

# Multiple myeloma metabolic biomarkers

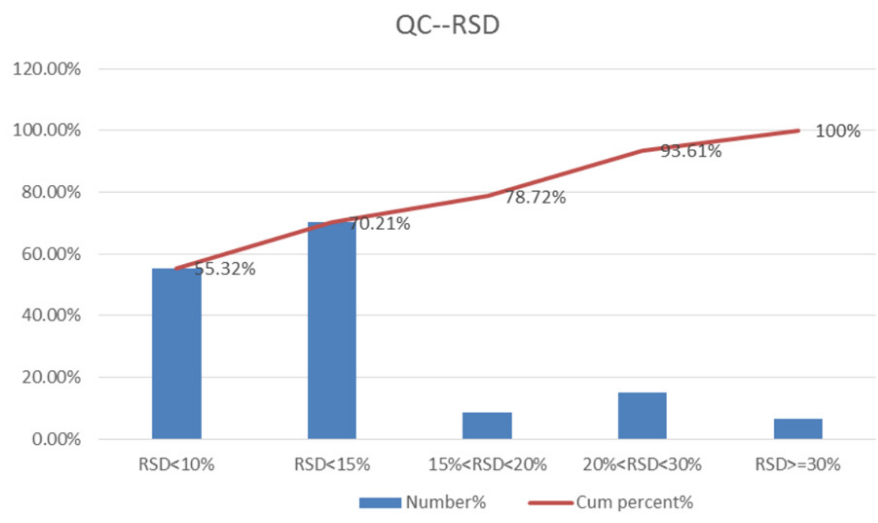


Figure S1. The distributions of relative standard deviation (RSD) of metabolites in all QC samples.

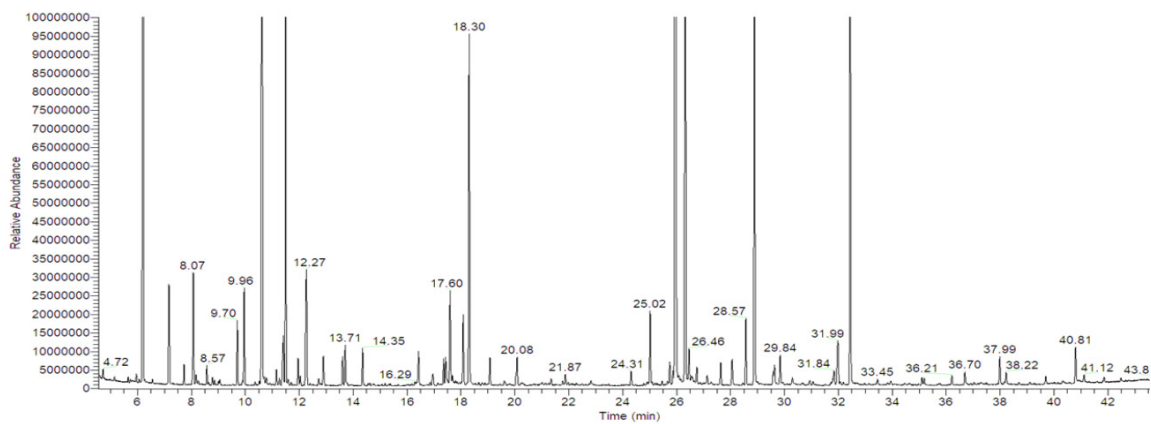


Figure S2. Typical total ion chromatograms from GC-MS analysis of serum.

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**Table S1.** 29 metabolites in discover validation set

Material	t.stat	p.value	FDR (0.05)
Myristic acid	19.508	2.50E-19	1.17E-17
L-Hydroxyproline	17.219	9.66E-18	2.27E-16
Cysteine	14.162	2.48E-15	3.08E-14
Palmitic Acid	14.132	2.62E-15	3.08E-14
L-Leucine	12.839	3.62E-14	3.40E-13
Stearic acid	11.441	7.63E-13	5.98E-12
L-Methionine	9.2833	1.35E-10	9.09E-10
L-Phenylalanine	-8.88	3.81E-10	2.24E-09
Serine	-8.7291	5.65E-10	2.68E-09
Glycerol	8.7258	5.70E-10	2.68E-09
L-Isoleucine	-8.6099	7.72E-10	3.30E-09
Tyrosine	8.0702	3.25E-09	1.27E-08
L-Valine	-6.4519	2.95E-07	1.07E-06
Citric acid	6.1611	6.81E-07	2.29E-06
L-Threonine	-5.8358	1.75E-06	5.47E-06
Myo-Inositol-2	5.7456	2.27E-06	6.67E-06
Oxalic acid	5.6618	2.90E-06	8.01E-06
Beta-Alanine	5.0548	1.69E-05	4.43E-05
Glycine	-4.2308	0.00018236	0.00045111
Glycolic acid	-3.9263	0.00043059	0.0010119
Asparagine	-3.6163	0.0010151	0.0022718
Hypotaurine	3.1654	0.0033892	0.0072407
9-Octadecenoic acid	-2.9115	0.0065028	0.013288
N-a-Acetyl-L-Lysine	2.7004	0.010977	0.020666
Lactic Acid	-2.6998	0.010992	0.020666
Urea	-2.5597	0.015404	0.027845
Maltose	2.5415	0.016083	0.027997
Malic acid	2.4923	0.018062	0.030318
Xylitol	-2.3831	0.023275	0.037722

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**Table S2.** 27 metabolites in external validation set

Material	t.stat	p.value	FDR (0.05)
Myristic acid	12.436	9.54E-18	2.77E-16
L-Hydroxyproline	11.934	5.15E-17	7.46E-16
Citric acid	11.71	1.10E-16	1.07E-15
Palmitic Acid	10.951	1.54E-15	1.11E-14
Stearic acid	9.1236	1.14E-12	6.61E-12
Glycerol	9.0714	1.38E-12	6.68E-12
L-Phenylalanine	-8.4782	1.27E-11	5.27E-11
Serine	-7.7635	1.90E-10	6.23E-10
L-Isoleucine	-7.7583	1.93E-10	6.23E-10
L-Leucine	6.7024	1.07E-08	3.11E-08
Cysteine	6.0579	1.22E-07	0.000000323
Tyrosine	5.9053	2.17E-07	0.000000524
L-Valine	-5.5403	8.40E-07	0.00000187
9-Octadecenoic acid	-5.3738	1.55E-06	0.00000321
L-Methionine	5.1219	3.86E-06	0.00000747
L-Threonine	-5.0948	4.26E-06	0.00000771
Oxalic acid	5.0786	4.52E-06	0.00000771
Beta-Alanine	4.8798	9.20E-06	0.0000148
Myo-Inositol-2	4.4941	3.55E-05	0.0000542
Glycolic acid	-3.7914	3.69E-04	0.00052888
hypotaurine	3.7797	3.83E-04	0.00052888
Malic acid	3.3886	1.29E-03	0.0017034
Asparagine	-3.0327	3.67E-03	0.0046263
Glycine	-2.7577	7.85E-03	0.009481
Urea	-2.6707	9.89E-03	0.011471
Maltose	2.3089	2.47E-02	0.027507
Xylitol	-2.1179	3.86E-02	0.041499

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**Table S3.** The association between metabolites and clinical characteristics among the patients with MM

Clinical Characters	n	Oxalic acid		Urea		Glycolic acid		Serine		L-Phenylalanine		Malic acid	
		Median (p25-p75)	P value	Median (p25-p75)	P value	Median (p25-p75)	P value	Median (p25-p75)	P value	Median (p25-p75)	P value	Median (p25-p75)	P value
Sex (n=55)													
Male	34	11.92 (8.16~15.96)	0.038*	222.66 (182.86~299.35)	0.038*	0.34 (0.2~1.2)	0.51	8.93 (5.26~10.06)	0.377	9.3 (7.84~12.71)	0.386	0.05 (0.03~0.08)	0.146
Female	21	16.96 (10.69~23.57)		171.08 (130.29~266.25)		0.3 (0.15~0.59)		6.06 (4.44~10.24)		8.67 (6.27~12.88)		0.04 (0.03~0.06)	
Karyotype (n=55)													
Abnormal	11	12.83 (6.49, 17.10)	0.487	235.4 (181.76~304.57)	0.247	0.35 (0.18~1.36)	0.643	5.13 (4.81~6.44)	0.016	7.34 (6.29~10.78)	0.053	0.03 (0.02~0.07)	0.313
Normal	44	12.71 (9.39~19.96)		194.8 (153.63~273.23)		0.32 (0.19~0.93)		9.04 (5.68~10.53)		9.72 (8.02~13.86)		0.04 (0.03~0.07)	
13q14 deletion (n=55)													
Yes	3	17.85 (6.24~)	0.661	184.61 (109.51~)	0.324	0.38 (0.34~)	0.342	10 (5.58~)	0.272	10.05 (8.98~)	0.342	0.03 (0.03~)	0.635
No	52	12.65 (8.60~17.55)		208.36 (155.42~297.49)		0.32 (0.19~1.00)		7.14 (5.01~9.86)		8.77 (6.65~12.43)		0.04 (0.03~0.07)	
Rb1 deletion (n=55)													
Yes	2	15.85 (6.24~)	0.982	152.97 (109.51~)	0.345	0.85 (0.34~)	0.366	7.84 (5.68~)	0.842	9.52 (8.98~)	0.875	0.03 (0.32~)	0.486
No	53	12.83 (8.76~17.74)		206.5 (156.82~297.36)		0.32 (0.19~0.97)		7.24 (5.03~10.05)		8.79 (6.71~12.86)		0.04 (0.03~0.07)	
1q21 amplification (n=55)													
Yes	6	10.4 (6.30~26.88)	0.645	243.17 (115.51~489.26)	0.703	0.34 (0.21~0.49)	0.885	4.96 (3.87~5.53)	0.010*	6.81 (6.00~8.37)	0.034*	0.03 (0.02~0.07)	0.282
No	49	12.94 (9.19~17.74)		205.49 (156.82~280.79)		0.32 (0.19~1.19)		8.87 (5.22~10.32)		9.43 (7.44~13.45)		0.04 (0.03~0.07)	
IgH (n=55)													
Abnormal	11	12.45 (6.59~17.85)	0.487	205.49 (184.41~478.24)	0.23	0.38 (0.29~1.22)	0.199	9.53 (5.49~10.00)	0.501	10.23 (6.12~14.04)	0.784	0.05 (0.02~0.10)	0.9
Normal	44	13.33 (9.39~19.90)		201.95 (153.63~273.23)		0.31 (0.18~0.85)		7.03 (5.01~10.14)		8.77 (6.84~12.43)		0.04 (0.03~0.07)	
FISH (n=55)													
Abnormal	15	12.45 (6.49~24.71)	0.545	196.43 (146.50~412.16)	0.623	0.35 (0.29~1.02)	0.257	6.06 (4.81~9.77)	0.637	8.98 (6.29~10.88)	0.65	0.05 (0.03~0.08)	0.806
Normal	40	13.33 (9.78~17.55)		208.36 (155.42~273.23)		0.29 (0.18~1.05)		7.75 (5.08~10.38)		8.98 (6.84~13.02)		0.04 (0.03~0.07)	
light.chain (n=55)													
Abnormal	50	12.64 (8.18~18.55)	0.521	201.44 (153.89~298.01)	0.619	0.33 (0.19~1.06)	0.599	7.03 (5.05~9.92)	0.244	8.88 (6.56~12.17)	0.282	0.04 (0.03~0.07)	0.831
Normal	5	14 (12.09~18.96)		206.5 (132.21~250.96)		0.43 (0.21~1.18)		9.64 (6.80~13.97)		11.71 (7.80~16.19)		0.04 (0.03~0.06)	
Renal.function (n=55)													
Yes	10	11.01 (6.23~13.21)	0.029	323.4 (193.49~499.17)	0.047	0.29 (0.17~0.74)	0.711	6.99 (4.40~10.02)	0.6	9.51 (6.56~15.46)	0.793	0.06 (0.03~0.09)	0.214
No	45	14.47 (9.19~21.04)		193.16 (150.00~270.99)		0.33 (0.19~1.19)		7.24 (5.22~10.11)		8.98 (6.71~12.30)		0.04 (0.03~0.06)	
Bone.destruction (n=55)													
Yes	49	12.83 (8.76~17.74)	0.906	197.4 (156.82~291.61)	0.645	0.34 (0.23~1.19)	0.015*	8.63 (5.39~10.11)	0.025*	9.43 (7.91~12.86)	0.032*	0.04 (0.03~0.07)	0.011*
No	6	12.86 (8.12~23.54)		229.81 (117.14~579.67)		0.12 (0.08~0.30)		3.32 (2.46~8.04)		5.97 (3.47~9.77)		0.02 (0.01~0.04)	

\*indicates p<0.05.

## Multiple myeloma metabolic biomarkers

**Table S4.** The models consisting of clinical characteristics combined with all single significant biomarkers (selected by P<0.1) on the treatment outcome

Variable	Univariate		Multivariate		Multivariate		Multivariate		Multivariate		Multivariate	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Sex (Female vs. Male)	0.73 (0.23, 2.39)	0.606										
Age (Continuous)	1.08 (1, 1.18)	0.061	1.12 (1, 1.24)	0.043	1.13 (1.01, 1.27)	0.038	1.1 (0.98, 1.24)	0.104	1.07 (0.96, 1.2)	0.244	1.05 (0.92, 1.2)	0.487
Karyotype (Abnormal vs. Normal)	0.73 (0.17, 3.14)	0.667										
13q14 (Abnormal vs. Normal)	1.03 (0.09, 12.16)	0.982										
Rb1 (Abnormal vs. Normal)	2.12 (0.12, 35.93)	0.603										
1q21 (Abnormal vs. Normal)	1.03 (0.17, 6.23)	0.973										
IgH (Abnormal vs. Normal)	1.22 (0.31, 4.88)	0.774										
FISH (Abnormal vs. Normal)	1.56 (0.45, 5.35)	0.483										
Abnormal light chain (Present vs. Not present)	2.06 (0.21, 19.91)	0.532										
Renal fuction (Abnormal vs. Normal)	0.86 (0.19, 3.79)	0.839										
Bone destruction (Present vs. Not present)	0.2 (0.03, 1.22)	0.081	0.06 (0.01, 0.58)	0.015	0.06 (0.01, 0.59)	0.016	0.05 (0, 0.77)	0.032	0.06 (0, 0.73)	0.027	0.03 (0, 0.99)	0.049
M protein percentage (Continuous)	1.91 (0.29, 12.66)	0.504										
Total protein (Continuous)	1.01 (0.99, 1.04)	0.359										
M protein (Continuous)	1.02 (0.99, 1.05)	0.136										
Plasmacyte percentage (Continuous)	1.02 (0.99, 1.05)	0.171										
Serum creatinine (Continuous)	0.9965 (0.9904, 1.0026)	0.26										
Hemoglobin (Continuous)	0.9922 (0.9679, 1.0171)	0.534										
Platelet (Continuous)	0.9986 (0.9896, 1.0078)	0.766										
Serum Cacium (Continuous)	0.04 (0, 0.84)	0.038	0.01 (0, 0.59)	0.027	0.01 (0, 0.84)	0.041	0.01 (0, 1.19)	0.059	0.01 (0, 0.95)	0.047	0.01 (0, 1.58)	0.075
Serum beta2-micro (Continuous)	0.95 (0.82, 1.1)	0.507										
Albumin (Continuous)	0.92 (0.83, 1.01)	0.077	0.97 (0.86, 1.1)	0.614	0.9927 (0.8784, 1.1219)	0.906	0.94 (0.81, 1.09)	0.394	0.95 (0.83, 1.09)	0.502	0.92 (0.78, 1.07)	0.28
LDH (Continuous)	1.0046 (0.9979, 1.0113)	0.177										
CRP (Continuous)	1.11 (0.99, 1.24)	0.079	1.1 (0.97, 1.26)	0.151	1.08 (0.94, 1.23)	0.263	1.16 (0.99, 1.37)	0.066	1.13 (0.97, 1.31)	0.126	1.21 (1, 1.46)	0.05
24 h urine protein (Continuous)	0.55 (0.2, 1.51)	0.25										
Beta-Alanine (High vs. Low cutoff =0.388)	4.25 (1.05, 17.2)	0.043			3.17 (0.66, 20.84)	0.136						
Cysteine (High vs. Low cutoff =0.102)	4.8 (1.4, 16.46)	0.013					11.84 (1.91, 73.59)	0.008			11.78 (1.53, 90.74)	0.018
Hypotaurine (High vs. Low cutoff =0.12)	6.46 (1.76, 23.71)	0.005							7.43 (1.38, 40.06)	0.02	7.06 (0.99, 50.51)	0.052

## Multiple myeloma metabolic biomarkers

**Table S5.** The models consisting of clinical characteristics combined with all single significant biomarkers (selected by P<0.1) on PFS

Variable	Univariate		Multivariate		Multivariate		Multivariate		Multivariate		Multivariate		Multivariate			
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value		
Sex (Female vs. Male)	0.6724 (0.2106, 2.147)	0.503														
Age (Continuous)	1.002 (0.939, 1.069)	0.96														
Karyotype (Abnormal vs. Normal)	1.579 (0.493, 5.056)	0.442														
13q14 (Abnormal vs. Normal)	1.841 (0.2403, 14.1)	0.577														
Rb1 (Abnormal vs. Normal)	2.958 (0.385, 22.73)	0.297														
1q21 (Abnormal vs. Normal)	2.245 (0.6507, 8.454)	0.193														
IgH (Abnormal vs. Normal)	0.9584 (0.2672, 3.437)	0.948														
FISH (Abnormal vs. Normal)	1.444 (0.4835, 4.312)	0.511														
Abnormal light chain (Present vs. Not present)	7.8E+07 (0, Inf)	0.998														
Renal function (Abnormal vs. Normal)	0.3602 (0.04709, 2.755)	0.325														
Bone destruction (Present vs. Not present)	0.5751 (0.1281, 2.581)	0.47														
M protein percentage (Continuous)	0.8784 (0.1527, 5.054)	0.885														
Total protein (Continuous)	1.004 (0.9809, 1.027)	0.763														
M protein (Continuous)	0.9999 (0.9776, 1.023)	0.994														
Plasmacyte percentage (Continuous)	1.027 (1.003, 1.053)	0.0288	1.024 (0.9984, 1.049)	0.0669	1.0305 (1.00389, 1.0579)	0.0244	1.0211 (0.9951, 1.048)	0.113	1.0184 (0.9928, 1.045)	0.1612	1.016 (0.9879, 1.044)	0.2736	1.0138 (0.9863, 1.042)	0.329	1.0229 (0.99786, 1.049)	0.0734

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Serum creatinine (Continuous)	0.9999 (0.9951, 1.005)	0.974														
Hemoglobin (Continuous)	0.9895 (0.9665, 1.013)	0.376														
Platelet (Continuous)	0.9968 (0.9887, 1.005)	0.44														
Serum Calcium (Continuous)	0.485 (0.05103, 4.609)	0.529														
Serum beta2-micro (Continuous)	0.9903 (0.8537, 1.149)	0.898														
Albumin (Continuous)	0.9509 (0.8783, 1.03)	0.214														
LDH (Continuous)	1.007 (1.001, 1.012)	0.0128	1.006 (1.0004, 1.012)	0.0352	1.005 (0.99954, 1.0105)	0.0724	1.0046 (0.99873, 1.010)	0.125	1.0052 (0.9998, 1.011)	0.0606	1.006 (1.0001, 1.012)	0.0446	1.0062 (1.0005, 1.012)	0.034	1.0045 (0.99884, 1.010)	0.12
CRP (Continuous)	1.002 (0.9004, 1.114)	0.975														
24 h urine protein (Continuous)	1.368 (0.6763, 2.766)	0.384														
Glycolic acid (High vs. Low cutoff =0.2)	0.2313 (0.08019, 0.6671)	0.00675			0.2521 (0.08322, 0.7639)	0.0148										
L-Valine (High vs. Low cutoff =6)	0.2554 (0.07074, 0.9221)	0.0372					0.3761 (0.09801, 1.443)	0.154								
Serine (High vs. Low cutoff =6)	0.3255 (0.1124, 0.9423)	0.0385							0.5193 (0.1618, 1.667)	0.2708						
Malic acid (High vs. Low cutoff =0.03)	0.3224 (0.1127, 0.9224)	0.0348									0.456 (0.1424, 1.461)	0.1862				
L-Phenylalanine (High vs. Low cutoff =0.102)	0.3115 (0.1083, 0.896)	0.0305											0.4368 (0.1321, 1.445)	0.175		
Xylitol(High vs. Low cutoff =0.075)	0.2328 (0.06494, 0.8346)	0.0252													0.2789 (0.07571, 1.028)	0.055