-05	7.9E-05	3.1E-05	1.8E-05	3.5	0.266	
C_0074	Hypoxanthine	Hypoxanthine	5.5E-03	7.3E-03	1.3E-03	1.1E-03	7.7E-04	9.4E-05	4.3	0.267	

A_0016	Succinic acid	Succinic acid	1.6E-03	1.2E-03	6.1E-04	3.0E-04	8.0E-04	3.3E-04	2.7	0.272	
C_0107	5-Hydroxylysine	5-Hydroxylysine	6.7E-05	2.4E-05	3.5E-04	1.9E-04	4.1E-05	N.A.	0.2	0.280	
A_0008	Isovaleric acid DL-2-Methylbutyric Acid Valeric acid	Isovaleric acid 2-Methylbutyric acid Valeric acid	1.3E-02	1.1E-02	2.4E-02	1.3E-02	3.2E-02	1.4E-02	0.5	0.285	
A_0051	3-(4-Hydroxyphenyl)propionic acid 2-(4-Hydroxyphenyl)propionic acid 3-(3-Hydroxyphenyl)propionic acid	3-(4-Hydroxyphenyl)propionic acid 2-(4-Hydroxyphenyl)propionic acid 3-(3-Hydroxyphenyl)propionic acid	1.4E-03	9.3E-04	5.2E-04	5.1E-04	4.2E-04	N.A.	2.6	0.286	
C_0169	XC0089	XC0089	9.8E-05	2.7E-05	6.4E-05	1.9E-05	7.9E-05	4.9E-05	1.5	0.289	
C_0095	Xanthine	Xanthine	5.4E-03	8.3E-03	8.6E-04	5.8E-04	9.3E-04	9.1E-04	6.3	0.289	

A_0027	2-Hydroxy-4-methylvaleric acid	2-Hydroxy-4-methylvaleric acid	3.1E-04	2.3E-04	6.6E-04	4.4E-04	3.6E-04	4.4E-04	0.5	0.311	
C_0021	Cadaverine	Cadaverine	5.8E-03	7.7E-03	1.6E-02	1.3E-02	6.5E-04	9.0E-04	0.4	0.316	
C_0012	β-Ala	b-Ala	7.4E-04	5.4E-04	2.7E-03	2.6E-03	9.2E-04	1.1E-03	0.3	0.318	
C_0009	Putrescine	Putrescine	6.7E-03	5.6E-03	2.4E-03	2.6E-03	5.2E-03	N.A.	2.8	0.318	
C_0040	2-Methylserine	2-Methylserine	1.1E-04	7.2E-05	1.7E-04	3.9E-05	5.0E-04	N.A.	0.7	0.318	
C_0129	N^8-Acetylspermidine	N8-Acetylspermidine	1.6E-04	1.0E-04	7.3E-05	9.0E-05	2.6E-05	N.A.	2.2	0.325	
C_0090	Glu	Glu	5.4E-02	6.0E-02	2.3E-02	1.6E-02	2.4E-02	2.7E-03	2.3	0.327	
C_0033	Uracil	Uracil	2.6E-03	3.8E-03	3.6E-04	2.3E-04	4.6E-04	N.A.	7.2	0.327	
C_0185	His-Glu	His-Glu	1.5E-05	8.4E-06	4.2E-05	2.4E-05	N.A.	N.A.	0.3	0.337	

C_0006	Isopropanolamine	Isopropanolamine	2.1E-04	1.8E-04	5.0E-04	4.0E-04	1.4E-04	3.9E-05	0.4	0.337	
C_0128	N^1-Acetylspermidine	N1-Acetylspermidine	9.7E-04	1.1E-03	3.0E-04	3.4E-04	4.0E-05	N.A.	3.2	0.337	
C_0118	Arg	Arg	2.5E-03	3.0E-03	4.7E-03	2.8E-03	2.9E-03	3.0E-03	0.5	0.344	
C_0085	γ-Butyrobetaine	Actinine	3.0E-03	2.4E-03	2.2E-02	2.7E-02	2.2E-02	4.7E-03	0.13	0.344	
A_0136	Cholic acid	Cholic acid	2.6E-03	1.6E-03	1.1E-02	1.2E-02	4.3E-02	5.8E-02	0.2	0.349	
C_0001	Trimethylamine	Trimethylamine	2.7E-03	1.8E-03	1.7E-03	5.7E-04	1.9E-03	3.0E-04	1.6	0.354	
C_0136	2,6-Diaminopimelic acid	2,6-Diaminopimelic acid	5.7E-04	7.5E-04	6.1E-05	2.0E-05	4.2E-05	N.A.	9.3	0.363	
C_0154	N^1,N^8-Diacetylspermidine	N1,N8-Diacetylspermidine	7.3E-04	8.7E-04	1.4E-04	1.1E-04	7.3E-05	8.8E-07	5.1	0.364	
A_0054	Uric acid	Uric acid	2.7E-04	3.7E-04	9.8E-05	2.3E-05	1.0E-04	6.1E-05	2.7	0.367	

C_0180	γ-Glu-Glu	g-Glu-Glu	2.5E-04	3.3E-04	7.8E-05	4.2E-08	8.2E-05	4.7E-05	3.2	0.369	
C_0025	3-Aminoisobutyric acid	3-Aminoisobutyric acid	1.1E-04	4.9E-05	2.2E-03	3.2E-03	1.3E-03	1.1E-03	0.05	0.374	
C_0017	Phenol	Phenol	9.0E-04	1.6E-03	2.1E-04	5.5E-05	2.3E-04	2.4E-05	4.3	0.376	
A_0095	N^2-Acetylaminoadipic acid	N2-Acetylaminoadipic acid	6.3E-05	4.5E-05	3.4E-05	1.4E-05	5.4E-05	N.A.	1.9	0.378	
A_0022	5-Oxoproline	Oxoproline	2.9E-04	4.4E-04	6.6E-05	1.3E-05	1.9E-04	1.1E-05	4.5	0.379	
C_0094	Guanine	Guanine	1.9E-04	1.7E-04	9.3E-05	8.5E-05	4.2E-05	1.4E-05	2.0	0.385	
C_0016	Glycerol	Glycerol	3.8E-02	4.9E-02	6.8E-02	4.1E-02	8.7E-02	7.0E-02	0.6	0.390	
C_0097	4-(β-Acetylaminoethyl)imidazole	4-(b-Acetylaminoethyl)imidazole	5.5E-03	1.1E-02	1.6E-04	1.1E-04	5.6E-05	2.0E-06	34	0.392	
C_0132	Gly-Leu	Gly-Leu	4.5E-04	2.1E-04	7.7E-04	5.1E-04	2.9E-04	1.7E-04	0.6	0.392	

A_0009	2-Hydroxybutyric acid	2-HBA	1.5E-04	6.0E-05	2.3E-04	8.0E-05	2.7E-04	N.A.	0.7	0.394	
C_0108	Methionine sulfoxide	Methionine sulfoxide	4.2E-03	7.9E-03	3.1E-04	1.9E-04	2.2E-04	1.9E-05	14	0.399	
A_0002	Propionic acid	Propionic acid	2.4E-02	1.9E-02	3.4E-02	1.4E-02	2.6E-02	1.3E-04	0.7	0.409	
C_0184	Guanosine	Guanosine	1.5E-04	9.2E-05	2.8E-04	2.3E-04	9.4E-05	3.6E-05	0.5	0.410	
A_0102	Pantothenic acid	Pantothenic acid	2.1E-04	2.6E-04	1.0E-03	1.4E-03	9.4E-04	1.1E-03	0.2	0.422	
A_0092	Syringic acid	Syringic acid	1.9E-04	2.6E-04	4.2E-05	5.3E-06	4.0E-05	N.A.	4.6	0.424	
A_0014	Hexanoic acid	Hexanoic acid	3.2E-04	1.9E-04	4.2E-03	6.8E-03	8.3E-03	1.1E-02	0.08	0.426	
C_0067	Gly-Gly	Gly-Gly	8.9E-05	4.7E-05	1.3E-04	4.2E-05	N.A.	N.A.	0.7	0.432	
C_0070	Asp	Asp	1.7E-02	2.5E-02	6.8E-03	4.8E-03	5.6E-03	7.9E-07	2.4	0.435	

C_0159	Cystine	Cystine	5.2E-05	5.1E-05	8.0E-05	4.5E-06	2.8E-05	N.A.	0.6	0.440	
C_0029	Diethanolamine	Diethanolamine	1.2E-04	1.4E-04	6.4E-05	8.7E-06	4.4E-05	N.A.	1.9	0.446	
C_0150	*N*-Acetylglucosylamine	N-Acetylglucosylamine	7.8E-05	5.0E-05	3.7E-05	1.8E-06	9.1E-05	N.A.	2.1	0.447	
A_0045	3-Hydroxyphenylacetic acid *p*-Hydroxyphenylacetic acid *p*-Anisic acid	3-Hydroxyphenylacetic acid 4-HPAA p-Anisic acid	7.0E-04	5.5E-04	4.5E-04	2.3E-04	8.2E-04	N.A.	1.6	0.453	
C_0172	γ-Glu-Ile γ-Glu-Leu	g-Glu-Ile g-Glu-Leu	1.4E-04	1.3E-04	6.7E-05	1.9E-05	N.A.	N.A.	2.1	0.457	
C_0037	5-Aminovaleric acid	5-Aminovaleric acid	5.1E-03	6.1E-03	1.8E-02	2.5E-02	3.4E-03	2.7E-03	0.3	0.459	
C_0003	XC0001	XC0001	6.6E-04	9.5E-04	3.1E-04	1.3E-04	6.4E-04	2.2E-04	2.1	0.460	
C_0007	Piperidine	Piperidine	2.0E-04	1.0E-04	7.8E-04	1.1E-03	1.0E-04	7.0E-05	0.3	0.461	

A_0049	Terephthalic acid	Terephthalic acid	1.4E-04	1.3E-04	8.8E-05	3.3E-05	1.0E-04	9.1E-06	1.5	0.467	
C_0089	Isoglutamic acid	Isoglutamic acid	1.0E-03	1.1E-03	6.7E-03	1.1E-02	1.0E-02	1.1E-02	0.2	0.468	
A_0029	*p*-Toluic acid *o*-Toluic acid *m*-Toluic acid	p-Toluic acid o-Toluic acid m-Toluic acid	1.3E-03	5.3E-04	2.2E-03	1.9E-03	3.7E-03	3.0E-04	0.6	0.470	
C_0005	Gly	Gly	1.8E-02	3.3E-02	5.7E-03	3.4E-03	3.7E-03	1.3E-03	3.1	0.471	
C_0123	Glucosamine	Glucosamine	1.7E-04	1.7E-04	8.2E-05	4.9E-05	4.5E-05	6.6E-06	2.0	0.475	
C_0145	Carboxymethyllysine	Carboxymethyllysine	7.1E-05	7.0E-05	2.2E-03	2.8E-03	8.3E-04	9.9E-04	0.03	0.475	
C_0182	Saccharopine	Saccharopine	4.3E-05	1.9E-06	1.1E-04	1.3E-04	4.5E-05	2.5E-05	0.4	0.489	
C_0084	4-Guanidinobutyric acid	4-GBA	1.2E-04	1.0E-04	7.0E-05	2.9E-05	N.A.	N.A.	1.7	0.493	
A_0025	*N*-Acetylalanine	N-Acetylalanine	6.2E-05	3.3E-05	4.7E-05	7.2E-06	3.0E-05	N.A.	1.3	0.511	

C_0111	Pyridoxamine	Pyridoxamine	8.5E-05	3.1E-05	1.2E-04	8.4E-05	1.6E-04	2.2E-05	0.7	0.512	
C_0061	Hydroxyproline	Hydroxyproline	1.8E-04	1.4E-04	2.6E-03	3.6E-03	N.A.	N.A.	0.07	0.518	
A_0039	2-Hydroxyglutaric acid	2-Hydroxyglutaric acid	2.8E-04	7.2E-05	3.2E-04	3.4E-05	6.5E-03	N.A.	0.9	0.518	
C_0063	Creatine	Creatine	4.4E-04	7.1E-04	4.5E-03	6.1E-03	2.5E-04	N.A.	0.10	0.521	
C_0101	XC0145 Ala-Ala	XC0145 Ala-Ala	1.9E-03	2.4E-03	9.9E-04	4.1E-04	5.5E-04	2.9E-04	1.9	0.522	
C_0052	Imidazole-4-acetic acid	Imidazole-4-acetic acid	1.7E-04	9.6E-05	7.0E-04	8.3E-04	1.0E-04	N.A.	0.2	0.531	
C_0113	1-Methylhistidine 3-Methylhistidine	1-Methylhistidine 3-Methylhistidine	4.6E-04	3.3E-04	2.7E-04	3.8E-04	9.2E-05	N.A.	1.7	0.537	
A_0085	*N*-Acetylmethionine	N-Acetylmethionine	3.9E-05	3.0E-05	2.5E-05	1.2E-05	2.5E-05	1.4E-05	1.5	0.540	
C_0119	Citrulline	Citrulline	9.6E-03	1.6E-02	4.8E-03	2.7E-03	2.8E-03	2.9E-04	2.0	0.546	

C_0080	1*H*-Imidazole-4-propionic acid	1H-Imidazole-4-propionic acid	1.5E-03	4.5E-04	4.0E-03	4.1E-03	9.3E-03	N.A.	0.4	0.549	
C_0153	2'-Deoxycytidine	dCyt	2.6E-04	3.7E-04	1.3E-04	1.7E-04	4.6E-05	3.0E-05	2.1	0.560	
C_0011	Ala	Ala	4.2E-02	6.8E-02	2.3E-02	1.1E-02	1.4E-02	1.3E-03	1.9	0.564	
C_0088	Lys	Lys	2.6E-02	4.1E-02	1.4E-02	7.1E-03	9.2E-03	2.1E-04	1.8	0.575	
C_0066	Alloisoleucine	Alloisoleucine	5.4E-03	1.0E-02	2.1E-03	2.6E-03	5.4E-04	5.7E-04	2.5	0.580	
C_0130	N^6-Acetyllysine	N6-Acetyllysine	1.1E-04	8.2E-05	1.6E-04	1.0E-04	9.6E-05	7.2E-06	0.7	0.585	
C_0055	Pipecolic acid	Pipecolic acid	2.2E-03	1.9E-03	4.6E-03	6.5E-03	5.0E-03	7.7E-04	0.5	0.593	
C_0161	Thymidine	Thymidine	4.1E-04	2.1E-04	3.4E-04	1.5E-04	4.9E-04	1.2E-04	1.2	0.606	
C_0181	Glu-Glu	Glu-Glu	9.7E-05	8.4E-05	1.6E-04	1.8E-04	5.8E-05	N.A.	0.6	0.607	

C_0140	SDMA	SDMA	1.5E-04	7.8E-05	2.2E-04	1.6E-04	1.5E-04	N.A.	0.7	0.608	
C_0173	γ-Glu-Asn	g-Glu-Asn	2.3E-05	7.1E-06	2.7E-05	5.4E-06	4.5E-05	N.A.	0.9	0.608	
C_0069	Ornithine	Ornithine	3.5E-03	5.2E-03	2.2E-03	1.8E-03	7.3E-04	2.1E-04	1.6	0.615	
A_0080	Kynurenic acid	Kynurenic acid	2.8E-05	1.2E-05	2.2E-05	1.1E-05	4.2E-05	1.9E-05	1.3	0.620	
C_0144	**Trp**	**Trp**	**2.8E-03**	**4.2E-03**	**1.7E-03**	**3.2E-04**	**7.7E-04**	**2.6E-04**	**1.7**	**0.621**	
A_0084	5-Hydroxyindoleacetic acid	5-Hydroxy-IAA	5.8E-05	3.3E-05	4.2E-05	3.4E-05	N.A.	N.A.	1.4	0.624	
C_0035	Pro	Pro	1.6E-02	2.8E-02	3.1E-02	4.4E-02	3.7E-03	2.0E-03	0.5	0.633	
C_0126	Tyr	Tyr	1.1E-02	1.9E-02	7.2E-03	1.7E-03	4.9E-03	2.9E-03	1.6	0.641	
C_0039	Thr	Thr	7.7E-03	1.0E-02	5.3E-03	2.7E-03	3.6E-03	1.1E-03	1.5	0.644	

C_0092	Met	Met	6.3E-03	1.1E-02	3.9E-03	1.9E-03	2.2E-03	2.5E-04	1.6	0.648	
C_0163	Uridine	Uridine	3.6E-04	2.2E-04	3.1E-04	8.2E-06	1.8E-04	1.4E-05	1.2	0.652	
C_0064	Ile	Ile	3.7E-02	6.3E-02	2.3E-02	1.1E-02	7.4E-03	9.8E-05	1.6	0.653	
C_0106	Carnitine	Carnitine	5.6E-04	5.7E-04	7.8E-04	6.3E-04	1.2E-03	1.0E-03	0.7	0.657	
A_0062	Isovalerylalanine-1 N-Acetylleucine-1	Isovalerylalanine N-Acetylleucine	1.1E-04	4.5E-05	1.6E-04	1.9E-04	7.9E-05	3.6E-05	0.7	0.660	
C_0028	Ser	Ser	7.9E-03	1.2E-02	5.2E-03	2.5E-03	3.2E-03	4.9E-04	1.5	0.661	
C_0176	2'-Deoxyguanosine	dGuanosine	2.2E-04	1.2E-04	3.6E-04	4.6E-04	1.0E-04	4.3E-05	0.6	0.664	
C_0026	GABA	GABA	4.7E-04	3.9E-04	7.4E-04	9.3E-04	2.7E-04	5.4E-05	0.6	0.673	
C_0023	2-Aminoisobutyric acid 2-Aminobutyric acid	2-Aminoisobutyric acid 2-Aminobutyric acid	8.9E-03	8.4E-03	6.5E-03	6.0E-03	1.8E-03	2.4E-04	1.4	0.673	

A_0030	*m*-Hydroxybenzoic acid *p*-Hydroxybenzoic acid	m-Hydroxybenzoic acid p-Hydroxybenzoic acid	7.0E-05	1.1E-05	7.6E-05	1.6E-05	7.3E-05	N.A.	0.9	0.677	
C_0098	His	His	1.9E-03	2.2E-03	2.5E-03	1.6E-03	1.8E-03	6.6E-04	0.8	0.679	
A_0018	5-Hydroxypentanoic acid	5-Hydroxypentanoic acid	1.2E-03	1.5E-03	6.1E-04	6.1E-04	5.0E-05	N.A.	2.0	0.681	
A_0078	XA0017	XA0017	1.3E-04	8.8E-05	8.9E-05	9.2E-05	2.3E-05	N.A.	1.4	0.686	
A_0141	Glycocholic acid	Glycocholic acid	4.3E-05	3.4E-06	3.8E-05	1.4E-05	5.6E-05	1.2E-05	1.1	0.686	
C_0048	Nicotinic acid	Nicotinic acid	1.8E-03	1.1E-03	1.5E-03	1.3E-03	9.6E-04	2.3E-04	1.2	0.713	
C_0157	Ser-Glu	Ser-Glu	1.4E-04	7.8E-05	1.7E-04	1.4E-04	6.8E-05	1.9E-05	0.8	0.720	
C_0027	Choline	Choline	2.0E-03	2.0E-03	2.3E-03	7.6E-04	1.7E-03	2.0E-03	0.8	0.722	
C_0086	Spermidine	Spermidine	5.9E-04	4.3E-04	6.9E-04	3.6E-04	4.8E-04	N.A.	0.8	0.726	

A_0026	Glutaric acid Methylsuccinic acid	Glutaric acid Methylsuccinic acid	1.2E-03	5.4E-04	9.5E-04	1.0E-03	1.0E-03	4.5E-04	1.3	0.738	
A_0010	3-Hydroxybutyric acid	3-HBA	3.0E-04	3.2E-05	2.3E-04	2.3E-04	N.A.	N.A.	1.3	0.740	
A_0028	Malic acid	Malic acid	2.1E-03	1.7E-03	2.4E-03	8.0E-04	2.1E-03	1.9E-04	0.9	0.743	
C_0105	*O*-Acetylhomoserine 2-Aminoadipic acid	O-Acetylhomoserine 2-Aminoadipic acid	1.3E-04	7.2E-05	1.1E-04	4.2E-05	1.2E-04	3.9E-05	1.1	0.754	
C_0139	*N*-Acetylhistidine	N-Acetylhistidine	1.3E-04	8.9E-05	1.0E-04	7.2E-05	2.6E-05	N.A.	1.2	0.757	
C_0065	Leu	Leu	5.4E-02	8.4E-02	4.3E-02	2.5E-02	1.6E-02	4.3E-03	1.3	0.784	
A_0075	4-Pyridoxic acid	4-Pyridoxic acid	8.0E-05	3.3E-05	9.1E-05	5.8E-05	1.4E-04	4.9E-05	0.9	0.791	
C_0110	Phe	Phe	2.2E-02	3.7E-02	1.8E-02	7.2E-03	9.4E-03	4.2E-03	1.2	0.805	
A_0116	*N*-Acetylmuramic acid	N-Acetylmuramic acid	1.8E-04	2.9E-04	1.4E-04	9.5E-05	3.1E-04	3.4E-04	1.3	0.813	

C_0170	XC0154	XC0154	1.2E-03	7.3E-04	1.1E-03	2.6E-04	1.3E-03	5.5E-05	1.1	0.819	
C_0191	Arg-Glu	Arg-Glu	7.3E-05	5.6E-05	6.4E-05	4.2E-05	3.4E-05	9.7E-06	1.1	0.834	
C_0146	Lipoamide	Lipoamide	1.2E-04	1.0E-04	9.7E-05	1.1E-04	2.6E-05	N.A.	1.2	0.849	
C_0178	Inosine	Inosine	6.5E-04	7.6E-04	7.3E-04	4.5E-04	2.9E-04	1.1E-04	0.9	0.849	
C_0124	Mannosamine	Mannosamine	1.4E-04	9.9E-05	1.6E-04	1.2E-04	8.5E-05	N.A.	0.9	0.858	
C_0183	γ-Glu-Met	g-Glu-Met	4.4E-05	3.5E-05	4.0E-05	1.6E-05	5.6E-05	3.1E-05	1.1	0.870	
A_0005	Butyric acid Isobutyric acid	Butyric acid Isobutyric acid	3.1E-02	3.0E-02	3.4E-02	8.9E-03	3.1E-02	3.9E-03	0.9	0.871	
C_0166	Octopine	Octopine	2.3E-04	7.7E-05	2.2E-04	1.4E-04	1.3E-04	N.A.	1.1	0.882	
A_0035	4-Acetamidobutanoic acid	4-Acetamidobutanoic acid	6.7E-05	2.0E-05	6.4E-05	2.3E-05	7.7E-05	4.0E-05	1.1	0.886	

A_0081	*N*-Acetylglutamic acid	N-AcGlu	3.8E-04	1.1E-04	3.5E-04	3.3E-04	2.2E-04	1.9E-05	1.1	0.900	
C_0087	Gln	Gln	3.4E-03	3.0E-03	3.2E-03	1.4E-03	1.8E-03	5.2E-04	1.1	0.905	
C_0038	Val	Val	4.0E-02	5.7E-02	3.7E-02	2.7E-02	1.2E-02	2.0E-03	1.1	0.912	
A_0060	Glycerol 3-phosphate	G3P	1.5E-04	4.1E-05	1.7E-04	2.0E-04	3.0E-04	N.A.	0.9	0.918	
C_0022	*N*,*N*-Dimethylglycine	DMG	1.0E-04	5.9E-05	9.8E-05	2.9E-05	N.A.	N.A.	1.0	0.945	
A_0072	1-Methyluric acid	1-Methyluric acid	9.6E-05	6.5E-05	9.3E-05	5.1E-05	8.5E-05	1.8E-05	1.0	0.959	
C_0014	Oxalic acid	Oxalic acid	8.3E-05	3.6E-05	8.1E-05	5.5E-05	4.4E-05	3.3E-06	1.0	0.972	
C_0131	*N*-Acetyllysine	N-Acetyllysine	1.2E-03	7.1E-04	1.2E-03	9.4E-04	1.1E-03	4.7E-04	1.0	0.978	
C_0175	Thiamine	Thiamine	3.3E-04	5.2E-04	3.2E-04	2.9E-04	2.7E-04	1.5E-04	1.0	0.982	

A_0012	Fumaric acid	Fumaric acid	3.6E-04	1.3E-04	3.6E-04	2.7E-04	2.1E-04	4.5E-05	1.0	0.984	
C_0116	*N*-Acetylornithine	N-AcOrn	6.4E-04	5.2E-04	6.5E-04	4.7E-04	1.9E-04	1.6E-05	1.0	0.989	
A_0023	4-Methyl-2-oxovaleric acid 3-Methyl-2-oxovaleric acid 2-Oxohexanoic acid	2-Oxoleucine 2K3MVA 2-Oxohexanoic acid	9.4E-04	1.3E-03	9.3E-04	1.0E-03	5.1E-04	3.6E-04	1.0	0.996	
C_0199	*S*-Adenosylmethionine	SAM	4.3E-05	2.2E-05	4.3E-05	4.2E-05	N.A.	N.A.	1.0	0.999	
C_0018	1-Aminocyclopropane-1-carboxylic acid	1-Aminocyclopropane-1-carboxylic acid	4.3E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0075	1-Methylnicotinamide	1-Methylnicotinamide	N.A.	N.A.	2.8E-05	1.3E-05	5.7E-05	N.A.	<1	N.A.	
C_0168	2'-Deoxyinosine	2'-Deoxyinosine	2.9E-04	1.7E-04	3.4E-04	N.A.	1.6E-04	N.A.	0.9	N.A.	
C_0045	2-Amino-2-(hydroxymethyl)-1,3-propanediol	2-Amino-2-(hydroxymethyl)-1,3-propanediol	3.5E-03	6.0E-04	1.1E-03	N.A.	9.1E-05	5.9E-05	3.1	N.A.	

A_0020	2-Aminoethylphosphonic acid	2-Aminoethylphosphonic acid	7.5E-05	8.3E-05	3.8E-04	N.A.	N.A.	N.A.	0.2	N.A.	
A_0099	2-Deoxyribose 1-phosphate	dR1P	6.4E-05	2.4E-06	N.A.	N.A.	4.1E-04	N.A.	1<	N.A.	
A_0036	2-Oxoglutaric acid	2-OG	6.6E-04	N.A.	6.3E-04	N.A.	4.3E-04	N.A.	1.0	N.A.	
A_0013	2-Oxoisovaleric acid	2-KIV	4.6E-04	N.A.	3.7E-04	N.A.	7.6E-05	N.A.	1.3	N.A.	
C_0046	2-Phenylethylamine	Phenylethylamine	9.4E-05	N.A.	1.6E-04	7.1E-05	2.8E-04	2.9E-04	0.6	N.A.	
A_0150	3'-Dephospho CoA	Dephospho-CoA	3.8E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0074	3,4-Dihydroxyhydrocinnamic acid	3,4-Dihydroxyhydrocinnamic acid	3.4E-04	3.8E-04	2.2E-04	N.A.	N.A.	N.A.	1.5	N.A.	
A_0056	3,4-Dihydroxyphenylacetic acid	DOPAC	3.4E-05	N.A.	6.8E-05	N.A.	N.A.	N.A.	0.5	N.A.	

C_0024	3-Aminobutyric acid	3-Aminobutyric acid	3.3E-04	N.A.	6.4E-04	8.2E-04	2.6E-04	1.4E-04	0.5	N.A.	
C_0015	3-Aminopropane-1,2-diol	3-Aminopropane-1,2-diol	3.7E-05	N.A.	4.4E-05	1.4E-05	5.7E-05	N.A.	0.8	N.A.	
C_0062	3-Guanidinopropionic acid	3-Guanidinopropionic acid	2.5E-05	N.A.	3.5E-05	7.4E-06	3.4E-05	N.A.	0.7	N.A.	
A_0007	3-Hydroxypropionic acid	b-Lactate	2.6E-04	1.7E-04	1.5E-04	N.A.	3.3E-04	2.8E-04	1.7	N.A.	
C_0093	3-Methyladenine	3-Methyladenine	5.1E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0077	3-Phosphoglyceric acid	3-PG	1.7E-04	N.A.	N.A.	N.A.	4.8E-05	N.A.	1<	N.A.	
C_0096	4-Aminosalicylic acid	4-Aminosalicylic acid	3.4E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0082	4-Methyl-5-thiazoleethanol	4-Methyl-5-thiazoleethanol	6.2E-05	5.8E-05	1.8E-05	N.A.	4.4E-05	N.A.	3.4	N.A.	
A_0038	4-Methylthio-2-oxobutyric acid	KMTB	8.6E-05	N.A.	1.1E-04	N.A.	N.A.	N.A.	0.8	N.A.	

A_0031	6-Hydroxynicotinic acid	6-Hydroxynicotinic acid	3.0E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0019	Acetoacetamide	Acetoacetamide	2.5E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0177	Adenosine	Adenosine	3.4E-05	1.3E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0037	Adipic acid	Adipic acid	N.A.	N.A.	4.0E-04	N.A.	3.6E-04	N.A.	<1	N.A.	
C_0100	Allantoin	Allantoin	3.0E-04	N.A.	2.2E-04	1.1E-04	3.9E-04	2.4E-05	1.3	N.A.	
C_0120	Alliin	Alliin	N.A.	N.A.	2.5E-05	5.9E-06	1.9E-04	N.A.	<1	N.A.	
C_0004	Aminoacetone	Aminoacetone	1.4E-03	N.A.	3.3E-04	N.A.	N.A.	N.A.	4.3	N.A.	
A_0126	AMP	AMP	4.5E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0043	Anserine_divalent	Anserine	1.2E-04	N.A.	1.8E-04	N.A.	N.A.	N.A.	0.7	N.A.	

C_0189	Argininosuccinic acid	ArgSuccinate	1.7E-05	3.9E-06	N.A.	N.A.	4.5E-05	N.A.	1<	N.A.	
A_0107	Ascorbate 2-sulfate	Ascorbate 2-sulfate	6.4E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0069	Ascorbic acid	Ascorbic acid	1.5E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0188	Atropine	Atropine	N.A.	N.A.	N.A.	N.A.	1.7E-04	N.A.	N.A.	N.A.	
C_0036	Betaine	Betaine	N.A.	N.A.	N.A.	N.A.	8.5E-04	N.A.	N.A.	N.A.	
C_0137	Caffeine	Caffeine	1.5E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0060	*cis*-4-Hydroxyproline	cis-Hydroxyproline	N.A.	N.A.	8.9E-05	4.3E-05	7.8E-05	N.A.	<1	N.A.	
A_0086	Citric acid	Citric acid	4.4E-04	3.1E-04	7.2E-04	N.A.	N.A.	N.A.	0.6	N.A.	
A_0120	CMP	CMP	4.3E-05	N.A.	2.8E-05	N.A.	N.A.	N.A.	1.5	N.A.	

C_0034	Creatinine	Creatinine	1.2E-03	8.6E-04	9.5E-03	N.A.	2.6E-04	N.A.	0.13	N.A.	
C_0044	Cys	Cys	4.3E-05	2.0E-06	3.1E-05	N.A.	N.A.	N.A.	1.4	N.A.	
C_0031	Cytosine	Cytosine	5.0E-05	4.4E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0123	dAMP	dAMP	1.6E-05	9.5E-07	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0117	dCMP	dCMP	3.1E-05	1.5E-05	2.4E-05	N.A.	3.3E-05	N.A.	1.3	N.A.	
A_0061	Decanoic acid	Decanoic acid	N.A.	N.A.	4.8E-04	4.2E-04	1.9E-04	N.A.	<1	N.A.	
A_0100	Desthiobiotin	Desthiobiotin	N.A.	N.A.	1.6E-04	N.A.	1.6E-04	N.A.	<1	N.A.	
A_0129	Digalacturonic acid	Digalacturonic acid	7.9E-05	4.3E-05	9.8E-05	N.A.	N.A.	N.A.	0.8	N.A.	
A_0057	Dihydroxyacetone phosphate	DHAP	7.8E-05	6.4E-06	6.5E-05	N.A.	2.0E-04	N.A.	1.2	N.A.	

C_0013	Dimethylaminoethanol	Dimethylaminoethanol	2.0E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0106	Dodecanedioic acid	Dodecanedioic acid	1.3E-04	7.7E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0119	dTMP	dTMP	4.9E-05	1.2E-05	2.2E-05	N.A.	N.A.	N.A.	2.3	N.A.	
A_0103	Ethyl glucuronide	Ethyl glucuronide	1.1E-04	N.A.	1.3E-04	6.4E-06	1.6E-04	5.2E-05	0.9	N.A.	
A_0065	Formiminoglutamic acid	Formiminoglutamic acid	6.6E-05	N.A.	6.4E-05	N.A.	1.2E-04	2.1E-05	1.0	N.A.	
A_0048	Formylanthranilic acid	Formylanthranilate	3.9E-05	N.A.	1.7E-05	N.A.	N.A.	N.A.	2.3	N.A.	
A_0110	Fructose 6-phosphate	F6P	2.6E-04	1.2E-05	2.4E-05	N.A.	N.A.	N.A.	11	N.A.	
A_0089	Galacturonic acid-1 Glucuronic acid-1	Galacturonic acid Glucuronic acid	8.8E-04	N.A.	1.9E-04	N.A.	N.A.	N.A.	4.7	N.A.	
A_0090	Galacturonic acid-2 Glucuronic acid-2	Galacturonic acid Glucuronic acid	1.1E-03	1.7E-03	5.2E-04	N.A.	N.A.	N.A.	2.2	N.A.	

C_0121	Gluconolactone	1,5-Gluconolactone	N.A.	N.A.	N.A.	N.A.	6.7E-04	N.A.	N.A.	N.A.	
A_0108	Glucose 1-phosphate	G1P	6.6E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0109	Glucose 6-phosphate	G6P	8.0E-04	6.2E-04	1.3E-04	N.A.	2.4E-04	N.A.	6.2	N.A.	
A_0059	Glycerol 2-phosphate	Glycerol 2-phosphate	N.A.	N.A.	3.3E-05	N.A.	N.A.	N.A.	<1	N.A.	
C_0171	Glycerophosphocholine	GPCho	3.8E-05	N.A.	2.1E-04	N.A.	7.8E-05	N.A.	0.2	N.A.	
A_0024	Heptanoic acid	Heptanoic acid	N.A.	N.A.	6.8E-04	N.A.	4.7E-04	N.A.	<1	N.A.	
C_0032	Histamine	Histamine	6.7E-04	1.2E-03	4.3E-05	N.A.	5.2E-05	N.A.	15	N.A.	
C_0160	Homocarnosine	Homocarnosine	4.2E-05	N.A.	6.6E-05	N.A.	N.A.	N.A.	0.6	N.A.	
C_0020	Homoserinelactone	Homoserinelactone	7.0E-05	5.5E-06	N.A.	N.A.	N.A.	N.A.	1<	N.A.	

C_0071	Hydroxyindole	Hydroxyindole	5.5E-04	2.0E-04	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0099	Imidazolelactic acid	Imidazolelactic acid	1.2E-04	N.A.	7.3E-04	4.8E-04	6.1E-04	N.A.	0.2	N.A.	
A_0068	**Indole-3-acetic acid**	**IAA**	**5.9E-05**	**N.A.**	**1.9E-04**	**2.6E-04**	**4.2E-05**	**N.A.**	**0.3**	**N.A.**	
A_0096	Indole-3-lactic acid 5-Methoxyindoleacetic acid	Indolelactic acid 5-MIAA	N.A.	N.A.	2.9E-04	1.9E-04	1.7E-04	1.8E-04	<1	N.A.	
A_0063	Isovalerylalanine-2 N-Acetylleucine-2	Isovalerylalanine N-Acetylleucine	6.6E-05	N.A.	6.9E-05	N.A.	N.A.	N.A.	1.0	N.A.	
A_0094	Lauric acid	Lauric acid	1.1E-04	N.A.	2.0E-04	N.A.	N.A.	N.A.	0.6	N.A.	
A_0040	Mevalonic acid	Mevalonic acid	N.A.	N.A.	1.4E-04	N.A.	N.A.	N.A.	<1	N.A.	
C_0008	Morpholine	Morpholine	N.A.	N.A.	8.4E-05	N.A.	1.2E-04	N.A.	<1	N.A.	
A_0098	Mucic acid	Mucic acid	5.4E-05	N.A.	1.0E-04	4.3E-05	3.0E-04	N.A.	0.5	N.A.	

A_0066	*N*-Acetylasparagine	N-Acetylasparagine	4.0E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0067	*N*-Acetylaspartic acid	N-Acetylaspartic acid	5.2E-04	4.0E-04	2.0E-04	N.A.	1.1E-04	N.A.	2.6	N.A.	
A_0079	*N*-Acetylglutamine	N-Acetylglutamine	5.1E-05	3.5E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0015	*N*-Acetylglycine	N-Acetylglycine	1.5E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0097	*N*-Acetylphenylalanine	N-Acetylphenylalanine	3.5E-05	2.9E-05	N.A.	N.A.	1.8E-05	N.A.	1<	N.A.	
A_0083	*N*-Carbamylglutamic acid	N-Carbamylglutamic acid	N.A.	N.A.	7.5E-05	N.A.	N.A.	N.A.	<1	N.A.	
A_0032	*N*-Ethylmaleimide_+H_2O	N-Ethylmaleimide	4.5E-05	2.3E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0070	*N*-Formylmethionine	N-Formylmethionine	1.5E-05	N.A.	2.9E-05	1.8E-05	2.9E-05	N.A.	0.5	N.A.	
C_0104	*N*-Methylglutamic acid	N-Methylglutamic acid	6.5E-05	N.A.	3.8E-04	N.A.	N.A.	N.A.	0.2	N.A.	

C_0072	*N*-Nitrosodiethanolamine	N-Nitrosodiethanolamine	N.A.	N.A.	1.3E-04	N.A.	N.A.	N.A.	<1	N.A.	
C_0186	N^1,N^{12}-Diacetylspermine	N1,N12-Diacetylspermine	2.1E-04	1.6E-04	5.9E-05	N.A.	N.A.	N.A.	3.5	N.A.	
C_0164	N^1-Acetylspermine	N1-Acetylspermine	3.2E-05	1.3E-05	3.0E-05	N.A.	N.A.	N.A.	1.0	N.A.	
A_0112	N^2-Phenylacetylglutamine	N2-Phenylacetylglutamine	N.A.	N.A.	7.2E-05	N.A.	N.A.	N.A.	<1	N.A.	
C_0117	N^5-Ethylglutamine	N5-Ethylglutamine	1.6E-04	6.7E-05	3.4E-04	N.A.	N.A.	N.A.	0.5	N.A.	
C_0047	Nicotinamide	Nicotinamide	9.0E-05	1.3E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0196	NMN	NicRN	2.4E-04	5.1E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0158	*N*'-Formylkynurenine	N-Formylkynurenine	5.1E-05	N.A.	2.1E-05	N.A.	N.A.	N.A.	2.4	N.A.	
C_0142	*O*-Acetylcarnitine	ALCAR	N.A.	N.A.	1.0E-04	N.A.	9.0E-05	N.A.	<1	N.A.	

C_0091	*O*-Acetylserine	O-Acetylserine	6.5E-05	3.1E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0047	*o*-Coumaric acid *p*-Coumaric acid	o-Coumaric acid p-Coumaric acid	3.8E-05	N.A.	3.2E-05	N.A.	N.A.	N.A.	1.2	N.A.	
A_0033	Octanoic acid	Octanoic acid	N.A.	N.A.	6.7E-04	1.0E-03	N.A.	N.A.	<1	N.A.	
C_0187	Ophthalmic acid	Ophthalmic acid	N.A.	N.A.	3.5E-05	N.A.	N.A.	N.A.	<1	N.A.	
A_0044	Oxypurinol	Oxypurinol	8.2E-05	6.4E-05	4.6E-05	N.A.	5.9E-05	N.A.	1.8	N.A.	
C_0078	*p*-Aminobenzoic acid	p-Aminobenzoic acid	4.3E-05	N.A.	6.6E-05	6.7E-05	4.8E-05	5.0E-06	0.6	N.A.	
C_0030	*p*-Aminophenol *m*-Aminophenol *o*-Aminophenol	p-Aminophenol m-Aminophenol 2-Aminophenol	9.7E-03	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0071	*p*-Hydroxyphenylpyruvic acid	HPP	N.A.	N.A.	7.8E-05	N.A.	N.A.	N.A.	<1	N.A.	
A_0046	Phenylpyruvic acid	Phenylpyruvate	6.4E-05	N.A.	1.1E-04	N.A.	N.A.	N.A.	0.6	N.A.	

C_0127	Phosphorylcholine	Phosphorylcholine	1.1E-04	4.2E-05	9.8E-05	N.A.	N.A.	N.A.	1.2	N.A.	
C_0049	Pyrazinamide	Pyrazinamide	6.6E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0112	Pyridoxine	Pyridoxine	5.6E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0004	Pyruvic acid	Pyruvic acid	7.3E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0198	Riboflavin	Riboflavin	8.3E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0105	Ribose 5-phosphate	R5P	6.9E-05	4.5E-05	3.8E-05	N.A.	4.7E-05	N.A.	1.8	N.A.	
A_0104	Ribulose 5-phosphate	Ru5P	1.2E-04	4.5E-05	8.7E-05	N.A.	5.3E-04	N.A.	1.3	N.A.	
C_0122	*S*-Carboxymethylcysteine	S-Carboxymethylcysteine	2.9E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0010	Sarcosine	Sarcosine	2.3E-04	7.0E-05	9.9E-05	N.A.	1.9E-04	N.A.	2.3	N.A.	

A_0115	Sedoheptulose 7-phosphate	S7P	1.3E-04	1.8E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0137	Sucrose 6'-phosphate	Sucrose 6'-phosphate	2.6E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0111	Sulfotyrosine	Sulfotyrosine	1.3E-04	N.A.	1.7E-04	N.A.	N.A.	N.A.	0.8	N.A.	
A_0042	Tartaric acid	Tartaric acid	1.5E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0050	Taurine	Taurine	4.5E-04	3.8E-04	9.8E-04	N.A.	N.A.	N.A.	0.5	N.A.	
C_0197	Thiamine phosphate	TMP	5.0E-05	5.4E-05	1.8E-05	N.A.	N.A.	N.A.	2.7	N.A.	
A_0041	Thiodiglycolic acid	Thiodiglycolic acid	1.1E-04	6.4E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0156	Thr-Asp	Thr-Asp	6.2E-05	4.7E-06	1.1E-04	N.A.	5.7E-05	N.A.	0.6	N.A.	
C_0058	*trans*-Glutaconic acid	trans-Glutaconic acid	2.0E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	

A_0101	Tridecanoic acid	Tridecanoic acid	N.A.	N.A.	3.0E-05	N.A.	N.A.	N.A.	<1	N.A.	
C_0076	Trigonelline	Trigonelline	1.2E-04	N.A.	4.5E-05	3.2E-05	N.A.	N.A.	2.6	N.A.	
C_0190	Trimethoprim	Trimethoprim	N.A.	N.A.	N.A.	N.A.	1.3E-04	N.A.	N.A.	N.A.	
C_0102	**Tryptamine**	**Tryptamine**	**6.2E-05**	**3.9E-05**	**5.7E-05**	**N.A.**	**5.2E-05**	**N.A.**	**1.1**	**N.A.**	
C_0138	Tyrosine methyl ester	Tyrosine methyl ester	1.1E-04	4.4E-05	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
A_0121	UMP	UMP	4.1E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0195	Val-Pro-Pro	Val-Pro-Pro	2.1E-05	N.A.	1.5E-04	N.A.	1.5E-04	N.A.	0.14	N.A.	
A_0055	Vanillic acid	Vanillic acid	2.2E-04	2.7E-04	1.7E-05	N.A.	2.3E-05	3.5E-06	13	N.A.	
A_0021	XA0003	XA0003	3.6E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	

A_0034	XA0004	XA0004	1.2E-03	N.A.	2.3E-05	N.A.	N.A.	N.A.	54	N.A.	
A_0052	XA0012	XA0012	1.9E-05	7.7E-06	5.8E-05	N.A.	N.A.	N.A.	0.3	N.A.	
A_0088	XA0019	XA0019	N.A.	N.A.	3.7E-05	N.A.	N.A.	N.A.	<1	N.A.	
A_0114	Xanthosine	Xanthosine	5.2E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0053	XC0016	XC0016	8.6E-05	N.A.	8.5E-05	N.A.	N.A.	N.A.	1.0	N.A.	
C_0057	XC0017	XC0017	5.5E-05	N.A.	4.1E-05	N.A.	N.A.	N.A.	1.4	N.A.	
C_0115	XC0040	XC0040	N.A.	N.A.	2.5E-05	N.A.	N.A.	N.A.	<1	N.A.	
C_0149	XC0065	XC0065	5.2E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0114	XC0147	XC0147	N.A.	N.A.	3.4E-05	N.A.	N.A.	N.A.	<1	N.A.	

C_0125	XC0148	XC0148	7.6E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0147	β-Ala-Lys	b-Ala-Lys	N.A.	N.A.	4.4E-05	N.A.	9.3E-05	N.A.	<1	N.A.	
A_0017	β-Hydroxyisovaleric acid	b-Hydroxyisovaleric acid	9.4E-05	N.A.	1.3E-04	N.A.	N.A.	N.A.	0.7	N.A.	
C_0148	γ-Glu-Ala	g-Glu-Ala	1.6E-04	1.9E-04	2.9E-05	N.A.	N.A.	N.A.	5.4	N.A.	
C_0192	γ-Glu-Citrulline	g-Glu-Citrulline	2.9E-04	N.A.	2.5E-05	N.A.	N.A.	N.A.	11	N.A.	
C_0179	γ-Glu-Gln	g-Glu-Gln	2.1E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0143	γ-Glu-Gly	g-Glu-Gly	3.0E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0174	γ-Glu-Ornitine	g-Glu-Ornitine	6.7E-05	N.A.	1.1E-04	N.A.	8.8E-05	N.A.	0.6	N.A.	
C_0155	γ-Glu-Ser	g-Glu-Ser	1.1E-04	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	

C_0167	γ-Glu-Thr	g-Glu-Thr	7.5E-05	N.A.	N.A.	N.A.	N.A.	N.A.	1<	N.A.	
C_0165	γ-Glu-Val	g-Glu-Val	8.3E-05	N.A.	4.3E-04	4.9E-04	4.1E-04	4.6E-04	0.2	N.A.	

The ID consists of the initial letter of the measurement mode and a serial number, where C indicates cationic mode and A indicates anionic mode.

†Candidate compound names obtained by matching with the HMT database.

¶The ratio of the detected mean values between the two groups was calculated using the latter as the denominator.

‖ The p values and their ranges for Welch's t-test are shown. (*<0.05)

Supplementary Table 6. Primer sequences for real time-PCR		
Gene		Primer sequence
ACTB	Forward	5'-CATGTACGTTGCTATCCAGGC-3'
	Reverse	5'-CTCCTTAATGTCACGCACGAT-3'
IL1B	Forward	5'-GAGCAACAAGTGGTGTTCTCC-3'
	Reverse	5'-AACACGCAGGACAGGTACAG-3'
IFNG	Forward	5'-TTCAGCTCTGCATCGTTTTGG-3'
	Reverse	5'-CACTCTTTTGGATGCTCTGGTC-3'
IL6	Forward	5'-CAGTTCCTGCAGAAAAAGGCAA-3'
	Reverse	5'-AGCTGCGCAGAATGAGATGA-3'
TNFA	Forward	5'-ATGTTGTAGCAAACCCTCAAGC-3'
	Reverse	5'-TGATGGCAGAGAGGAGGTTG-3'

ACE2	Forward	5'-GTCCCGGAGCCGTATCAATG-3'
	Reverse	5'-GGAGGCATAAGGATTTTCTCCAC-3'
AHR	Forward	5'-TCAACAGCAACAGTCCTTGG-3'
	Reverse	5'-CCCATAGGGTAGTCCAGCTCT-3'
CYP1A1	Forward	5'-GGTCAAGGAGCACTACAAAACC-3'
	Reverse	5'-TGGACATTGGCGTTCTCAT-3'
CARD9	Forward	5'-GCGCCTCAAAGAGAGTTTTG-3'
	Reverse	5'-TCAGTGTCGGTGTTGTCGC-3'
IL22	Forward	5'-CCCATCAGCTCCCACTGC-3'
	Reverse	5'-GGCACCACCTCCTGCATATA-3'
IL22BP	Forward	5'-GGAACACTGGTTGCCTGAAC-3'
	Reverse	5'-ACACTGCTGTTGCCAGTAAGT-3'

4. References to the Supplemental Material

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