Supplementary table S1. Comparison of clinical variable at baseline and 6 months after tocilizumab treatment.

Variable	Baseline N= 35	6 months N= 35	p
Age	53.42 ± 10.57	53.85 ± 10.60	0.87
DAS28ESR	5.78 ± 0.99	3.32 ± 1.05	**<0.001**
ESR	52.29 ± 31.44	19.39 ± 26.27	**<0.001**
CRP	1.99 ± 2.69	0.20 ± 0.45	**<0.001**
Swollen joints	6.00 ± 4.08	2.00 ± 2.67	**<0.001**
Tender joints	9.26 ± 6.32	3.03 ± 3.59	**<0.001**
VAS patient, score	67.43 ± 18.10	38.94 ± 22.16	**<0.001**
VAS medic, score	55.40 ± 21.58	23.47 ± 17.06	**<0.001**
HAQ, score	1.41 ± 0.68	0.91 ± 0.61	**0.002**
SDAI, score	29.53 ± 11.41	11.87 ± 6.98	**<0.001**
CDAI, score	27.54 ± 10.54	11.27 ± 7.12	**<0.001**

Continue variables expressed in mean ± standard deviation; Categorical variables expressed in percentage. RF: rheumatoid factor; IU: International units; Anti-CCP: anti-cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: Visual analogue scale; HAQ: health assessment questionnaire; DAS-28: disease activity score in base of 28 joints; SDAI: simple disease activity index; CDAI: clinical disease activity index.

Supplementary table S2. Comparison of clinical variables between non-responders and responders at baseline.

Variable	Non responders (No resp + Moderate) N= 18	Responders (Good) N= 17	p
Age, years	51.88 ± 11.15	55.11 ± 9.98	0.37
Tobacco use, n (%)	5 (27.8)	3 (17.6)	0.69
Diabetes, n (%)	1 (5.6)	32(11.8)	0.60
Hypertension, n (%)	4 (22.2)	6 (30)	0.72
Dyslipidemia n (%)	2 (11.1)	5 (29.4)	0.23
RF, positive (%)	12 (66.7)	11 (64.7)	1.00
Anti-CCP positive (%)	11 (61.1)	12 (70.6)	0.72
Seropositive, n (%)	14 (77.8)	14 (82.4)	1.00
ESR,	61.75 ± 36.63	39.67 ± 16.75	**0.002**
CRP, mg/Dl	1.87 ± 2.31	2.15 ± 3.21	0.89
Swollen joints,	5.50 ± 4.20	6.67 ± 3.96	0.81
Tender joints,	8.90 ± 6.59	9.73 ± 5.91	0.54
VAS patients,	68.25 ± 19.33	66.33 ± 16.92	0.70
VAS medic,	59.85 ± 21.59	49.47 ± 20.79	0.36
DAS28-ESR	5.94 ± 0.93	5.76 ± 0.91	0.30
HAQ, score	1.58 ± 0.65	1.18 ± 0.67	0.11
SDAI, score	29.08 ± 11.38	30.13 ± 11.82	0.87
CDAI, score	27.21 ± 10.43	27.98 ± 11.04	0.84
IL-6, pg/mL	379.91 ± 301.12	805.15 ± 1165.75	0.27
sIL6R, pg/mL	355043.25 ± 312953	312714 ± 357374	0.79
IL-6/sIL-6R	0.001 ± 0.001	0.005 ± 0.010	0.20

Continuous variables expressed in mean ± standard deviation; Categorical variables expressed in percentage. The response was evaluated using EULAR criteria and they were classified as a Responders = Good response and, Non-responders = moderate response and no response. RF: rheumatoid factor; Anti-CCP: anti-cycle citrullinated peptide; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analogue scale; DAS28: disease activity score in base of 28 joints; HAQ: health assessment questionnaire; SDAI: simple disease activity index; CDAI: clinical disease activity index; IL-6: interleukin-6.

Supplementary Table S3. Comparison of metabolites concentration between non-responders and responders at baseline.

Variable µM	Baseline		
	Non-responders N= 18	Responders N= 17	P
3-Hydroxybutyrate	12.96 ± 7.57	26.86 ± 19.82	**0.01**
5,6-Dihydrothymine	17.25 ± 8.29	19.26 ± 10.02	0.52
Acetate,	177. ± 112.89	162.78 ± 90.96	0.66
Acetoacetate	21.97 ± 24.14	28.58 ± 15.68	0.35
Acetone	795.51 ± 1365.32	335.88 ± 365.87	0.19
Adipate	280.40 ± 256.80	206.77 ± 86.01	0.27
Alanine	132.79 ± 50.44	148.15 ± 55.29	0.40
Arginine	22.95 ± 15.02	28.39 ± 17.39	0.33
Betaine	9.78 ± 5.50	10.26 ± 7.53	0.83
Butyrate	14.33 ± 6.37	16.78 ± 5.60	0.24
Carnitine	5.99 ± 4.34	9.80 ± 8.28	0.10
Choline	9.11 ± 3.04	9.87 ± 2.31	0.41
Citrate	8.14 ± 3.61	8.36 ± 4.99	0.88
Creatine	10.38 ± 3.22	11.85 ± 4.45	0.27
Creatine phosphate	19.42 ± 11.43	22.23 ± 10.23	0.45
Creatinine	7.17 ± 2.82	7.58 ± 3.67	0.71
Dimethylamine	4.20 ± 3.85	3.99 ± 2.88	0.86
Formate	70.54 ± 61.24	58.20 ± 37.13	0.47
Fumarate	2.46 ± 1.53	2.68 ± 1.45	0.66
Glutamate	107.79 ± 29.51	119.37 ± 26.16	0.23
Glutamine	41.14 ± 33.85	32.34 ± 25.57	0.39
Glycine	88.05 ± 32.77	97.84 ± 29.01	0.36
Isobutyrate	7.79 ± 2.60	9.77 ± 2.29	**0.02**
Isoleucine	27.11 ± 8.98	29.88 ± 6.39	0.30
Isovalerate	10.22 ± 5.49	13.13 ± 5.64	0.13
Lactate	3141.23 ± 1205.49	3432.57 ± 1592.72	0.54
Leucine	41.29 ± 15.16	48.41 ± 13.62	0.15

Lysine	48.22 ± 13.96	57.36 ± 12.68	**0.05**
Methionine	5.80 ± 2.76	6.06 ± 2.78	0.78
Methylamine	2.44 ± 0.93	2.92 ± 1.25	0.21
Methylsuccinate	3.99 ± 1.70	4.00 ± 1.45	0.98
O-Phosphocholine	19.15 ± 7.80	23.45 ± 4.97	0.06
Ornithine	38.37 ± 14.35	44.28 ± 13.12	0.21
Phenylalanine	18.92 ± 5.18	22.88 ± 4.59	**0.02**
Proline	49.77 ± 14.88	58.85 ± 20.37	0.14
Pyruvate	6.91 ± 2.02	8.30 ± 4.64	0.27
Sarcosine	2.58 ± 3.17	4.63 ± 2.84	0.053
Serine	38.08 ± 16.14	37.30 ± 8.36	0.85
sn-Glycero-3-phosphocholine	46.29 ± 29.99	75.13 ± 41.51	**0.02**
Succinate	11.39 ± 5.01	12.35 ± 4.88	0.57
Threonine	41.25 ± 19.58	46.68 ± 13.20	0.35
Trimethylamine N-oxide	5.82 ± 5.85	5.75 ± 2.87	0.96
Tryptophan	15.54 ± 6.46	20.37 ± 4.51	**0.01**
Tyrosine	30.64 ± 10.35	37.64 ± 7.96	**0.03**
Valine	88.78 ± 24.94	100.58 ± 21.66	0.14

Variables expressed in mean ± standard deviation. The response was evaluated using EULAR criteria. Responders = Good response; Non-responders = moderate and no response. Concentration are expressed in μM

Supplementary Table S4. Comparison of metabolites concentration between baseline and 6 months after treatment.

Variables	Normal range (µM)	Baseline N= 35	6 months N= 35	p
3-Hydroxybutyrate	22-700	19.71 ± 16.22	21.47± 16.77	0.66
5,6-Dihydrothymine	ND	18.22 ± 9.09	21.28 ± 9.63	0.18
Acetate	26.8-57	170.60 ± 101.61	143.72 ± 65.60	0.19
Acetoacetate	4.1-77.1	25.18 ± 20.46	27.65 ± 15.38	0.57
Acetone	24.8-84	572.26 ± 1024.69	366.76 ± 415.48	0.27
Adipate	0.08-0.1	244.64 ± 194.55	243.33 ± 208.76	0.98
Alanine	200-579	140.25 ± 52.64	187.86 ± 47.90	**<0.001**
Arginine	72.5-112	25.59 ± 16.21	33.41 ± 18.79	0.07
Betaine	23.9-42.1	10.01 ± 6.47	11.64 ± 6.93	0.31
Butyrate	0.3-1.5	15.52 ± 6.03	15.94 ± 5.56	0.76
Carnitine	26.0-79	7.84 ± 6.74	5.67 ± 4.95	0.13
Choline	8.70-19.8	9.48 ± 2.70	11.18 ± 2.48	**0.008**
Citrate	30-400	8.24 ± 4.27	10.21 ± 4.45	0.06
Creatine	33.8-75.8	11.09 ± 3.88	13.82 ± 5.07	**0.01**
Creatine phosphate	ND	20.78 ± 10.80	22.23 ± 8.61	0.54
Creatinine	35-122	7.36 ± 3.22	7.73 ± 2.86	0.62
Dimethylamine	3.33-53.22	4.10 ± 3.36	3.58 ± 1.88	0.43
Formate	23.90-219.5	64.55 ± 50.63	60.66 ± 30.85	0.70
Fumarate	0 - 4	2.57 ± 1.48	2.43 ± 1.07	0.66
Glutamate	20-110	113.41 ± 28.14	120.55 ± 37.38	0.37
Glutamine	502-670	36.87 ± 30.01	56.20 ± 26.64	**0.006**
Glycine	120-320	92.81 ± 30.95	108.30 ± 33.61	**0.04**
Isobutyrate	0.7 – 4.4	8.75 ± 2.62	9.57 ± 2.75	0.21
Isoleucine	30-108	28.46 ± 7.85	31.63 ± 7.01	0.08
Isovalerate	0.3 – 2.7	11.63 ± 5.68	12.62 ± 4.69	0.42
Lactate	740-2400	3282.74 ± 1393.72	4061.33 ± 833.77	**0.006**
Leucine	70-180	44.75 ± 14.67	51.62 ± 14.63	**0.05**
Lysine	71-151	52.66 ± 13.95	61.54 ± 12.35	**0.006**
Methionine	13-45	5.93 ± 2.32	5.64 ± 2.32	0.63
Methylamine	0.37-4	2.68 ± 1.11	2.88 ± 1.23	0.46

Methylsuccinate	ND	3.99 ± 1.56	4.33 ± 2.28	0.47
O-Phosphocholine	1.2 - 3.2	21.24 ± 6.84	21.54 ± 4.21	0.82
Ornithine	39-71	41.24 ± 13.89	46.81 ± 13.75	0.09
Phenylalanine	48-66	20.84 ± 5.22	22.85 ± 7.83	0.21
Proline	108-228	54.18 ± 18.09	68.41 ± 23.22	**0.006**
Pyruvate	22-258	7.58 ± 3.56	7.78 ± 3.27	0.81
Sarcosine	0-5	3.58 ± 3.15	4.21 ±3.07	0.40
Serine	95-133	37.70 ± 12.78	49.75 ± 18.19	**0.002**
SNG3PC	ND	60.30 ± 38.40	53.88 ± 25.34	0.41
Succinate	0-32	11.85 ± 4.90	13.45 ± 5.32	0.19
Threonine	85-231	43.88 ± 16.77	52.24 ± 17.14	**0.04**
TMAO	18.44-59.18	5.78 ± 4.58	5.03 ± 3.90	0.46
Tryptophan	37-51	17.88 ± 6.04	20.47 ± 5.40	0.06
Tyrosine	47-71	34.04 ± 9.79	38.12 ± 8.11	0.06
Valine	151-273.6	94.51 ± 23.82	106.88 ± 18.16	**0.02**

Continuous variables expressed in mean ± standard deviation; Concentration of metabolites is expressed in μM. L= low, M= medium (within range), H= high compared to reference concentration from HMDB, PubChem and KEGG. SG3PC: Sn-glycero-3-phoshocholine, TMAO: trimethylamine N-oxide; ND: no data available in uM. [1]Normal range in adult's blood according to the Human Metabolome data base. https://hmdb.ca/

Comparison of metabolites' concentration between <55 years old and >= 55 years old patients at baseline.

Variables	<=55 years old (n=19)	>55 years old (n=16)	p
Swollen Joints	5.11 ± 4.52	7.06 ± 3.32	0.34
Tender joints	9.05 ± 6.17	9.50 ± 6.50	0.84
VAS Patient	66.79 ± 17.38	68.19 ± 19.46	0.82
VAS Medic	51.89 ± 21.33	59.56 ± 21.81	0.3
HAQ	1.34 ± 0.59	1.50 ± 0.78	0.5
DAS28	5.81 ± 1.09	5.74 ± 0.89	0.84
SDAI	27.00 ± 10.54	32.54 ± 12.00	0.15
CDAI	26.03 ± 9.96	29.34 ± 11.25	0.36
3-Hydroxybutyrate uM	16.24 ± 12.82	23.83 ± 19.14	0.18
5,6-Dihydrothymine uM	16.85 ± 8.48	19.86 ± 9.80	0.34
Acetate uM	158.98 ± 93.64	184.41 ± 111.83	0.47
Acetoacetate uM	18.78 ± 15.80	32.79 ± 23.13	**0.04**
Acetone uM	681.45 ± 1313.22	442.61 ± 525.44	0.5
Adipate uM	199.16 ± 132.97	298.66 ± 242.58	0.13
Alanine uM	135.52 ± 62.02	145.88 ± 40.04	0.57
Arginine uM	23.47 ± 18.87	28.11 ± 12.49	0.39
Betaine uM	9.94 ± 7.12	10.11 ± 5.85	0.94
Butyrate uM	13.44 ± 6.66	18.00 ± 4.16	**0.019**
Carnitine uM	8.27 ± 8.06	7.33 ± 4.96	0.69
Choline uM	8.95 ± 2.74	10.12 ± 2.59	0.2
Citrate uM	7.95 ± 4.90	8.60 ± 3.52	0.66
Creatine uM	11.14 ± 4.77	11.03 ± 2.62	0.93
Creatine phosphate uM	18.71 ± 10.74	23.26 ±10.68	0.22
Creatinine uM	6.07 ± 2.80	8.91 ± 3.07	**0.007**
Dimethylamine uM	3.81 ±3.00	4.45 ± 3.82	0.58
Formate uM	52.64 ± 46.16	78.69 ± 53.49	0.13
Fumarate uM	2.54 ± 1.52	2.61 ± 1.47	0.89
Glucose uM	554.39 ± 609.36	744.38 ± 594.04	0.36
Glutamate uM	108.49 ± 27.17	119.25 ± 29.03	0.27
Glutamine uM	32.12 ± 27.05	42.51 ± 33.18	0.31
Glycine uM	87.26 ± 32.66	99.40 ± 28.38	0.25
Isobutyrate uM	8.64 ± 3.33	8.89 ± 1.49	0.77
Isoleucine uM	27.69 ± 9.18	29.37 ± 6.07	0.52
Isovalerate uM	11.23 ± 7.00	12.12 ± 3.72	0.65
Lactate uM	3070.75 ± 1425.21	3534.48 ± 1356.79	0.33
Leucine uM	42.47 ± 16.27	47.46 ± 12.50	0.32
Lysine uM	52.86 ± 16.23	52.43 ± 11.17	0.93

Methionine uM	5.47 ± 2.30	6.48 ± 3.16	0.28
Methylamine uM	2.90 ± 1.34	2.41 ± 0.71	0.18
Methylsuccinate uM	3.97 ± 1.57	4.03 ± 1.60	0.92
O-Phosphocholine uM	19.08 ± 7.94	23.81 ± 4.18	**0.03**
Ornithine uM	39.15 ±14.70	43.73 ± 12.89	0.34
Phenylalanine uM	20.30 ± 6.12	21.49 ± 4.02	0.51
Proline uM	51.03 ± 16.42	57.91 ± 19.77	0.27
Pyruvate uM	7.77 ± 4.46	7.36 ± 2.19	0.74
Sarcosine uM	3.63 ± 3.47	3.52 ± 2.83	0.92
Serine uM	35.97 ± 15.91	39.75 ± 7.61	0.37
sn-Glycero-3-phosphocholine uM	48.96 ± 32.32	73.78 ± 41.62	0.06
Succinate uM	11.07 ± 5.05	12.79 ± 4.70	0.31
Threonine uM	43.17 ± 20.80	44.74 ± 10.83	0.78
Trimethylamine N-oxide uM	6.17 ± 5.62	5.32 ± 3.04	0.59
Tryptophan uM	18.05 ± 6.78	17.69 ± 5.23	0.87
Tyrosine uM	31.83 ± 9.63	36.66 ± 9.63	0.15
Valine uM	91.77 ± 30.27	97.77 ± 12.90	0.44
IL6 pg/mL	701.84 ± 1006.99	396.30 ± 464.41	0.27
sIL6R pg/mL	283455 ± 291132	400370 ± 376162	0.30
IL6/sIL6R	0.005 ± 0.009	0.002 ± 0.005	0.39

Comparison of metabolites' concentration between High Activity DAS28 > 5.1 and moderate activity DAS28 ≤5.1 at baseline.

Variables	Moderate activity (n=9)	High activity (n=26)	P
Age	50.50 ± 11.76	54.50 ± 10.54	0.32
Swollen Joints	3.11 ± 2.20	7.00 ± 4.13	**0.01**
Tender joints	2.22 ± 1.79	11.69 ± 5.27	**<0.001**
VAS Patient	51.11 ± 5.53	73.08 ± 17.51	**<0.001**
VAS Medic	43.78 ± 21.66	59.42 ± 20.45	0.06
HAQ	1.15 ± 0.58	1.50 ± 0.70	0.18
SDAI	15.92 ± 4.10	34.24 ± 9.05	**<0.001**
CDAI	14.82 ± 4.17	31.94 ± 8.20	**<0.001**
3-Hydroxybutyrate uM	24.11 ± 17.84	18.19 ± 15.71	0.35
5,6-Dihydrothymine uM	18.82 ± 8.44	18.02 ± 9.46	0.82
Acetate uM	152.12 ± 107.44	177.00 ± 100.91	0.53
Acetoacetate uM	23.66 ± 13.98	25.71 ± 22.48	0.80
Acetone uM	425.12 ± 545.31	623.20 ± 1149.56	0.62
Adipate uM	264.21 ± 298.32	237.87 ± 151.04	0.73
Alanine uM	149.71 ±7.15	136.98 ±47.78	0.54
Arginine uM	30.84 ± 18.69	23.78 ± 15.24	0.27
Betaine uM	13.26 ± 8.61	8.89 ± 5.31	0.08
Butyrate uM	16.47 ± 7.48	15.20 ±5.58	0.59
Carnitine uM	9.59 ± 8.38	7.24 ± 6.16	0.37
Choline uM	9.70 ± 3.24	9.41 ± 2.55	0.78
Citrate uM	8.93 ± 6.20	8.01 ± 3.51	0.58
Creatine uM	11.99 ±4.66	12.30 ± 9.23	0.12
Creatine phosphate uM	24.04 ± 10.26	19.66 ± 10.95	0.30
Creatinine uM	7.29 ± 3.00	7.39 ± 3.35	0.93
Dimethylamine uM	4.09 ± 3.85	4.11 ± 3.26	0.98
Formate uM	47.27 ± 28.25	70.53 ± 55.55	0.11
Fumarate uM	3.53 ± 1.90	2.23 ± 1.17	**0.02**
Glucose uM	583.83 ± 530.51	661.12 ± 632.43	0.74
Glutamate uM	105.90 ± 16.68	116.01 ± 31.00	0.36
Glutamine uM	38.32 ± 25.19	36.37 ± 31.95	0.87
Glycine uM	89.09 ± 27.20	94.10 ± 32.54	0.68
Isobutyrate uM	9.70 ± 2.95	8.43 ± 2.47	0.21
Isoleucine uM	26.33 ± 6.24	29.19 ± 8.31	0.35
Isovalerate uM	12.74 ± 7.89	11.25 ± 4.83	0.5
Lactate uM	3282.56 ± 1636.66	3282.80 ± 1335.87	1.00
Leucine uM	43.86 ± 14.16	45.06 ± 15.11	0.83

Lysine uM	53.51 ± 14.78	52.37 ± 13.95	0.84
Methionine uM	4.80 ± 1.18	6.32 ± 3.02	0.15
Methylamine uM	3.10 ± 1.50	2.53 ± 0.93	0.19
Methylsuccinate uM	4.88 ± 1.77	3.69 ± 1.39	**0.04**
O-Phosphocholine uM	20.04 ± 6.95	21.65 ± 6.89	0.55
Ornithine uM	40.44 ± 12.00	41.52 ± 14.70	0.84
Phenylalanine uM	22.58 ± 5.04	20.24 ± 5.25	0.25
Proline uM	54.28 ± 17.24	54.14 ± 18.70	0.98
Pyruvate uM	9.31 ± 5.73	6.99 ± 2.30	0.26
Sarcosine uM	3.16 ± 3.03	3.73 ± 3.23	0.64
Serine uM	35.32 ± 11.99	38.52 ± 13.17	0.52
sn-Glycero-3-phosphocholine uM	52.73 ± 29.61	62.92 ± 41.20	0.50
Succinate uM	12.96 ± 5.97	11.47 ± 4.55	0.44
Threonine uM	38.62 ± 12.43	45.71 ± 17.88	0.28
Trimethylamine N-oxide uM	6.33 ± 3.07	5.59 ± 5.04	0.68
Tryptophan uM	20.17 ± 4.32	17.10 ± 6.41	0.19
Tyrosine uM	37.37 ± 8.99	32.89 ± 9.97	0.24
Valine uM	96.00 ± 27.52	94.00 ± 22.99	0.83
IL6 pg/mL	462.65 ± 735.93	596.61 ± 844.89	0.67
sIL6R pg/mL	421449.56 ± 457203.18	307636.08 ± 276040.52	0.49
IL6/sIL6R	0.00± 0.00	0.00 ± 0.01	0.58

High Activity DAS28 > 5.1 and moderate activity DAS28 ≤5.1

Comparison of metabolites' concentration between ESR High ≥ 30 mm/h vs normal < 30 mm/h at baseline.

Variables	ESR Normal (n=9)	ESR High (n= 26)	P
Age	52.44 ± 9.98	53.76 ± 10.94	0.75
Swollen Joints	7.33 ± 4.92	5.54 ± 3.74	0.26
Tender joints	13.67 ± 6.91	7.73 ± 5.30	**0.01**
VAS Patient	73.00 ± 17.85	65.50 ± 18.12	0.29
VAS Medic	68.67 ± 14.00	50.81 ± 22.04	**0.03**
HAQ	1.49 ± 0.63	1.39 ± 0.71	0.71
DAS28	5.71 ± 1.13	5.80 ± 0.96	0.81
SDAI	37.29 ±13.72	26.85 ± 9.36	**0.01**
CDAI	35.17 ±11.73	24.90 ± 8.89	**0.01**
3-Hydroxybutyrate uM	17.05 ± 12.26	20.63 ± 17.51	0.58
5,6-Dihydrothymine uM	22.85 ± 7.00	16.62 ± 9.30	0.08
Acetate uM	171.33 ± 91.02	170.35 ± 106.72	0.98
Acetoacetate uM	26.95 ± 4.99	24.57 ± 23.66	0.63
Acetone uM	202.01 ± 100.73	700.43 ± 1165.10	0.21
Adipate uM	264.05 ± 161.55	237.92 ± 207.22	0.73
Alanine uM	161.09 ± 54.91	133.04 ± 50.93	0.17
Arginine uM	15.28 ± 10.45	29.16 ± 16.45	**0.02**
Betaine uM	13.07 ± 8.83	9.95 ± 5.24	0.10
Butyrate uM	16.57 ± 5.72	15.16 ± 6.20	0.55
Carnitine uM	10.35 ± 9.79	6.97 ± 5.30	0.34
Choline uM	11.22 ± 1.98	8.88 ± 2.68	**0.02**
Citrate uM	10.16 ± 4.64	7.59 ± 4.02	0.12
Creatine uM	13.00 ± 5.22	10.43 ± 3.16	0.08
Creatine phosphate uM	20.74 ± 11.34	20.80 ± 10.84	0.99
Creatinine uM	8.44 ±3.72	6.99 ± 3.02	0.25
Dimethylamine uM	3.91 ± 1.62	4.17 ± 3.81	0.78
Formate uM	77.39 ± 53.13	60.10 ± 50.03	0.38
Fumarate uM	2.79 ± 1.73	2.49 ± 1.40	0.61
Glucose uM	737.52 ± 568.52	607.91 ± 616.46	0.58
Glutamate uM	125.22 ± 19.85	109.32 ± 29.72	0.33
Glutamine uM	28.03 ± 29.12	39.93 ± 30.26	0.31
Glycine uM	103.94 ± 24.77	88.95 ± 32.34	0.21
Isobutyrate uM	9.64 ± 1.03	8.44 ± 2.93	0.24
Isoleucine uM	32.02 ± 8.84	27.2 ± 7.24	0.11
Isovalerate uM	14.23 ± 4.53	10.73 ± 5.83	0.12
Lactate uM	3571.67 ± 1151.03	3182.73 ± 1475.57	0.48
Leucine uM	54.07 ± 15.14	41.53 ± 13.32	**0.02**

Lysine uM	59.33 ± 11.82	50.35 ± 14.09	0.09
Methionine uM	6.32 ± 1.78	5.79 ± 3.01	0.63
Methylamine uM	3.15 ± 1.52	2.51 ± 0.91	0.26
Methylsuccinate uM	4.63 ± 1.40	3.77 ± 1.58	0.16
O-Phosphocholine uM	22.00 ± 4.35	20.97 ± 7.57	0.70
Ornithine uM	48.13 ± 12.69	38.86 ± 13.71	0.08
Phenylalanine uM	22.64 ± 2.65	20.22 ± 5.77	0.10
Proline uM	67.02 ± 23.30	49.73 ± 13.83	0.10
Pyruvate uM	9.01 ± 5.24	7.09 ± 2.73	0.17
Sarcosine uM	4.4 ± 4.53	3.29 ± 2.57	0.50
Serine uM	39.37 ± 15.82	37.12 ± 11.86	0.66
sn-Glycero-3-phosphocholine uM	69.37 ± 23.79	57.16 ± 42.24	0.42
Succinate uM	11.61 ± 2.12	11.94 ± 5.58	0.80
Threonine uM	48.40 ± 15.01	42.32 ± 17.34	0.36
Trimethylamine N-oxide uM	4.63 ± 2.54	6.18 ± 5.08	0.39
Tryptophan uM	19.98 ± 4.14	17.16 ± 6.48	0.23
Tyrosine uM	39.22 ± 9.14	32.24 ± 9.53	0.06
Valine uM	100.9 ± 18.49	92.30 ± 25.35	0.36
IL6 pg/mL	793.23 ± 841.55	482.17 ± 799.64	0.33
sIL6R pg/mL	309878 ± 323279	346256 ± 335792	0.78
IL6/sIL6R	0.005 ± 0.006	0.003 ± 0.007	0.58

Comparison of metabolites' concentration between CRP negative <2.0 mg/L vs positive ≥2.0 mg/L at baseline.

Variables	CRP Negative (n= 25)	CRP Positive (n= 10)	P
Age	50.8 ± 10.68	60.00 ± 7.18	**0.01**
Swollen Joints	5.44 ± 3.91	7.40 ± 4.35	0.20
Tender joints	9.20 ± 6.60	9.40 ± 5.50	0.93
VAS Patient	65.36 ± 17.61	72.60 ± 19.20	0.29
VAS Medic	51.40 ± 18.95	65.40 ± 25.43	0.08
HAQ	1.37 ± 0.69	1.51 ± 0.68	0.59
DAS28	5.63 ± 1.00	6.15 ± 0.91	0.16
SDAI	28.88 ± 10.03	36.16 ± 12.46	**0.03**
CDAI	26.31 ± 10.00	30.60 ± 11.79	0.28
3-Hydroxybutyrate uM	20.30 ± 16.79	18.24 ± 15.45	0.74
5,6-Dihydrothymine uM	17.37 ± 10.00	20.35 ± 6.22	0.29
Acetate uM	171.50 ± 113.49	168.37 ± 68.16	0.92
Acetoacetate uM	26.93 ± 23.27	20.82 ± 10.36	0.43
Acetone uM	449.32 ± 423.04	879.63 ± 1827.59	0.48
Adipate uM	256.94 ± 222.79	213.90 ± 95.68	0.56
Alanine uM	143.54 ± 61.38	132.00 ± 17.38	0.40
Arginine uM	22.38 ± 15.10	33.63 ± 16.84	0.06
Betaine uM	9.88 ± 6.64	10.34 ± 6.35	0.85
Butyrate uM	10.55 ± 6.94	15.45 ± 2.97	0.95
Carnitine uM	8.22 ± 7.66	6.90 ± 3.74	0.50
Choline uM	9.90 ± 2.92	8.42 ± 1.71	0.14
Citrate uM	8.25 ± 4.86	8.23 ± 2.44	0.98
Creatine uM	11.38 ± 4.32	10.36 ± 2.50	0.49
Creatine phosphate uM	20.34 ± 10.98	21.89 ± 10.84	0.71
Creatinine uM	6.95 ± 3.30	8.41 ± 2.88	0.23
Dimethylamine uM	4.33 ± 3.76	3.53 ± 2.12	0.53
Formate uM	62.72 ±52.51	69.12 ± 47.94	0.74
Fumarate uM	2.57 ± 1.58	2.55 ± 1.23	0.96
Glucose uM	578.68 ± 573.46	797.63 ± 671.28	0.34
Glutamate uM	111.02 ± 29.91	119.39 ± 23.45	0.43
Glutamine uM	35.31 ± 31.21	40.76 ± 27.96	0.63
Glycine uM	93.40 ± 32.21	91.32 ± 29.09	0.86
Isobutyrate uM	8.93 ± 2.86	8.31 ± 1.96	0.53
Isoleucine uM	27.72 ± 8.75	30.29 ± 4.79	0.39
Isovalerate uM	12.50 ± 6.40	9.47 ± 2.27	**0.04**
Lactate uM	3251.23 ± 1513.42	3361.51 ± 1104.79	0.81
Leucine uM	45.12 ± 16.97	43.82 ± 6.64	0.75

Lysine uM	53.84 ± 15.81	49.71 ± 7.42	0.30
Methionine uM	5.97 ± 2.60	6.29 ± 3.16	0.63
Methylamine uM	2.90 ± 1.19	2.11 ± 0.57	**0.05**
Methylsuccinate uM	4.27 ± 1.59	3.31 ± 1.32	0.10
O-Phosphocholine uM	20.38 ± 7.57	23.39 ± 4.09	0.24
Ornithine uM	43.38 ± 15.23	35.88 ± 8.14	0.06
Phenylalanine uM	21.22 ± 5.82	19.90 ± 3.38	0.51
Proline uM	52.84 ± 20.41	55.72 ± 9.55	0.92
Pyruvate uM	7.88 ± 4.13	6.83 ± 1.18	0.25
Sarcosine uM	3.73 ± 3.42	3.21 ± 2.43	0.66
Serine uM	37.18 ± 14.78	38.99 ± 5.65	0.60
sn-Glycero-3-phosphocholine uM	55.68 ± 32.66	71.86 ± 50.18	0.26
Succinate uM	12.18 ± 5.65	11.02 ± 2.07	0.38
Threonine uM	45.89 ± 18.63	38.87 ± 9.89	0.27
Trimethylamine N-oxide uM	4.89 ± 3.03	8.01 ± 6.86	0.07
Tryptophan uM	18.27 ± 6.64	16.92 ± 4.29	0.56
Tyrosine uM	34.21 ± 11.03	33.61 ± 6.16	0.87
Valine uM	94.08 ± 27.44	95.58 ± 11.57	0.82
IL6 pg/mL	608.59 ± 914.14	446.08 ± 477.74	0.60
sIL6R pg/mL	369000 ± 356762	256656 ± 240135	0.37
IL6/sIL6R	0.003 ± 0.007	0.004 ± 0.005	0.95

Comparison of metabolites' concentration between RF Positive>25 IU/mL vs negative ≤25 IU/mL at baseline.

Variables	RF Positive (n= 23)	RF Negative (n= 12)	P
Age	53.23 ± 10.62	54.11 ± 11.640	0.83
Swollen Joints	6.00 ± 3.71	6.00 ± 4.90	1.00
Tender joints	10.57 ± 6.29	6.75 ± 5.53	0.08
VAS Patient	68.83 ± 18.16	64.75 ± 18.47	0.53
VAS Medic	58.17 ± 20.42	50.08 ± 23.65	0.30
HAQ	1.43 ± 0.73	1.38 ± 0.60	0.81
DAS28	5.95 ± 0.92	5.45 ± 1.08	0.16
SDAI	31.35 ± 11.23	26.06 ± 11.42	0.20
CDAI	29.27 ± 9.46	24.23 ± 12.11	0.18
3-Hydroxybutyrate uM	16.97 ± 13.98	24.97 ± 19.42	0.17
5,6-Dihydrothymine uM	17.50 ± 8.75	19.63 ± 9.97	0.55
Acetate uM	154.97 ± 96.43	200.57 ± 108.74	0.21
Acetoacetate uM	24.46 ± 21.38	26.58 ± 19.39	0.77
Acetone uM	689.88 ± 1234.34	346.83 ± 334.61	0.35
Adipate uM	244.62 ± 214.96	244.68 ± 156.76	0.99
Alanine uM	134.76 ± 54.11	150.78 ± 50.27	0.40
Arginine uM	22.47 ± 13.74	31.58 ± 19.37	0.12
Betaine uM	10.27 ± 6.69	9.53 ± 6.30	0.76
Butyrate uM	13.96 ± 5.78	18.53 ± 5.55	**0.03**
Carnitine uM	7.80 ± 6.50	7.92 ± 7.49	0.96
Choline uM	9.58 ± 2.84	9.30 ± 2.53	0.78
Citrate uM	8.59 ± 3.53	7.60 ± 5.56	0.52
Creatine uM	10.69 ± 3.84	11.87 ± 4.01	0.40
Creatine phosphate uM	19.44 ± 8.95	23.36 ± 13.76	0.32
Creatinine uM	7.54 ± 2.86	7.47 ± 4.03	0.67
Dimethylamine uM	3.57 ± 3.33	5.13 ± 3.33	0.19
Formate uM	59.89 ± 46.99	73.48 ± 58.09	0.46
Fumarate uM	2.83 ± 1.21	2.08 ± 1.85	0.16
Glucose uM	690.33 ± 671.40	547.16 ± 448.40	0.51
Glutamate uM	110.23 ± 27.66	119.51 ± 29.27	0.36
Glutamine uM	38.52 ± 31.82	33.71 ± 27.25	0.66
Glycine uM	95.11 ± 32.50	88.39 ± 28.56	0.55
Isobutyrate uM	8.56 ± 2.82	9.13 ± 2.26	0.54
Isoleucine uM	28.34 ± 6.96	28.68 ± 9.66	0.91
Isovalerate uM	11.71 ± 5.94	11.49 ± 5.38	0.92
Lactate uM	3126.03 ± 1410.75	3583.11 ± 1368.84	0.36
Leucine uM	42.14 ± 12.05	49.75 ± 18.27	0.15

Lysine uM	52.01 ± 12.61	57.66 ± 15.46	0.27
Methionine uM	6.03 ± 3.17	5.74 ± 1.72	0.77
Methylamine uM	2.73 ± 0.98	2.58 ± 1.36	0.70
Methylsuccinate uM	4.08 ± 1.76	3.83 ± 1.134	0.65
O-Phosphocholine uM	20.80 ± 6.97	22.09 ± 6.80	0.60
Ornithine uM	39.87 ± 14.02	43.88 ± 13.86	0.43
Phenylalanine uM	20.66 ± 6.15	21.20 ± 2.92	0.77
Proline uM	50.90 ± 13.36	60.47 ± 24.26	0.14
Pyruvate uM	6.84 ± 2.56	9.01 ± 4.76	0.09
Sarcosine uM	3.15 ± 3.01	4.41 ± 3.37	0.27
Serine uM	3.15 ± 3.01	4.41 ± 3.37	0.02
sn-Glycero-3-phosphocholine uM	61.20 ± 43.44	58.88 ± 27.92	0.85
Succinate uM	11.01 ± 5.17	13.48 ± 4.06	0.16
Threonine uM	40.69 ± 15.83	50.02 ± 17.49	0.12
Trimethylamine N-oxide uM	5.71 ± 5.10	5.92 ± 3.58	0.90
Tryptophan uM	17.93 ± 6.97	17.81 ± 3.95	0.96
Tyrosine uM	31.95 ± 9.49	38.04 ± 9.49	0.08
Valine uM	90.52 ± 21.11	102.16 ± 27.67	0.17
IL6 pg/mL	595.09 ± 869.92	499.05 ± 712.04	0.74
sIL6R pg/mL	406337.26 ± 371521.65	203818.92 ± 166185.82	**0.03**
IL6/sIL6R	0.004 ± 0.008	0.003 ± 0.004	0.64

Comparison of metabolites' concentration between Anti-CCP Positive ≥20 vs negative <20 at baseline.

Variables	Anti-CCP Positive (n= 23)	Anti-CCP Negative (n= 12)	P
Tobacco positive, n (%)	5 (21.7)	3 (25)	1.00
Age	54.60±10.21	51.17 ± 11.34	0.37
Swollen Joints	6.30 ± 3.97	5.42 ± 4.40	0.55
Tender joints	9.17 ± 5.79	9.42 ± 7.28	0.91
VAS Patient	64.22 ± 16.50	73.58 ± 20.13	0.15
VAS Medic	53.52 ± 18.87	59.00 ± 26.58	0.48
HAQ	1.40 ± 0.72	1.44 ± 0.64	0.89
DAS28	5.83 ± 1.04	5.67 ± 0.93	0.64
SDAI	29.32 ± 10.52	29.94 ±13.45	0.88
CDAI	27.25 ± 9.31	28.09 ± 13.03	0.83
3-Hydroxybutyrate uM	19.33 ± 15.96	20.44 ± 17.43	0.85
5,6-Dihydrothymine uM	17.23 ± 9.44	20.13 ± 8.46	0.38
Acetate uM	175.17 ± 107.35	161.86 ± 93.48	0.72
Acetoacetate uM	29.08 ± 22.49	17.71 ± 13.74	0.12
Acetone uM	583.05 ± 1221.28	551.60 ± 509.64	0.93
Adipate uM	225.33 ± 207.96	281.66 ± 167.98	0.42
Alanine uM	141.46 ± 50.41	137.93 ± 58.95	0.85
Arginine uM	26.97 ± 12.58	22.96 ± 20.00	0.57
Betaine uM	10.61 ± 7.16	8.88 ± 4.97	0.46
Butyrate uM	15.47 ± 5.54	15.63 ± 7.15	0.94
Carnitine uM	9.48 ± 6.95	4.71 ± 5.25	0.04
Choline uM	10.07 ± 2.23	8.35 ± 3.23	0.07
Citrate uM	9.00 ± 4.51	6.82 ± 3.52	0.15
Creatine uM	12.22 ± 3.78	8.93 ± 3.22	0.02
Creatine phosphate uM	22.26 ± 9.20	17.96 ± 13.35	0.33
Creatinine uM	7.17 ± 2.85	7.74 ± 3.95	0.62
Dimethylamine uM	4.32 ± 3.90	3.69 ± 2.07	0.61
Formate uM	56.16 ± 39.48	80.63 ± 66.16	0.26
Fumarate uM	2.76 ± 1.52	2.21 ± 1.37	0.30
Glucose uM	698.50 ± 616.99	531.50 ± 579.63	0.44
Glutamate uM	112.61 ± 27.44	114.94 ± 30.64	0.82
Glutamine uM	39.63 ± 31.62	31.57 ± 27.16	0.45
Glycine uM	100.54 ± 28.60	77.99 ± 30.98	0.03
Isobutyrate uM	9.42 ± 2.39	7.48 ± 2.67	0.03
Isoleucine uM	28.18 ± 6.27	28.98 ± 10.55	0.81
Isovalerate uM	12.30 ± 5.58	10.37 ± 5.89	0.35
Lactate uM	3288.92 ± 1463.73	3270.89 ± 1310.98	0.97

Leucine uM	44.94 ± 12.63	44.39 ± 18.61	0.92
Lysine uM	54.04 ± 11.27	50.02 ± 18.33	0.42
Methionine uM	5.57 ± 2.20	6.63 ± 3.56	0.28
Methylamine uM	3.04 ± 1.17	1.98 ± 0.49	<0.01
Methylsuccinate uM	4.17 ± 1.75	3.65 ± 1.10	0.29
O-Phosphocholine uM	22.64 ± 5.72	18.56 ± 8.21	0.09
Ornithine uM	41.88 ± 12.59	40.02 ± 16.65	0.71
Phenylalanine uM	21.84 ± 4.81	18.93 ± 5.66	0.12
Proline uM	53.64 ± 11.11	55.20 ± 27.62	0.85
Pyruvate uM	7.71 ± 4.14	7.34 ± 2.19	0.77
Sarcosine	3.82 ± 2.88	3.12 ± 3.71	0.54
Serine uM	36.36 ± 9.05	40.27 ± 18.17	0.49
sn-Glycero-3-phosphocholine uM	67.77 ± 39.53	45.99 ± 33.05	0.11
Succinate uM	12.36 ± 5.47	10.89 ± 3.58	0.41
Threonine uM	42.84 ± 16.95	45.90 ± 16.98	0.61
Trimethylamine N-oxide uM	5.99 ± 5.16	5.39 ± 3.38	0.72
Tryptophan uM	18.45 ± 6.53	16.81 ± 5.06	0.45
Tyrosine uM	34.52 ± 8.04	33.13 ± 12.88	0.69
Valine uM	96.59 ± 16.43	90.53 ± 34.47	0.57
IL6 pg/mL	701.69 ± 932.66	294.73 ±410.73	0.16
sIL6R pg/mL	351055.91 ± 355418.51	309774.83 ± 281442.92	0.73
IL6/sIL6R	0.00 ± 0.01	0.00 ± 0.00	0.04

Comparison of metabolites' concentration between women and men at baseline.

Variables	Female (n=35)	Male (n=5)	P
Age	53.43 ± 10.58	54.00 ± 14.02	0.91
Swollen Joints	6 ± 4.08	9.20 ± 7.98	0.16
Tender joints	9.26 ± 6.23	11.80 ± 9.01	0.42
VAS Patient	67.43 ± 18.09	77.60 ± 14.79	0.24
VAS Medic	55.40 ± 21.58	63.6 ± 25.78	0.44
HAQ	1.41 ± 0.68	1.32 ± 0.37	0.78
DAS28	5.77 ± 0.99	6.04 ± 1.19	0.58
SDAI	29.53 ± 11.41	37.03 ± 19.33	0.22
CDAI	27.54 ± 10.54	35.12 ± 18.41	0.41
Diabetes mellitus II, n (%)	3 (8.6)	1 (20)	0.43
Hypertention, n (%)	8 (22.9)	2 (40)	0.58
Dyslipidemia, n (%)	7 (20)	1 (20)	1.00
Tocilizumab monotherapy, n (%)	24 (68.6)	2 (40)	0.32
Methotrexate, n (%)	16 (45.7)	2 (40)	1.00
Leflunomide, n (%)	8 (22.9)	0 (0)	0.56
Sulfasalazine, n (%)	2 (5.7)	0(0)	1.00
Corticoides, n (%)	24 (68.6)	3 (60)	1.00
3-Hydroxybutyrate uM	19.71 ± 16.22	16.40 ± 2.90	0.28
5,6-Dihydrothymine uM	18.26 ± 8.97	26.74 ± 7.85	**0.05**
Acetate uM	171.59 ± 10.32	211.22 ± 72.69	0.40
Acetoacetate uM	25.23 ± 20.16	32.10 ± 22.56	0.49
Acetone uM	572.99 ± 1009.66	2558.72 ± 4461.44	0.38
Adipate uM	242.63 ± 192.13 ±	263.86 ± 154.40	0.83
Alanine uM	139.78 ± 51.92	153.42 ± 28.18	0.59
Arginine uM	25.43 ± 16.01	22.50± 9.11	0.68
Betaine uM	10.15 ± 6.43	11.44 ± 5.95	0.64
Butyrate uM	15.43 ± 5.97	17.12 ± 6.30	0.58
Carnitine uM	7.65 ± 6.75	4.46 ± 6.31	0.30
Choline uM	9.44 ± 2.68	9.96 ± 2.43	0.71
Citrate uM	8.33 ± 4.24	12.12 ± 8.02	0.34
Creatine uM	11.08 ± 3.83	20.10 ± 20.84	0.39
Creatine phosphate uM	20.84 ± 10.65	24.44 ± 11.57	0.49
Creatinine uM	7.39 ± 3.18	9.68 ± 2.51	0.13
Dimethylamine uM	4.13 ± 3.32	5.28 ± 4.05	0.48
Formate uM	65.20 ± 50.06	76.36 ± 54.53	0.63
Fumarate uM	2.56 ± 1.45	2.42 ± 0.76	0.83
Glucose uM	631.90 ± 595.23	313.84 ± 192.42	0.24
Glutamate uM	113.20 ±27.77	138.28 ± 23.08	**0.07**

Glutamine uM	37.75 ±30.05	52.20 ±28.55	0.29
Glycine uM	92.83 ±30.50	76.02 ±13.75	**0.05**
Isobutyrate uM	8.79 ± 2.59	9.00 ±1.03	0.84
Isoleucine uM	28.41 ± 7.74	34.32 ± 3.40	0.10
Isovalerate uM	11.59 ±5.60	11.90 ± 3.70	0.92
Lactate uM	3286.50 ±1373.85	4858.74 ±1242.17	**0.02**
Leucine uM	44.42 ±14.60	48.12 ±9.64	0.62
Lysine uM	53.08 ± 13.97	63.28 ± 8.13	0.11
Methionine uM	5.85 ± 2.74	15.66 ± 23.19	0.40
Methylamine uM	2.70 ± 1.10	2.54 ± 0.76	0.79
Methylsuccinate uM	3.98 ± 1.54	3.76 ± 1.07	0.75
O-Phosphocholine uM	21.04 ± 6.85	20.86 ± 1.74	0.90
Ornithine uM	41.47 ± 13.76	54.64 ± 14.98	**0.05**
Phenylalanine uM	20.86 ± 5.15	28.34 ± 11.88	0.23
Proline uM	53.78 ± 17.98	50.40 ±16.83	0.66
Pyruvate uM	7.61 ± 3.51	26.60 ±43.61	0.38
Serine uM	38.12 ±12.84	38.64 ± 12.90	0.88
sn-Glycero-3-phosphocholine uM	59.38 ±38.25	32.08 ± 14.28	0.11
Succinate uM	11.83 ± 4.83	19.36 ± 4.87	**<0.01**
Threonine uM	43.55 ± 16.65	37.92 ± 8.01	0.44
Trimethylamine N-oxide uM	5.70 ±4.55	4.90 ± 1.70	0.67
Tryptophan uM	17.75 ± 6.01	19.44 ± 5.28	0.59
Tyrosine uM	33.93 ± 9.68	36.48 ± 6.74	0.59
Valine uM	94.89 ± 23.59	112.28 ± 26.46	0.13

Comparison of metabolites' concentration between patients with and without diabetes and mellitus type 2 at baseline.

Variables	No n= 32	Yes n=3	p
3-Hydroxybutyrate uM	18.31± 15.513	34.63 ± 19.53	0.10
5,6-Dihydrothymine uM	18.85 ± 8.96	11.60 ± 9.46	0.19
Acetate uM	175.64 ± 102.44	116.93 ± 90.29	0.35
Acetoacetate uM	24.78 ± 19.88	24.80 ± 4.45	1.00
Acetone uM	607.64 ± 1065.93	194.93 ± 32.18	0.51
Adipate uM	255.05 ± 200.49	133.67 ± 13.37	0.31
Alanine uM	143.01 ± 53.97	110.80 ± 23.14	0.32
Arginine uM	25.51 ± 16.661	29.00 ± 3.14	0.33
Betaine uM	10.61 ± 6.40	8.03 ± 4.40	0.50
Butyrate uM	15.45 ± 6.25	16.33 ± 3.54	0.81
Carnitine uM	7.66 ± 6.78	9.80 ± 7.31	0.61
Choline uM	9.51 ± 2.82	9.20 ± 0.56	0.85
Citrate uM	9.28 ± 3.58	7.80 ± 3.38	0.50
Creatine uM	10.88 ± 3.99	13.33 ± 1.27	0.30
Creatine phosphate uM	21.38 ± 10.94	14.50 ± 8.10	0.30
Creatinine uM	7.27 ± 3.18	8.37 ± 4.27	0.58
Dimethylamine uM	4.40 ± 3.35	1.20 ± 0.90	0.11
Formate uM	67.01 ± 52.25	38.27 ± 11.44	0.36
Fumarate uM	2.56 ± 1.52	2.67 ± 1.19	0.91
Glucose uM	535.94 ± 475.36	1764.43 ± 757.01	**<0.01**
Glutamate uM	114.32 ± 29.05	103.77 ± 15.05	0.54
Glutamine uM	36.71 ± 30.76	38.57 ± 25.27	0.92
Glycine uM	91.80 ± 29.90	103.53 ± 47.31	0.54
Isobutyrate uM	8.74 ± 2.72	8.87 ± 1.46	0.94
Isoleucine uM	28.20 ± 8.05	31.17 ± 5.49	0.54
Isovalerate uM	11.75 ± 5.88	10.40 ± 3.03	0.70
Lactate uM	3408.46 ± 1348.77	1348.77	0.08
Leucine uM	45.32 ± 15.08	38.67 ± 8.55	0.46
Lysine uM	53.25 ± 14.32	46.43 ± 8.19	0.43
Methionine uM	6.10 ± 2.80	4.17 ± 0.35	0.25
Methylamine uM	2.73 ± 1.13	2.17 ± 0.91	0.41
Methylsuccinate uM	4.16 ± 1.50	2.20 ± 1.15	**0.04**
O-Phosphocholine uM	20.96 ± 7.00	24.27 ± 4.61	0.43
Ornithine uM	42.33 ± 13.08	29.63 ± 20.20	0.13
Phenylalanine uM	21.22 ± 5.03	16.80 ± 6.71	0.16
Proline uM	54.50 ± 18.70	50.77 ± 11.12	0.74
Pyruvate uM	7.85 ± 3.59	4.73 ± 1.50	0.15

Serine uM	38.25 ± 13.12	31.87 ± 7.34	0.42
sn-Glycero-3-phosphocholine uM	56.93 ± 37.01	96.30 ± 41.45	0.09
Succinate uM	12.29 ± 4.85	7.23 ± 2.86	0.09
Threonine uM	44.02 ± 17.44	42.47 ± 8.18	0.88
Trimethylamine N-oxide uM	5.74 ± 4.76	6.27 ± 2.36	0.85
Tryptophan uM	17.98 ± 6.27	16.87 ± 2.76	0.77
Tyrosine uM	34.43 ± 9.94	29.90 ± 8.49	0.45
Valine uM	94.78 ± 24.75	91.70 ± 11.75	0.83

Comparison of metabolites' concentration between patients with and without hypertension at baseline.

Variables	No n= 27	Yes n= 8	p
3-Hydroxybutyrate uM	19.6 ± 15.33	20.10 ± 20.14	0.94
5,6-Dihydrothymine uM	19.63 ± 8.42	13.50 ± 10.29	0.09
Acetate uM	170.52 ± 96.11	170.90 ± 125.86	0.99
Acetoacetate uM	22.47 ± 16.70	32.59 ± 25.09	0.19
Acetone uM	376.40 ± 415.92	1233.33 ± 1951.15	0.26
Adipate uM	235.38 ± 205.10	275.90 ± 161.68	0.61
Alanine uM	139.68 ± 59.21	142.19 ± 20.88	0.86
Arginine uM	23.08 ± 13.93	35.01 ± 19.59	0.06
Betaine uM	10.58 ± 6.38	9.73 ± 6.17	0.74
Butyrate uM	14.64 ± 6.10	18.50 ± 5.05	0.11
Carnitine uM	8.04 ± 7.18	7.18 ± 5.35	0.76
Choline uM	9.69 ± 2.72	8.80 ± 2.69	0.42
Citrate uM	9.67 ± 3.72	7.41 ± 2.24	0.11
Creatine uM	11.21 ± 4.25	10.69 ± 2.44	0.74
Creatine phosphate uM	19.91 ± 10.83	23.73 ± 10.87	0.39
Creatinine uM	7.02 ± 3.19	8.53 ± 3.25	0.25
Dimethylamine uM	3.94 ± 2.73	4.76 ± 5.07	0.67
Formate uM	59.17 ± 46.63	82.71 ± 62.35	0.25
Fumarate uM	2.55 ± 1.50	2.63 ± 1.50	0.90
Glucose uM	610.29 ± 607.70	745.73 ± 606.57	0.58
Glutamate uM	110.68 ± 26.66	122.63 ± 32.89	0.30
Glutamine uM	36.13 ± 27.95	39.36 ± 38.27	0.79
Glycine uM	93.86 ± 33.39	89.28 ± 22.18	0.72
Isobutyrate uM	8.74 ± 2.65	8.80 ± 2.69	0.96
Isoleucine uM	27.82 ± 8.67	30.60 ± 3.59	0.20
Isovalerate uM	11.49 ± 6.17	12.13 ± 3.83	0.79
Lactate uM	3228.58 ± 1412.93	3465.53 ± 1403.63	0.68
Leucine uM	43.85 ± 15.00	47.80 ± 14.00	0.51
Lysine uM	52.35 ± 14.67	53.71 ± 12.01	0.81
Methionine uM	5.28 ± 2.01	8.13 ± 3.76	0.07
Methylamine uM	2.72 ± 1.18	2.53 ± 0.89	0.67
Methylsuccinate uM	4.07 ± 1.51	3.75 ± 1.82	0.62
O-Phosphocholine uM	20.88 ± 7.39	22.45 ± 4.72	0.58
Ornithine uM	41.85 ± 14.24	39.19 ± 13.34	0.64
Phenylalanine uM	20.86 ± 5.66	20.79 ± 3.72	0.97
Proline uM	53.13 ± 19.28	57.70 ± 13.79	0.54
Pyruvate uM	7.70 ± 3.91	7.21 ± 2.12	0.74

Serine uM	36.33 ± 13.63	42.34 ± 8.46	0.25
sn-Glycero-3-phosphocholine uM	58.77 ± 41.31	65.46 ± 28.03	0.67
Succinate uM	11.73 ± 5.08	12.29 ± 4.53	0.78
Threonine uM	43.21 ± 17.98	46.16 ± 12.55	0.67
Trimethylamine N-oxide uM	5.63 ± 5.04	6.31 ± 2.72	0.72
Tryptophan uM	18.57 ± 6.50	15.59 ± 3.52	0.23
Tyrosine uM	33.76 ± 10.56	34.99 ± 7.13	0.76
Valine uM	91.33 ± 23.07	105.24 ± 24.70	0.15

Comparison of metabolites' concentration between patients with and wihout dyslipidemia at baseline.

Variables	No n=28	Yes n= 7	p
3-Hydroxybutyrate uM	16.30 ± 12.97	33.37 ± 2.50	0.08
5,6-Dihydrothymine uM	19.25 ± 8.55	14.13 ± 10.74	0.19
Acetate uM	177.98 ± 101.03	141.13 ± 106.33	0.40
Acetoacetate uM	22.36 ± 18.97	34.49 ± 17.04	0.13
Acetone uM	585.97 ± 1123.57	517.46 ± 511.12	0.88
Adipate uM	254.44 ± 213.70	205.44 ± 82.05	0.56
Alanine uM	139.97 ± 57.98	141.39 ± 23.97	0.95
Arginine uM	23.09 ± 14.01	36.66 ± 19.49	**0.04**
Betaine uM	11.20 ± 6.49	7.11 ± 4.01	0.12
Butyrate uM	14.58 ± 5.94	19.30 ± 5.17	0.06
Carnitine uM	7.90 ± 7.09	7.60 ± 5.58	0.92
Choline uM	9.88 ± 2.80	7.91 ± 1.56	0.09
Citrate uM	9.31 ± 3.71	8.53 ± 2.91	0.61
Creatine uM	11.14 ± 4.17	10.90 ± 2.66	0.89
Creatine phosphate uM	19.49 ± 10.56	25.96 ± 10.96	0.16
Creatinine uM	7.45 ± 3.32	7.04 ± 3.02	0.77
Dimethylamine uM	4.22 ± 3.17	3.76 ± 4.21	0.75
Formate uM	65.05 ± 52.53	62.53 ± 45.87	0.91
Fumarate uM	2.56 ± 1.47	2.61 ± 1.61	0.93
Glucose uM	529.63 ± 473.03	1087.69 ± 866.53	0.15
Glutamate uM	114.76 ± 28.36	108.03 ± 28.77	0.58
Glutamine uM	35.59 ± 31.47	41.99 ± 24.71	0.62
Glycine uM	92.52 ± 31.78	93.96 ± 29.65	0.92
Isobutyrate uM	8.68 ± 2.62	9.06 ± 2.82	0.74
Isoleucine uM	27.98 ± 8.41	30.39 ± 4.99	0.48
Isovalerate uM	11.62 ± 6.11	11.69 ± 3.80	0.98
Lactate uM	3320.24 ± 1331.96	3132.73 ± 1729.39	0.76
Leucine uM	44.73 ± 14.75	44.83 ± 15.54	1.00
Lysine uM	51.95 ± 14.34	55.51 ± 12.89	0.55
Methionine uM	5.67± 2.44	6.99 ± 3.74	0.26
Methylamine uM	2.66 ± 1.19	2.76 ± 0.76	0.84
Methylsuccinate uM	4.14 ± 1.49	3.41 ± 1.83	0.28
O-Phosphocholine uM	20.74 ± 7.13	23.24 ± 5.53	0.40
Ornithine uM	42.65 ± 12.37	35.60 ± 18.96	0.24
Phenylalanine uM	20.93 ± 5.35	20.50 ± 5.07	0.85
Proline uM	53.56 ± 18.96	56.66 ± 15.11	0.69
Pyruvate uM	7.53 ± 3.78	7.83 ± 2.72	0.84

Serine uM	36.33 ± 13.74	43.20 ± 5.64	0.21
sn-Glycero-3-phosphocholine uM	56.81 ± 37.88	74.29 ± 40.17	0.29
Succinate uM	11.69 ± 4.72	12.53 ± 5.93	0.69
Threonine uM	42.98 ± 17.72	47.51 ± 12.74	0.53
Trimethylamine N-oxide uM	5.55 ± 4.96	6.73 ± 2.62	0.55
Tryptophan uM	18.34 ± 6.47	16.09 ± 3.70	0.39
Tyrosine uM	33.84 ± 10.28	34.86 ± 8.19	0.39
Valine uM	91.4 ± 22.57	106.97 ± 26.42	0.12

Comparison of metabolites' concentration between metabolites at baseline vs at 6 months in non responders.

Variables	Non-Responders Baseline n=18		Non-Responders 6 months n=18		p
	Mean	**±SD**	**Mean**	**±SD**	
3-Hydroxybutyrate uM	12.96	7.57	20.92	19.24	0.11
5,6-Dihydrothymine uM	17.25	8.29	22.44	8.81	0.08
Acetate uM	177.99	112.89	140.83	74.55	0.25
Acetoacetate uM	21.19	21.52	23.15	8.87	0.72
Acetone uM	795.52	1365.32	203.01	125.70	0.08
Adipate uM	280.41	256.80	201.13	66.17	0.22
Alanine uM	132.79	50.44	190.36	56.32	**<0.01**
Arginine uM	23.36	14.45	32.64	16.32	0.08
Betaine uM	9.78	5.50	11.78	6.01	0.31
Butyrate uM	14.33	6.37	15.09	5.93	0.71
Carnitine uM	5.99	4.34	6.07	5.51	0.96
Choline uM	9.11	3.04	11.44	2.85	**0.02**
Citrate uM	8.73	3.02	10.36	3.01	0.11
Creatine uM	10.38	3.22	12.98	2.76	**0.01**
Creatine phosphate uM	19.42	11.43	21.93	9.10	0.47
Creatinine uM	7.17	2.83	8.53	3.26	0.19
Dimethylamine uM	4.27	3.78	3.46	1.56	0.41
Formate uM	70.54	61.24	59.65	35.59	0.52
Fumarate uM	2.46	1.53	2.49	0.83	0.94
Glucose uM	518.00	579.41	494.46	251.06	0.88
Glutamate uM	107.79	29.51	127.29	46.11	0.14
Glutamine uM	41.14	33.85	50.56	23.85	0.34
Glycine uM	88.06	32.77	113.73	30.92	**0.02**
Isobutyrate uM	7.79	2.60	9.40	3.11	0.10
Isoleucine uM	27.11	8.99	32.54	7.67	0.06
Isovalerate uM	10.22	5.49	12.86	4.71	0.13
Lactate uM	3141.23	1205.69	3977.79	1066.96	**0.03**
Leucine uM	41.29	15.17	53.12	14.67	**0.02**
Lysine uM	48.22	13.96	60.92	12.20	**0.01**
Methionine uM	5.81	2.76	5.72	2.47	0.92
Methylamine uM	2.44	0.93	2.72	0.93	0.38
Methulsuccinate uM	3.99	1.70	4.19	2.63	0.79
O-Phosphocholine uM	19.16	7.81	21.82	4.23	0.21

Ornithine uM	38.37	14.36	44.97	13.26	0.16
Phenylalanine uM	18.92	5.18	22.50	8.73	0.14
Proline uM	49.77	14.88	70.60	24.96	**0.01**
Pyruvate uM	6.91	2.02	7.56	2.28	0.38
Serine uM	38.08	16.14	50.48	20.06	**0.05**
sn-Glycero-3-phosphocholine uM	46.29	29.99	51.02	23.93	0.60
Succinate uM	11.39	5.02	13.25	6.87	0.36
Threonine uM	41.26	19.59	54.33	17.22	**0.04**
Trimethylamine N-oxide uM	5.82	5.85	4.91	3.90	0.59
Tryptophan uM	15.54	6.46	19.47	5.03	**0.05**
Tyrosine uM	30.64	10.35	38.11	7.07	**0.02**
Valine uM	88.78	24.94	109.11	20.00	**0.01**

Comparison of metabolites' concentration between metabolites at baseline vs at 6 months in responders.

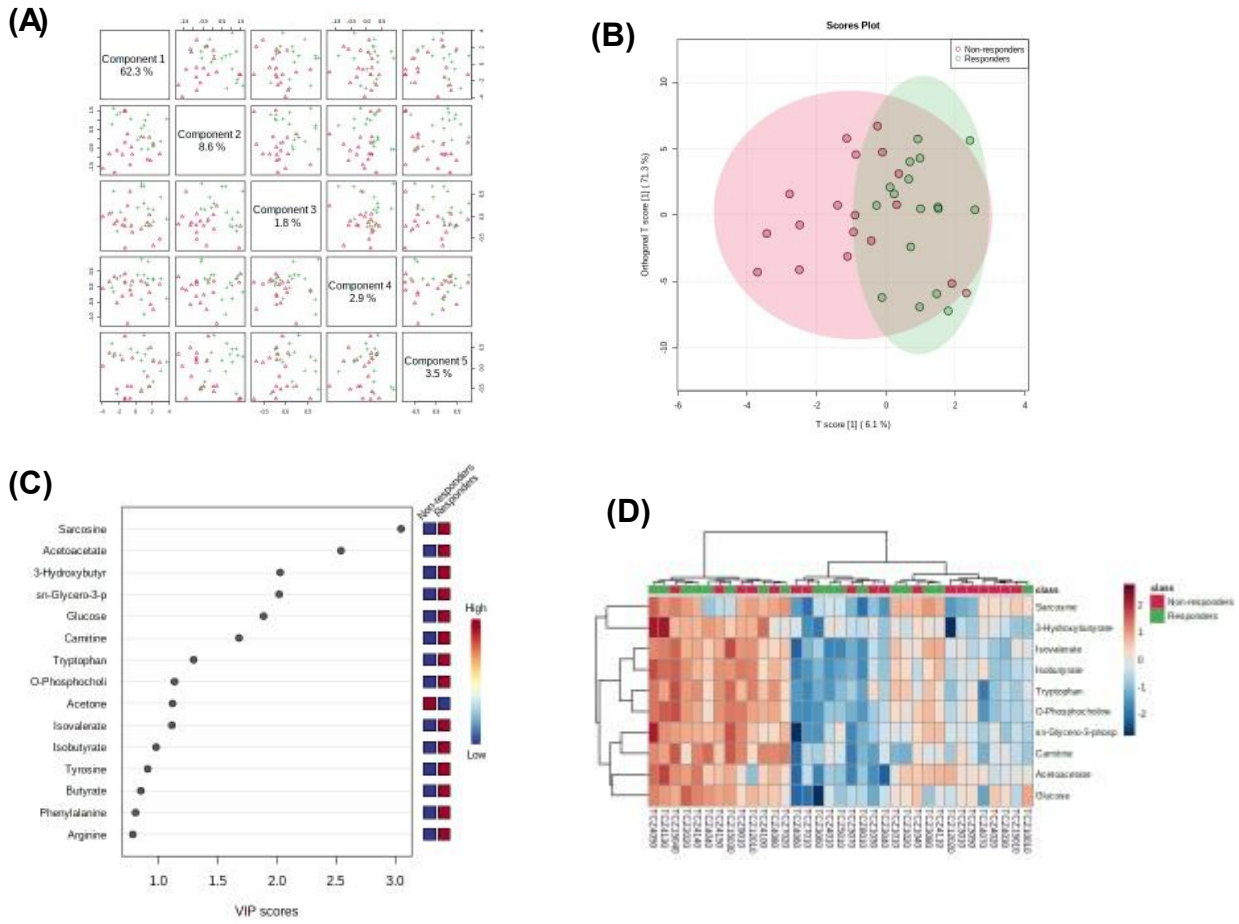
Variables	Responders Baseline n=17		Responders 6 months n=17		p
	Mean	±SD	Mean	±SD	
3-Hydroxybutyrate uM	26.86	19.82	22.06	14.28	0.42
5,6-Dihydrothymine uM	19.26	10.03	20.04	10.57	0.83
Acetate uM	162.78	90.96	146.79	56.75	0.54
Acetoacetate uM	28.58	15.68	32.42	19.30	0.53
Acetone uM	335.88	365.87	540.15	536.58	0.20
Adipate uM	206.78	86.01	288.02	289.55	0.28
Alanine uM	148.15	55.30	185.23	38.61	**0.03**
Arginine uM	28.39	17.39	31.32	13.41	0.59
Betaine uM	11.02	7.07	11.51	7.98	0.85
Butyrate uM	16.78	5.56	16.85	5.17	0.97
Carnitine uM	9.80	8.29	5.25	4.42	0.06
Choline uM	9.88	2.31	10.89	2.06	0.18
Citrate uM	9.61	4.06	11.38	4.35	0.23
Creatine uM	11.85	4.45	14.71	6.70	0.15
Creatine phosphate uM	22.24	10.24	22.55	8.33	0.92
Creatinine uM	7.58	3.67	6.88	2.15	0.51
Dimethylamine uM	3.98	2.89	3.65	2.27	0.71
Formate uM	58.20	37.14	61.73	25.97	0.75
Fumarate uM	2.68	1.45	2.37	1.29	0.51
Glucose uM	771.74	613.42	720.86	515.50	0.80
Glutamate uM	119.36	26.16	113.42	24.46	0.50
Glutamine uM	32.34	25.58	62.19	28.80	**<0.01**
Glycine uM	97.84	29.01	102.55	36.27	0.68
Isobutyrate uM	9.77	2.29	9.74	2.38	0.97
Isoleucine uM	29.88	6.39	30.66	6.56	0.73
Isovalerate uM	13.13	5.64	12.38	4.81	0.68
Lactate uM	3432.57	1592.72	4149.78	501.52	0.09
Leucine uM	48.41	13.62	50.04	14.87	0.74
Lysine uM	57.36	12.69	62.19	12.85	0.28
Methionine uM	6.06	2.78	5.56	2.22	0.57
Methylamine uM	2.92	1.26	3.06	1.49	0.78
Methulsuccinate uM	4.00	1.45	4.48	1.93	0.42
O-Phosphocholine uM	23.45	4.97	21.26	4.31	0.18
Ornithine uM	44.29	13.12	48.77	14.38	0.35
Phenylalanine uM	22.88	4.57	23.22	7.00	0.87
Proline uM	58.85	20.37	66.10	21.75	0.32

Pyruvate uM	8.30	4.64	8.02	4.14	0.85
Serine uM	37.30	8.37	48.98	16.56	**0.02**
sn-Glycero-3-phosphocholine uM	75.14	41.51	56.92	27.14	0.14
Succinate uM	12.35	4.88	13.66	3.14	0.36
Threonine uM	46.68	13.20	50.04	17.30	0.53
Trimethylamine N-oxide uM	5.75	2.87	4.79	3.19	0.37
Tryptophan uM	20.37	4.52	21.53	5.73	0.52
Tyrosine uM	37.64	7.96	38.15	9.33	0.87
Valine uM	100.58	21.66	104.52	16.26	0.55

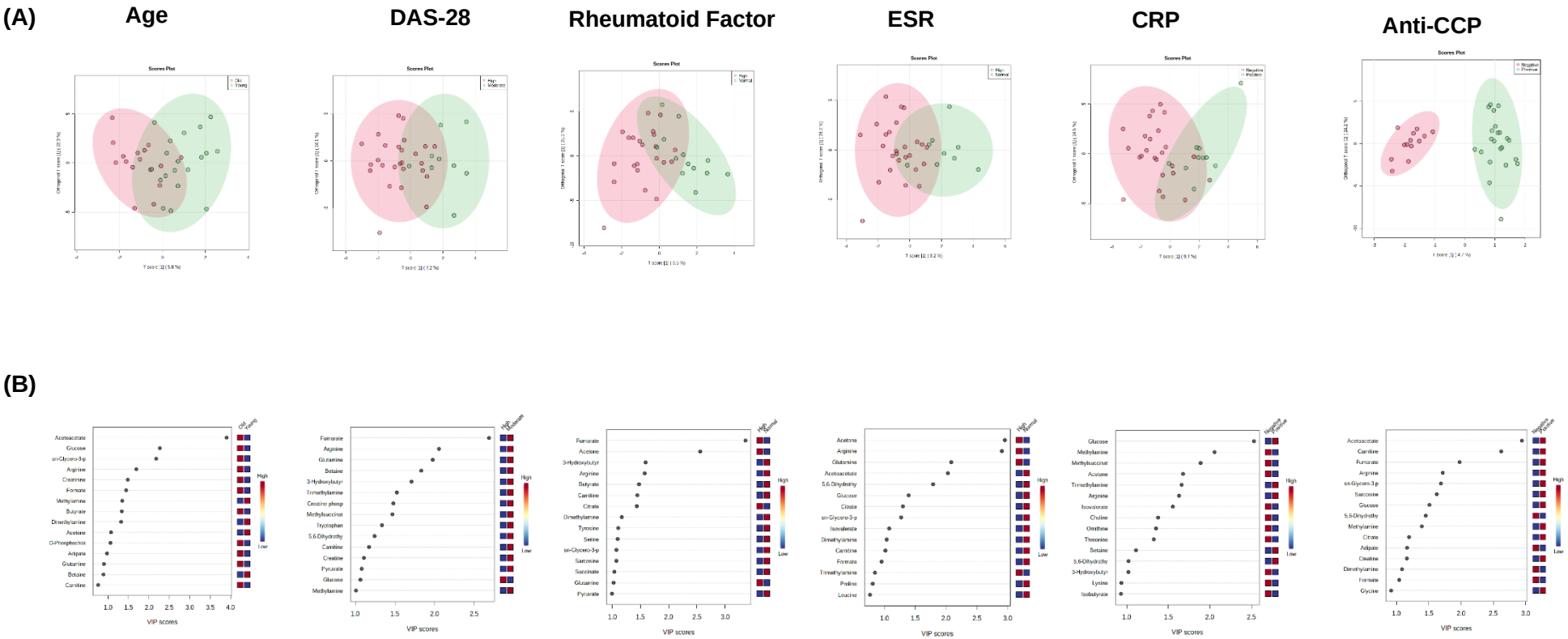
Comparison of metabolites' concentration at 6 months of patients who were non-responders at 6 monhts, but were either good responders or non-responders at 12 months.

Variables	Non-Responders n= 9		Late Responders n=8		p
	Mean	±SD	Mean	±SD	
3-Hydroxybutyrate uM	26.62	26.17	14.93	5.62	0.24
5,6-Dihydrothymine uM	24.53	7.85	20.65	10.30	0.39
Acetate uM	167.57	94.24	112.50	38.52	0.14
Acetoacetate uM	19.87	6.88	27.23	10.14	0.10
Acetone uM	183.11	117.29	230.05	145.29	0.47
Adipate uM	225.51	84.02	179.46	30.98	0.16
Alanine uM	187.01	70.24	195.41	44.78	0.78
Arginine uM	29.63	17.27	37.29	15.96	0.36
Betaine uM	11.90	6.94	11.75	5.71	0.96
Butyrate uM	15.96	6.72	15.11	4.91	0.77
Carnitine uM	5.26	5.78	6.79	5.81	0.59
Choline uM	11.76	3.72	11.41	1.70	0.81
Citrate uM	11.43	3.08	8.96	2.66	0.10
Creatine uM	12.50	3.19	13.83	2.22	0.34
Creatine phosphate uM	23.77	9.06	19.19	9.51	0.33
Creatinine uM	8.81	3.97	8.48	2.65	0.84
Dimethylamine uM	4.29	1.75	2.68	0.81	**0.03**
Formate uM	69.51	48.09	49.99	13.48	0.29
Fumarate uM	2.48	0.98	2.48	0.75	0.99
Glucose uM	496.86	301.53	480.81	218.75	0.90
Glutamate uM	124.44	51.20	134.24	44.42	0.68
Glutamine uM	49.09	24.67	55.74	23.20	0.58
Glycine uM	105.51	32.16	123.28	30.80	0.26
Isobutyrate uM	10.18	3.96	8.55	1.99	0.31
Isoleucine uM	35.68	8.15	30.29	5.78	0.14
Isovalerate uM	14.02	3.72	11.99	5.79	0.40
Lactate uM	4144.04	1239.21	3906.61	919.56	0.66
Leucine uM	51.77	13.77	56.24	16.41	0.55
Lysine uM	62.86	13.24	58.38	12.15	0.48
Methionine uM	5.80	2.85	5.13	1.70	0.56
Methylamine uM	2.24	0.88	3.19	0.81	**0.04**
Methulsuccinate uM	4.32	3.35	4.08	1.97	0.86
O-Phosphocholine uM	22.30	4.38	21.11	4.51	0.59

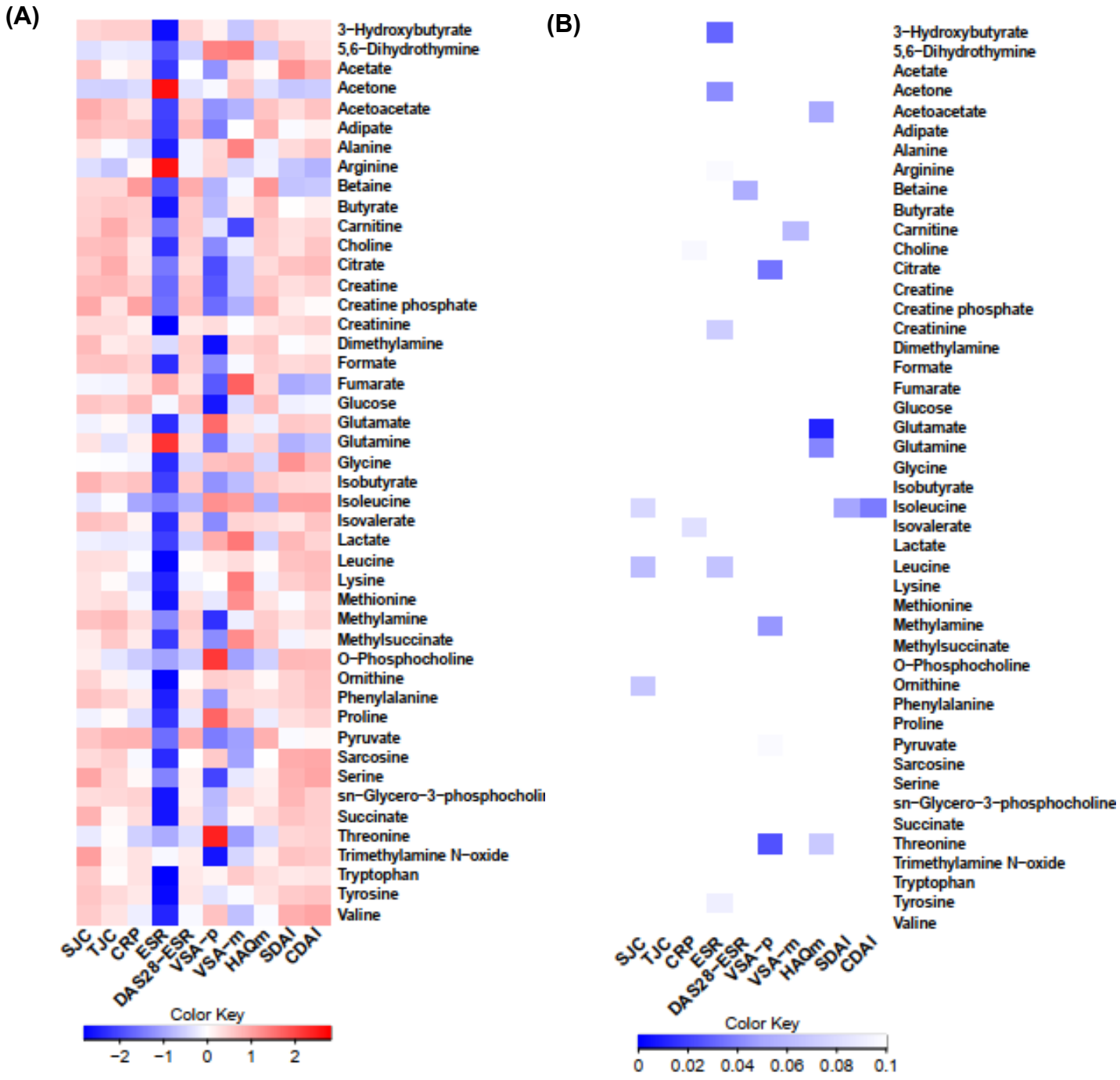
Ornithine uM	51.19	14.86	38.40	8.60	**0.05**
Phenylalanine uM	22.43	12.42	22.01	2.43	0.93
Proline uM	67.76	25.99	76.04	25.51	0.52
Pyruvate uM	8.16	2.50	7.19	2.00	0.40
Serine uM	47.20	18.24	55.45	23.23	0.43
sn-Glycero-3-phosphocholine uM	45.29	23.40	60.30	23.48	0.21
Succinate uM	13.22	7.27	13.83	7.16	0.87
Threonine uM	51.30	14.92	59.35	20.04	0.36
Trimethylamine N-oxide uM	5.50	4.97	4.18	2.76	0.52
Tryptophan uM	18.08	5.59	21.05	4.50	0.25
Tyrosine uM	37.50	7.28	38.58	7.72	0.77
Valine uM	113.21	22.85	107.08	16.96	0.54



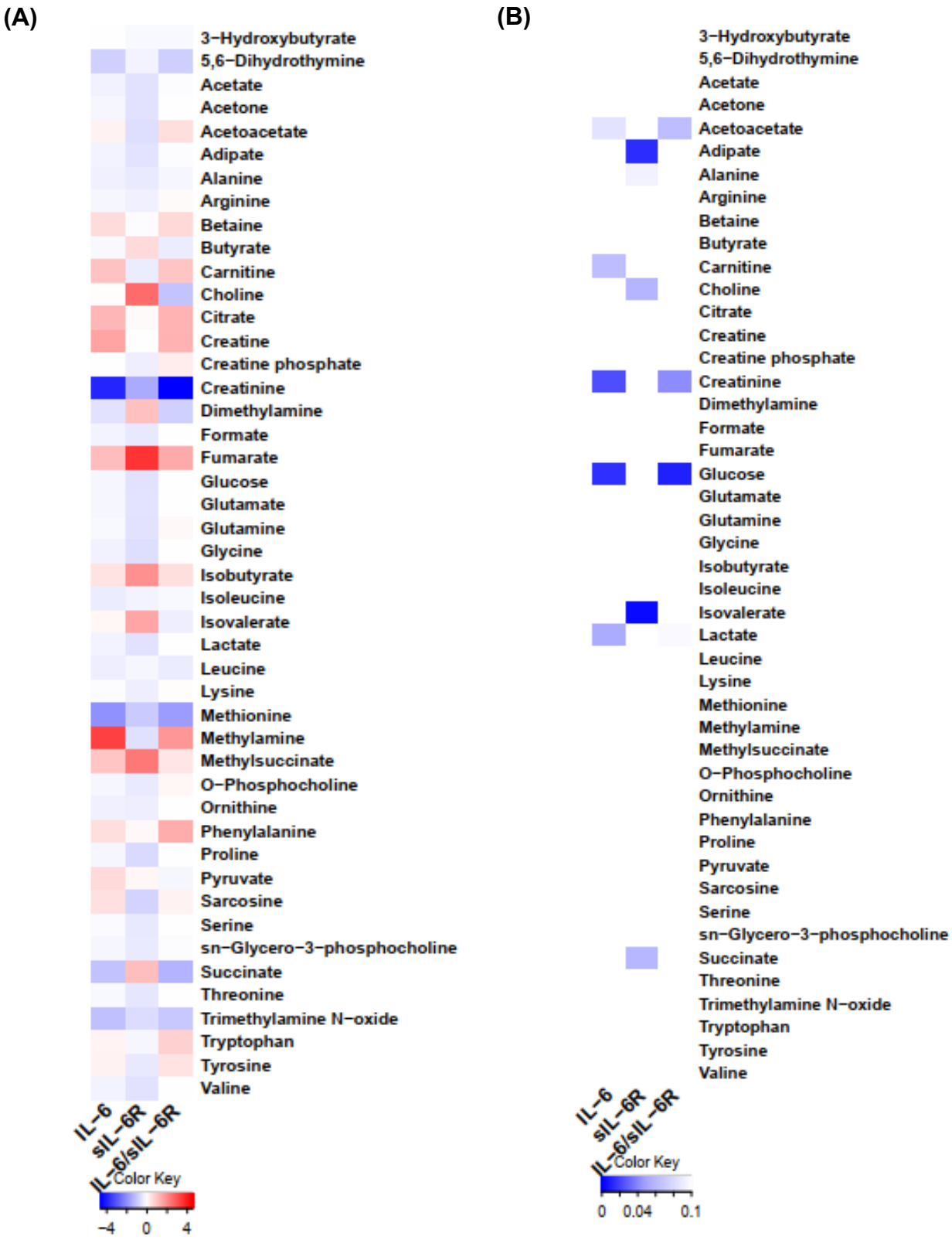
Supplementary Figure S1. Plasma metabolic profile and IL-6, IL-6R and IL6/IL-6R ratio discriminate responders and non-responders. (A) Pairwise score plots between the 5 principal components showing a total explained variance is 79.1%. (B) Orthogonal PLS-DA between non-responders and responders at baseline. (C) Important features identified by PLS-DA. (D) Concentration of metabolites in format Heatmap based in Euclidean distances, shows clustering between responders and non-responders according to metabolites obtained from Supplementary Figure S1C.



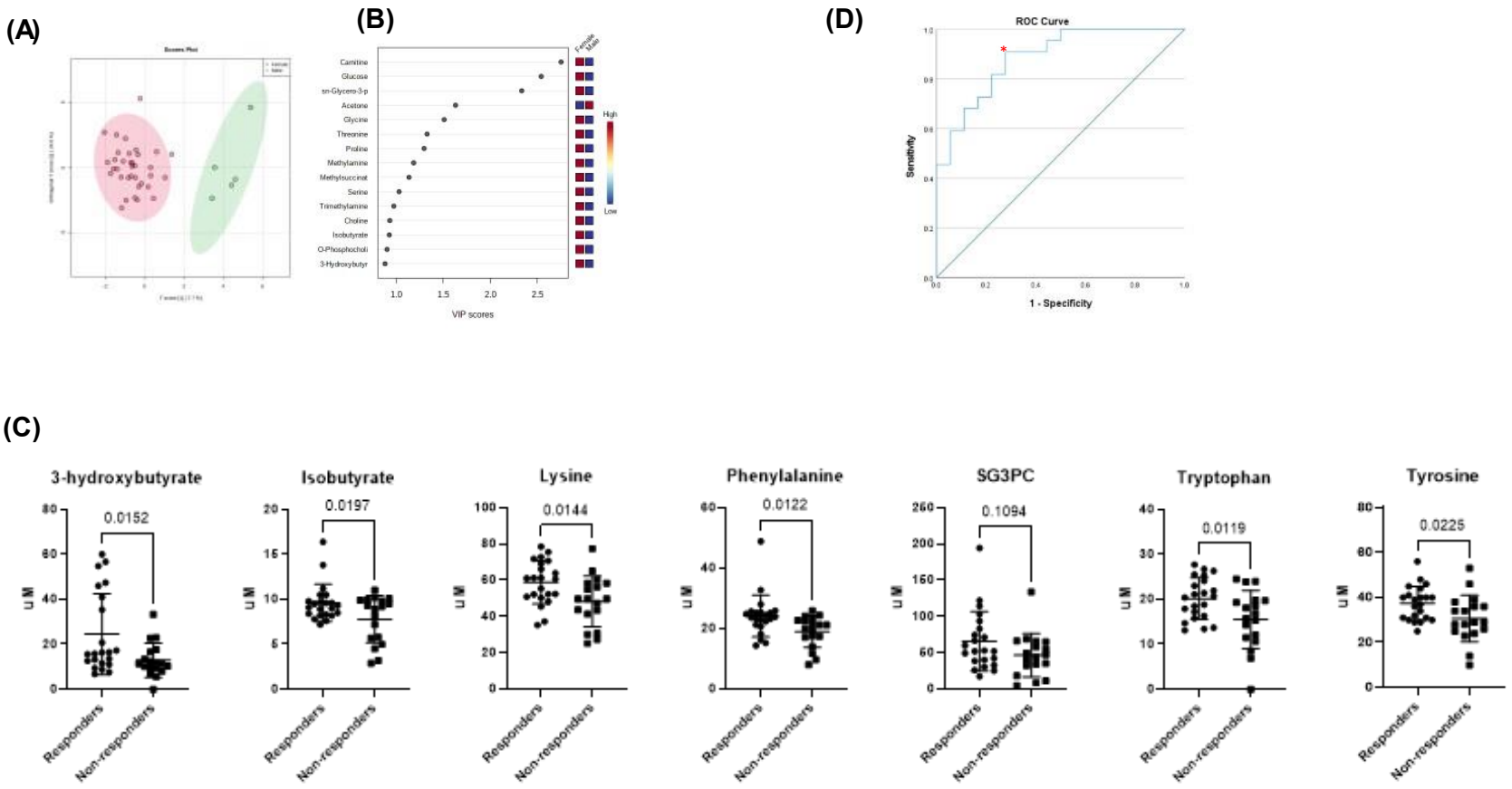
Supplementary figure S2. Discrimination between different clinical parameter according to metabolite's concentration. (A) Orthogonal PLS-DA from plasma metabolic profile of patients according to different clinical variable shows the influence of metabolites to categorize them according to the cutoff value. (B) Important features identified. Age (young <55 years vs old ≥ 55 years), DAS28 (High activity vs moderate activity), RF (Positive>25 IU/mL vs negative ≤25 IU/mL), ESR (High ≥ 30 mm/h vs normal < 30 mm/h) and CRP (negative <2.0 mg/L vs positive ≥2.0 mg/L) and anti CCP (positive >20 IU/mL vs negative anti-CCP ≤20 IU/mL)



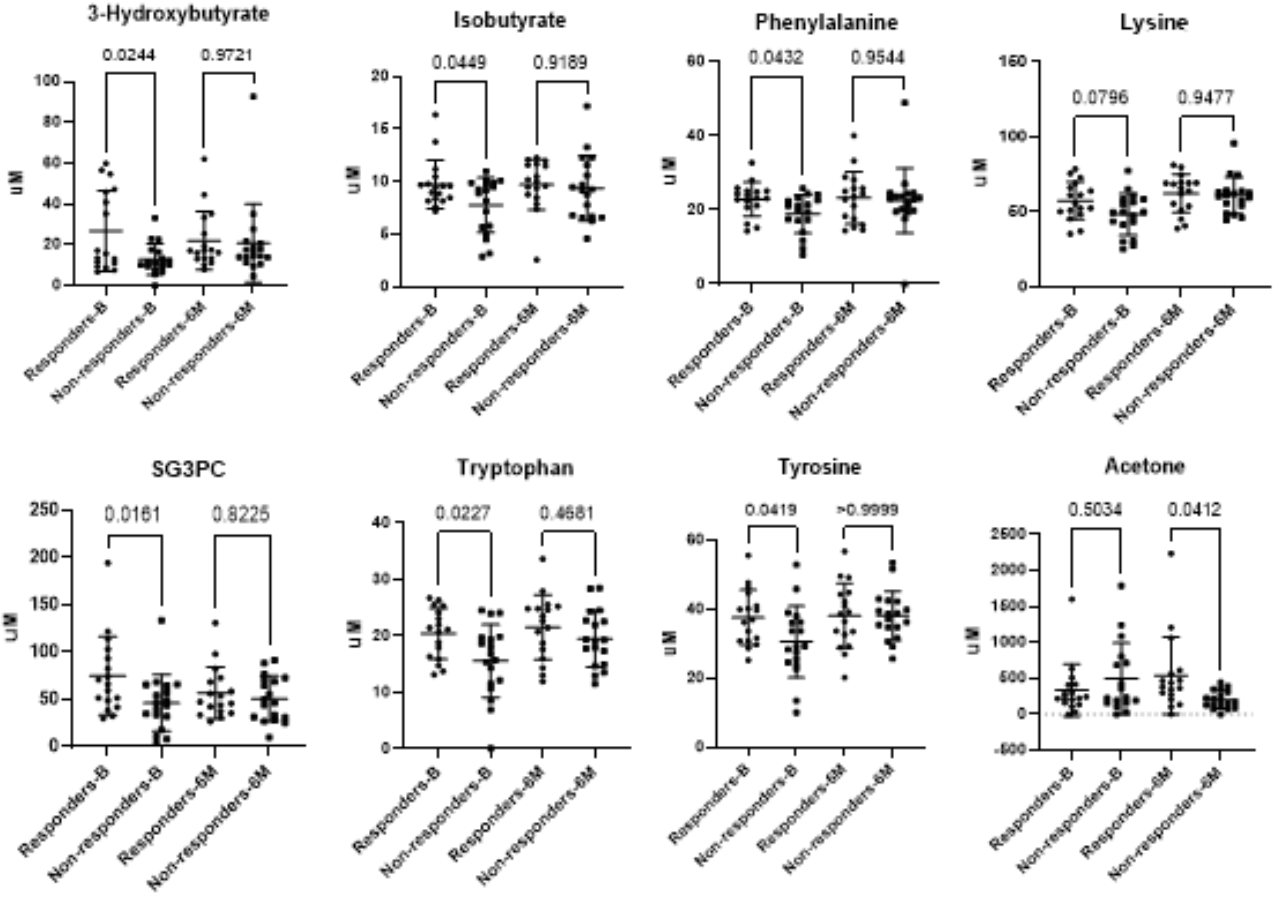
Supplementary Figure S3. Pearson correlation adjusted by age, DM, and DL between clinical variables and metabolites obtained by ^{1}H-NMR before TCZ treatment. (A) The strength of association for each pair were used to form a clustered heatmap, to lend insight into which clinical scores were correlated with which groups of polar metabolites. (B) Correlation significant P-values are displaying on figure S3-B where the row and column order was preserved from figure S3-A. DAS-28: Disease activity score 28; SDAI: Simple disease activity index; CDAI: Clinical disease activity index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.



Supplementary Figure S4. Pearson correlation adjusted by age, DM, and DL between IL-6, sIL-6R, IL-6/IL-6R and metabolites obtained by ^{1}H-NMR before TCZ treatment. (A) The strength of association for each pair were used to form a clustered heatmap, to lend insight into which interleukins were correlated with which groups of polar metabolites. (B) Correlation significant p-values are displaying on figure S4-B where the row and column order was preserved from figure S4-A.



Supplementary Figure S5. **A)** Orthogonal PLS-DA between men and women at baseline. **B)** Important features identified by PLS-DA. **C)** Concentrations of specific polar metabolites at baseline that are different between TCZ responders and non-responders measured by ^{1}H-NMR before treatment with TCZ (n=40 patients). p values are shown in the graphics. **D)** Receiver operating characteristic (ROC) curve for the model probability $p_{\text{responders}}$ before treatment based on binary logistic regression analyzing all 40 patients. The area under the curve (AUC) was 0.886 with a $p<0.001$. The patients with elevated phenylalanine and 3-hydroxybutyrate had 1.14 chances to response to tocilizumab, with a sensitivity and specificity of 80%.



Supplementary Figure S6. Concentrations of specific polar metabolites that are different between TCZ responders and non-responders measured by ^{1}H-NMR before (B-baseline) and after treatment (6M-6 months) with TCZ. p values are shown in the graphics.