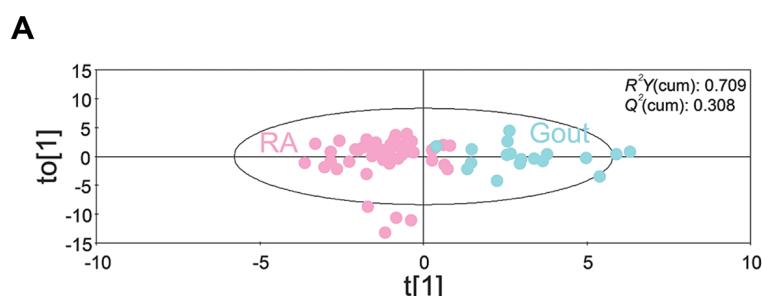
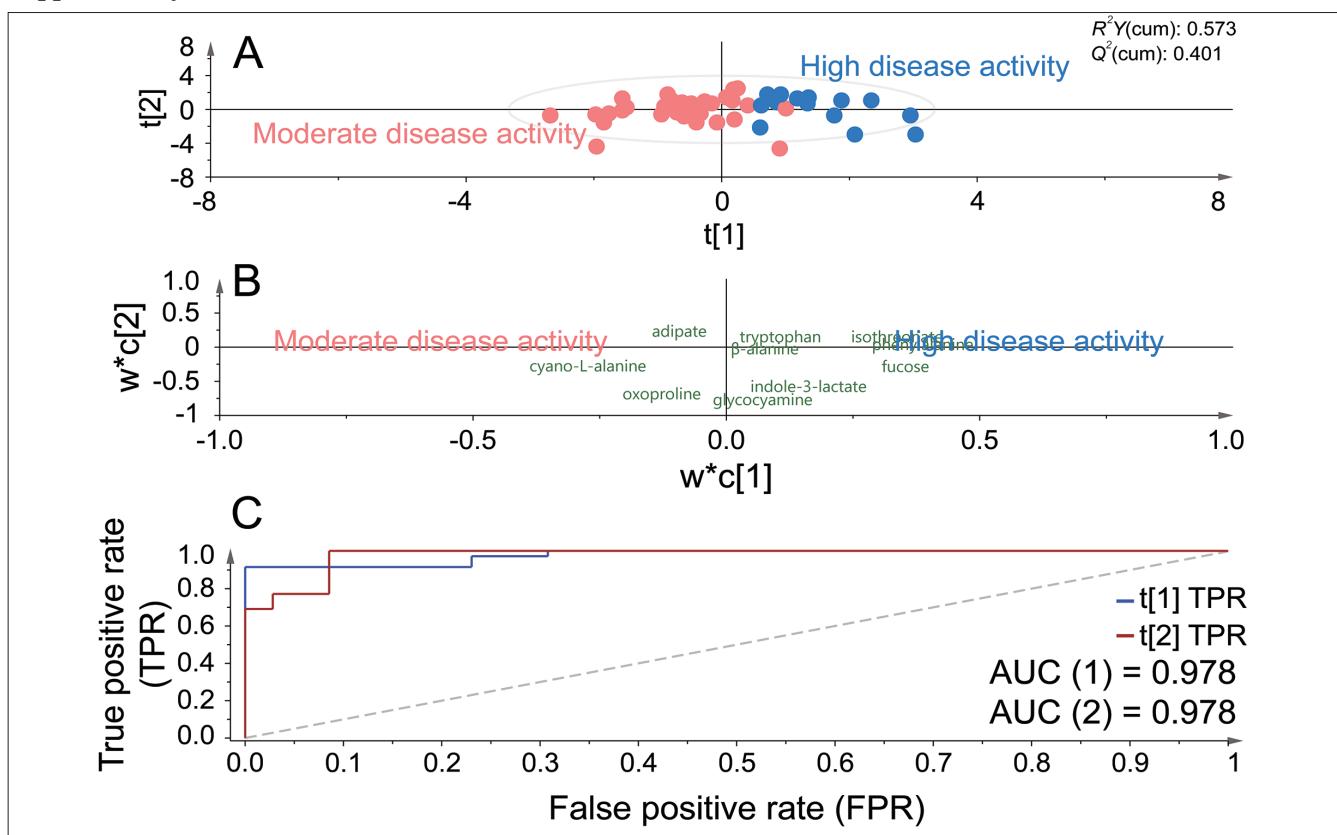
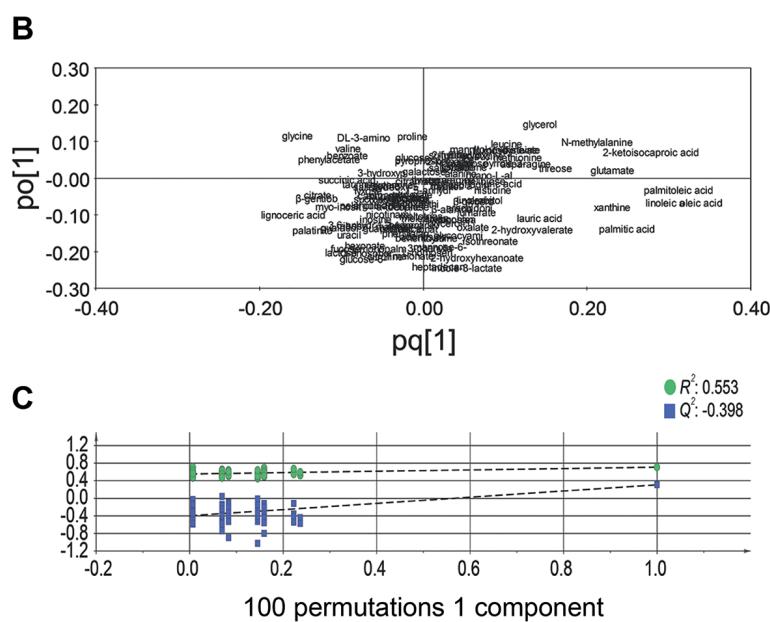


Supplementary file



Suppl. Fig. 1. The score plot (A), loading plot (B), and permutation tests (C) of the PLS-DA. Rheumatoid arthritis (RA) patients ($n=48$) and gouty arthritis patients ($n=18$) were used. The PLS-DA score plot revealed clear discrimination between two groups. The numbers represent the sample numbers. In the permutation tests with 100 iterations (C), the Y-axis intercepts of R^2 and Q^2 are 0.553 and -0.398, respectively, indicating that the original model is valid.



Suppl. Fig. 2. The score plot (A), loading plot (B), and ROC curve (C) of the OPLS-DA using 10 metabolites which are specifically related with the disease activity of rheumatoid arthritis (RA). The RA patients with moderate ($n=35$) and high disease activity ($n=13$) were used.

Suppl. Table S1. Metabolites identified in synovial fluid and classified on the basis of their chemical structures

Identification of metabolites		
Amines		
2-hydroxypyridine	3-hydroxypyridine	5'-deoxy-5'-methylthioadenosine
glycocyamine	guanosine	hypoxanthine
inosine	O-phosphorylethanolamine	thymine
uracil	urea	uric acid
	uridine	xanthine
Amino acids		
alanine	asparagine	asparagine dehydrated
aspartate	cyano-L-alanine	glutamate
glutamine	glycine	histidine
isoleucine	L-citrulline	L-cysteine
leucine	L-homoserine	lysine
methionine	N-methylalanine	ornithine
oxoproline	phenylalanine	proline
serine	threonine	tryptophan
tyrosine	valine	β-alanine

Suppl. Table S3. Spearman's rank correlation coefficients for relation between metabolites concentration and DAS28-ESR(3) in patients with RA.

Metabolites	N	Spearman R (ESR vs. intensity)	t(N-2)	p-value
citrate	48	-0.542	-4.370	7.02.E-05
asparagine	48	-0.354	-2.566	1.36.E-02
β-alanine	48	-0.323	-2.317	2.50.E-02
oxoproline	48	-0.307	-2.187	3.38.E-02
cyano-L-alanine	48	-0.302	-2.151	3.67.E-02
glycocyamine	48	0.315	2.251	2.92.E-02
adipate	48	0.323	2.314	2.52.E-02
phenylalanine	48	0.341	2.464	1.75.E-02
tryptophan	48	0.352	2.552	1.41.E-02
isothreonate	48	0.358	2.598	1.26.E-02
fucose	48	0.453	3.447	1.22.E-03
indole-3-lactate	48	0.479	3.700	5.75.E-04

Suppl. Table S4. Spearman's rank correlation coefficients for relation between metabolites concentration and WBC count in patients with RA

Metabolites	N	Spearman R (WBC vs. intensity)	t(N-2)	p-value
asparagine	42	-0.367	-2.498	1.67.E-02
benzoate	42	-0.308	-2.051	4.69.E-02
citramalate	42	-0.511	-3.756	5.51.E-04
citrate	42	-0.550	-4.166	1.61.E-04
hypoxanthine	42	0.322	2.148	3.78.E-02
lauric acid	42	-0.347	-2.337	2.45.E-02
pyrophosphate	42	-0.375	-2.555	1.45.E-02
thymine	42	0.507	3.722	6.08.E-04
tyrosine	42	-0.384	-2.632	1.20.E-02
uridine	42	-0.359	-2.434	1.95.E-02
valine	42	0.314	2.093	4.28.E-02
xanthine	42	0.363	2.465	1.81.E-02
xylose	42	-0.352	-2.379	2.22.E-02

Suppl. Table S5. The demographics and laboratory findings of the patients with gout.

	Gout (n=18)	RA (n=48)	p-value
Demographics			
Male (%)	16 (88.9)	15 (31.3)	<0.001
Age (mean ± SD)	47.8 ± 15.3	56.6 ± 14.0	0.031
Laboratory findings			
SF WBC (/mm ³)	15,885.9 ± 25,610.5	11,873.5 ± 13,246.8	0.558
CRP (mg/dl)	2.54 ± 3.12	2.88 ± 3.32	0.73
ESR (mm/hr)	35.92 ± 29.35	62.88 ± 32.87	0.012

Suppl. Table S2. VIP and loading values of the PLS-DA model discriminating RA patients with moderate and high disease activity metabolites.

	VIP value	Loading score 1	Loading score 2		VIP value	Loading score 1	Loading score 2
1,2,4-benzenetriol	0.589	0.053	-0.015	linolenic acid	0.554	0.060	0.052
1,5-anhydroglucitol	1.120	0.111	0.150	lysine	0.576	-0.062	-0.056
1-monopalmitin	0.886	0.033	-0.107	lyxose	0.491	-0.039	-0.080
1-monostearin	0.944	-0.039	-0.163	malate	0.856	0.030	-0.105
2-hydroxyhexanoate	1.081	0.067	-0.092	malonate	1.059	0.013	-0.155
2-hydroxypyridine	0.982	-0.107	-0.088	maltotriose	0.771	0.075	-0.004
2-hydroxyvalerate	1.935	0.210	0.184	mannitol	0.646	-0.041	0.054
2-ketoadipic acid	0.890	0.032	0.153	mannose	1.175	-0.128	-0.085
2-ketoisocaproic acid	1.352	0.079	0.233	mannose-6-phosphate	0.923	0.010	-0.136
3,6-anhydro-D-galactose	1.861	0.203	0.151	melezitose	1.114	0.116	0.027
3-hydroxypyridine	0.743	0.058	0.121	melibiose	0.180	0.011	-0.015
3-phenyllactate	0.996	0.062	-0.084	methionine	0.357	-0.019	0.035
5'-deoxy-5'-methylthioadenosine	1.115	0.100	0.169	myo-inositol	0.236	0.017	0.039
adenosine-5-monophosphate	1.133	0.107	-0.015	myristic acid	0.539	-0.055	-0.069
adipate	0.285	0.004	-0.041	nicotinamide	0.977	0.004	-0.149
alanine	0.390	-0.043	-0.027	N-methylalanine	0.970	-0.071	0.062
arabitol	1.125	0.107	0.161	oleic acid	0.743	0.071	-0.008
arachidonic acid	0.748	-0.050	-0.127	O-phosphorylethanolamine	1.403	0.100	-0.097
asparagine	1.007	-0.105	-0.121	ornithine	0.782	0.039	0.135
asparagine dehydrated	0.220	0.007	0.038	oxalate	0.920	0.094	0.016
aspartate	0.661	0.007	-0.097	oxoproline	1.360	-0.097	-0.228
behenic acid	0.807	-0.016	-0.134	palatinitol	0.818	0.068	-0.037
benzoate	0.623	-0.026	0.071	palmitic acid	0.975	0.020	-0.135
capric acid	0.351	-0.034	-0.049	palmitoleic acid	0.798	0.066	-0.036
cholic acid	0.411	-0.007	-0.068	pelargonic acid	0.302	0.031	0.004
citramalate	1.357	-0.147	-0.124	phenylacetate	0.745	-0.080	-0.036
citrate	2.249	-0.207	-0.332	phenylalanine	1.832	0.200	0.144
citrulline	1.203	0.016	-0.175	phosphogluconic acid	0.604	-0.063	-0.015
cyano-L-alanine	1.047	-0.093	-0.159	phthalic acid	1.601	0.175	0.115
DL-3-aminoisobutyrate	1.384	0.081	0.238	proline	1.037	-0.113	-0.066
fructose	1.002	-0.094	0.016	pyrophosphate	0.552	-0.009	0.079
fucose	2.158	0.235	0.132	pyrrole-2-carboxylate	0.286	-0.011	0.034
fumarate	1.040	0.113	0.069	pyruvate	0.999	-0.104	-0.023
galactonate	1.058	0.115	0.088	ribose	0.509	0.000	-0.079
galactose	0.456	-0.046	-0.006	salicylaldehyde	0.940	-0.095	-0.122
glucose	0.700	-0.018	0.093	salicylic acid	1.292	0.127	0.176
glucose-6-phosphate	1.735	0.162	-0.028	serine	0.325	0.000	-0.050
glutamate	0.224	0.014	0.038	stearic acid	0.473	0.010	-0.065
glutamine	0.200	0.005	-0.027	succinate	0.552	0.060	0.041
glycerate	0.236	-0.017	0.015	sucrose	0.701	0.074	0.080
glycerol	1.324	-0.070	0.132	sulfuric acid	0.445	0.023	0.077
glycerol-1-phosphate	0.907	-0.051	-0.156	taurine	0.500	0.054	0.025
glycine	1.006	-0.101	-0.006	terephthalate	0.837	0.086	0.103
glycocyamine	0.929	0.061	-0.073	threitol	0.434	-0.041	-0.063
glycolate	0.510	0.028	-0.050	threonine	0.880	-0.062	-0.148
guaiacol	1.449	0.157	0.143	threose	0.676	-0.072	-0.024
guanosine	0.739	0.070	-0.009	thymine	1.717	0.181	0.055
heptadecanoic acid	1.155	0.076	-0.090	trehalose	1.251	0.131	0.148
hexonate	1.423	0.152	0.061	tryptophan	1.582	0.171	0.158
histidine	0.433	0.022	-0.045	tyrosine	1.118	-0.122	-0.074
hypoxanthine	0.745	0.052	-0.053	uracil	1.213	0.091	-0.073
indole-3-lactate	1.577	0.155	0.001	urea	1.025	0.032	0.175
inosine	0.831	-0.027	-0.142	uric acid	0.464	-0.050	-0.048
isoleucine	0.151	0.007	0.026	uridine	1.167	-0.127	-0.074
isothreonate	1.694	0.184	0.096	valine	0.565	-0.047	0.024
lactose	1.676	0.179	0.071	xanthine	0.669	0.063	-0.010
lauric acid	0.707	-0.034	-0.122	xylose	0.299	-0.026	-0.046
L-citrulline	0.654	0.060	-0.013	α-tocopherol	0.911	0.099	0.066
L-cysteine	1.413	0.101	0.237	β-alanine	0.725	-0.026	-0.124
leucine	0.585	0.016	0.099	β-gentiobiose	0.795	0.086	0.081
L-homoserine	1.132	0.009	-0.169	β-glycerolphosphate	1.034	-0.088	-0.162
lignoceric acid	0.512	0.040	-0.028	β-hydroxybutyrate	1.075	0.068	0.184
linoleic acid	1.245	-0.069	-0.215				

Suppl. Table S6. VIP and loading values of the PLS-DA model discriminating RA patients with gout patients

Metabolites	VIP	Loading score 1	Loading score 2	Metabolites	VIP	Loading score 1	Loading score 2
1,2,4-benzenetriol	0.865	-0.047	0.104	linolenic acid	0.437	0.029	0.045
1,5-anhydroglucitol	0.267	-0.020	0.022	lysine	0.267	0.013	-0.034
1-monopalmitin	1.329	-0.072	0.160	lyxose	0.766	-0.069	0.023
1-monostearin	0.609	-0.003	0.091	malate	0.896	-0.048	0.108
2-hydroxyhexanoate	1.218	0.004	0.182	malonate	1.233	-0.032	0.177
2-hydroxypyridine	0.416	0.005	-0.062	maltotriose	0.624	-0.026	0.083
2-hydroxyvalerate	1.030	0.062	0.116	mannitol	0.557	0.023	-0.075
2-keto adipic acid	0.307	0.000	-0.046	mannose	0.353	0.020	-0.042
2-ketoisocaproic acid	1.892	0.168	-0.067	mannose-6-phosphate	1.052	-0.012	0.156
3,6-anhydro-D-galactose	1.236	-0.093	0.104	melezitose	0.643	-0.024	0.088
3-hydroxypyridine	0.729	-0.066	-0.020	melibiose	0.368	0.034	0.001
3-phenyllactate	1.086	-0.018	0.160	methionine	0.788	0.064	-0.055
5'-deoxy-5'-methylthioadenosine	0.574	-0.052	0.015	myo-inositol	1.227	-0.106	0.060
adenosine-5-monophosphate	0.921	-0.025	0.132	myristic acid	0.081	0.004	0.011
adipate	0.486	-0.037	0.041	nicotinamide	0.821	-0.058	0.079
alanine	0.221	0.017	-0.017	N-methylalanine	1.532	0.128	-0.092
arabitol	0.540	0.041	0.046	oleic acid	2.656	0.241	0.052
arachidonic acid	0.474	0.019	0.064	O-phosphorylethanolamine	1.455	-0.083	0.171
asparagine	0.028	-0.002	-0.003	ornithine	0.787	0.057	-0.072
asparagine dehydrated	0.817	0.071	-0.040	oxalate	0.798	0.029	0.110
aspartate	0.663	-0.057	0.034	oxoproline	0.797	-0.036	0.104
behenic acid	0.963	-0.030	0.136	palatinitol	1.602	-0.128	0.117
benzoate	1.114	-0.095	-0.060	palmitic acid	1.950	0.164	0.114
capric acid	0.755	-0.066	0.035	palmitoleic acid	2.264	0.207	0.022
cholic acid	0.849	-0.069	0.059	pelargonic acid	0.984	-0.083	0.059
citramalate	0.321	-0.029	0.000	phenylacetate	1.379	-0.122	-0.050
citrate	1.298	-0.117	0.034	phenylalanine	0.956	-0.043	0.125
citrulline	1.341	-0.056	0.179	phosphogluconic acid	0.126	0.010	0.008
cyano-L-alanine	0.421	0.038	-0.013	phthalic acid	0.895	-0.044	0.113
DL-3-aminoisobutyrate	1.151	-0.085	-0.102	proline	0.760	-0.028	-0.104
fructose	0.680	0.044	-0.072	pyrophosphate	0.463	-0.030	-0.048
fucose	1.463	-0.091	0.161	pyrrole-2-carboxylate	0.652	0.054	-0.041
fumarate	0.593	0.029	0.075	pyruvate	0.935	0.073	-0.073
galactonate	0.838	-0.033	0.113	ribose	1.148	-0.083	0.106
galactose	0.289	-0.023	-0.021	salicylaldehyde	0.213	0.002	-0.032
glucose	0.487	-0.030	-0.055	salicylic acid	0.770	-0.070	0.014
glucose-6-phosphate	1.527	-0.083	0.184	serine	0.569	-0.052	0.011
glutamate	1.715	0.156	-0.025	stearic acid	0.540	-0.039	0.050
glutamine	0.590	-0.054	0.011	succinic acid	1.125	-0.103	-0.002
glycerate	0.420	-0.033	0.033	sucrose	0.809	-0.069	0.043
glycerol	1.342	0.092	-0.133	sulfuric acid	0.410	0.002	-0.061
glycerol-1-phosphate	0.665	0.001	0.100	taurine	0.875	-0.080	0.009
glycine	1.664	-0.138	-0.107	terephthalate	0.474	-0.037	0.038
glycocyamine	0.861	0.007	0.129	threitol	0.101	0.005	0.013
glycolate	0.479	-0.035	0.042	threonine	0.160	-0.015	-0.002
guaiacol	1.333	-0.101	0.112	threose	1.186	0.107	-0.029
guanosine	1.003	-0.061	0.113	thymine	0.897	-0.003	0.134
heptadecanoic acid	1.364	-0.014	0.203	trehalose	0.566	-0.036	0.061
hexonate	1.330	-0.078	0.153	tryptophan	0.613	0.000	0.092
histidine	0.515	0.045	0.022	tyrosine	0.267	0.014	-0.033
hypoxanthine	0.510	-0.033	0.055	uracil	1.260	-0.085	0.128
indole-3-lactate	1.380	0.005	0.206	urea	0.405	0.025	-0.044
inosine	0.920	-0.063	0.091	uric acid	0.605	0.055	0.007
isoleucine	0.518	0.031	-0.059	uridine	0.381	0.029	-0.032
isothreonate	1.024	0.034	0.143	valine	1.079	-0.087	-0.076
lactose	1.549	-0.096	0.170	xanthine	1.791	0.159	0.063
lauric acid	1.110	0.086	0.088	xylose	0.653	-0.053	0.046
L-citrulline	0.445	-0.029	0.046	α-tocopherol	0.664	-0.048	0.062
L-cysteine	0.845	0.063	-0.073	β-alanine	0.456	0.005	0.068
leucine	0.886	0.061	-0.087	β-gentiobiose	1.392	-0.125	0.042
L-homoserine	1.161	-0.023	0.170	β-glycerophosphate	0.427	0.026	0.048
lignoceric acid	1.805	-0.158	0.081	β-hydroxybutyrate	0.467	0.021	-0.061
linoleic acid	2.307	0.209	0.052				