

	Pre		Post	
	Women (n = 8)	Men (n = 4)	Women (n = 8)	Men (n = 4)
Age (years)	78.63 ± 1.39	78 ± 1.87		
Body weight (kg)	69.19 ± 2.22	74.23 ± 4.24	69.01 ± 3.07	73.78 ± 4.67
TUG	10.53 ± 0.48	9.15 ± 0.57	10.07 ± 0.48	9.2 ± 0.77
SPPB score	6.75 ± 0.67	7.75 ± 1.03	7.5 ± 0.65	9.25 ± 0.85
Robust (10-12)	0 (0%)	1 (25%)	1 (12.5%)	2 (50%)
Prefrail (7-9)	5 (62.5%)	1 (25%)	5 (62.5%)	2 (50%)
Frail (4-6)	3 (37.5%)	2 (25%)	2 (25%)	0 (0%)

Supplementary File S1. Description of Primary Care setting cohort according to gender before and after 12-week exercise training intervention.

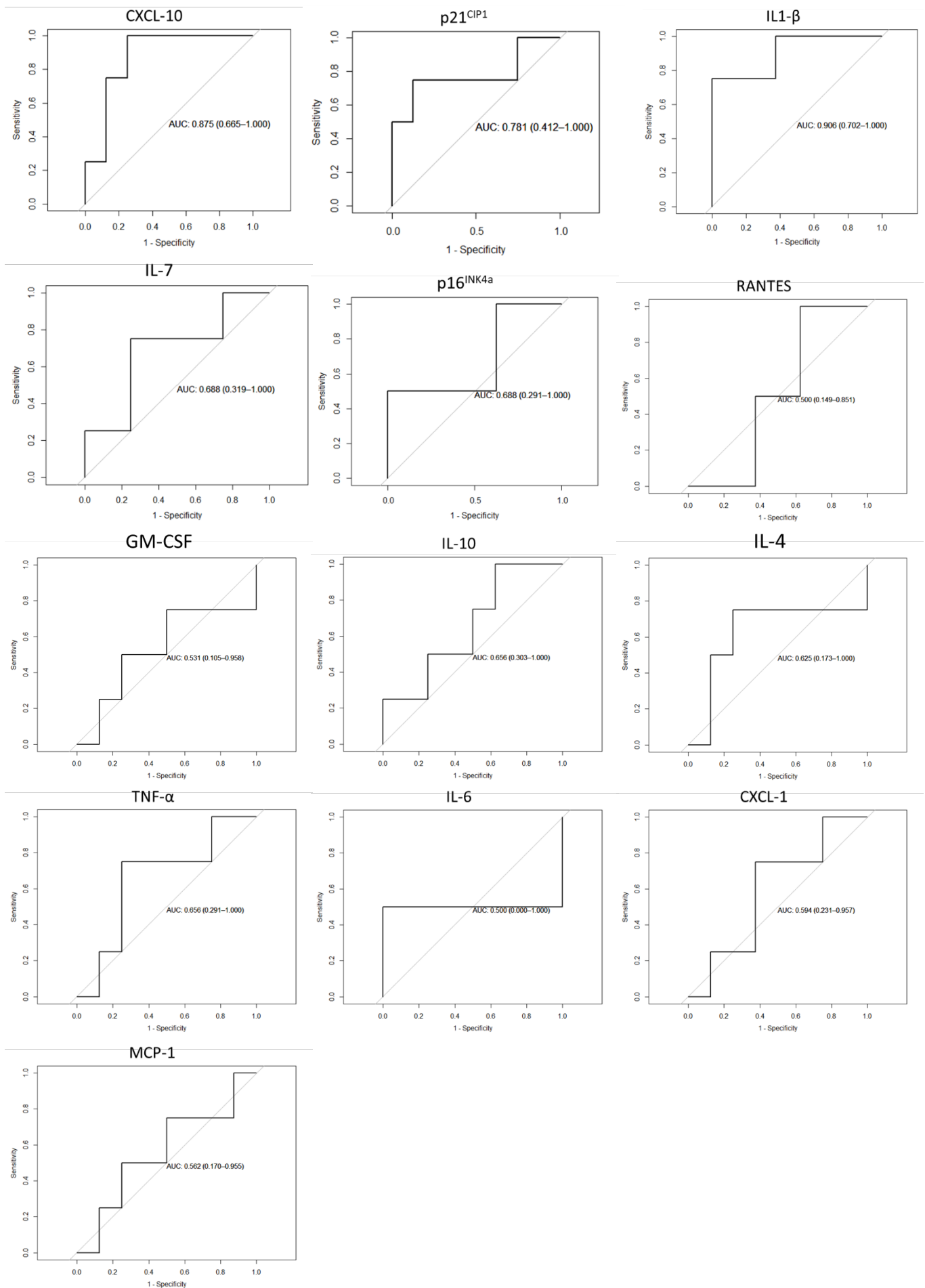
Marker	Pre	Post	p-value
ENA-78	1717 ± 229.9	1815 ± 263.1	0.5186 ^a
G-CSF	590.1 ± 68.86	479.7 ± 64.85	0.0989 ^b
GM-CSF	520.4 ± 109	415.3 ± 92.51	0.0366 ^b
GRO	2291 ± 446.5	2801 ± 549.3	0.1302 ^b
GRO-alpha	1530 ± 248.9	1160 ± 201.7	0.021 ^a
I-309	786.5 ± 209.2	1002 ± 222	0.0015 ^a
IL-1alpha	939.3 ± 249.8	910.3 ± 194.8	0.9697 ^a
IL-1beta	1540 ± 317.8	1370 ± 280	0.064 ^a
IL-2	581.5 ± 115.4	603.2 ± 121.9	0.8501 ^a
IL-3	1856 ± 380.1	1846 ± 357.8	>0.9999 ^a
IL-4	635.8 ± 123	732.3 ± 129.3	0.0425 ^a
IL-5	1319 ± 274.4	1381 ± 260.4	0.5693 ^a
IL-6	640.7 ± 93.83	509.2 ± 105.4	0.064 ^a
IL-7	534.3 ± 122	351.6 ± 60.96	0.0342 ^a
IL-8	2124 ± 487.1	2199 ± 521	0.3804 ^a
IL-10	817 ± 183.5	586.1 ± 119.8	0.0122 ^a
IL12-p40	1304 ± 224.6	1330 ± 233.5	>0.999 ^a
IL-13	406.8 ± 51.17	468.4 ± 55.15	0.2334 ^a
IL-15	939.8 ± 191.8	992.4 ± 170.4	0.4697 ^a
IFN-gamma	1362 ± 117	1361 ± 132.8	0.985 ^b
MCP-1	6061 ± 1062	6199 ± 1008	0.6377 ^a
MCP-2	1465 ± 371.8	1379 ± 322	0.3804 ^a
MCP-3	793.3 ± 157.1	721.6 ± 151.8	0.6772 ^a
M-CSF	1922 ± 417.2	1840 ± 406.5	0.9097 ^a
MDC	1874 ± 278	1751 ± 242.6	0.6564 ^b
MIG	5056 ± 666.4	4589 ± 542.2	0.463 ^b
MIP-1 beta	2296 ± 531.8	2163 ± 448.7	0.4238 ^a
MIP-1-delta	5157 ± 624.3	5428 ± 695.8	0.3385 ^b
RANTES	11,088 ± 1781	12,916 ± 1696	0.0133 ^b
SCF	1239 ± 281.2	1159 ± 237.6	0.2661 ^a
SDF-1	2469 ± 844.5	2266 ± 758.2	0.4238 ^a
TARC	1217 ± 191.5	1095 ± 128.8	0.2112 ^b
TGF-beta 1	689.3 ± 221.9	581.3 ± 159.8	0.2334 ^a
TNF-alpha	1037 ± 191.7	954.8 ± 184.1	0.3804 ^a
TNF-beta	1058 ± 253.9	1012 ± 243	0.8501 ^a
EGF	2619 ± 336.4	2931 ± 397.9	0.0782 ^a
IGF-1	3308 ± 334.8	2830 ± 306.1	0.2231 ^b
Angiogenin	17,941 ± 984.2	18,099 ± 1558	0.8605 ^b
Oncostatin M	1579 ± 303.5	1826 ± 297.6	0.1514 ^a
TPO	889.3 ± 213.9	1041 ± 258.4	0.0425 ^a
VEGF	1068 ± 277.9	1022 ± 234	0.791 ^a
PDGF-BB	2624 ± 567.6	2517 ± 416.6	0.8501 ^a
Leptin	8658 ± 1934	9398 ± 1825	0.3394 ^a
BDNF	5719 ± 1000	5736 ± 815.4	0.9657 ^b
BLC	1068 ± 257.8	920.9 ± 173.7	0.2661 ^b
CK beta 8-1	867.7 ± 210.1	732.2 ± 141.7	0.2036 ^a

Marker	Pre	Post	p-value
Eotaxin	2490 ± 495.3	2351 ± 304.6	0.585 ^b
Eotaxin-2	1615 ± 351.7	1493 ± 218.8	0.5026 ^b
Eotaxin-3	1122 ± 148.5	1033 ± 102.8	0.5186 ^a
FGF-4	1065 ± 271.5	1027 ± 216.7	0.9697 ^a
FGF-6	405.9 ± 35.43	419.8 ± 43.88	0.5518 ^b
FGF-7	663.8 ± 187	593.6 ± 158	0.3013 ^a
FGF-9	1471 ± 363.7	1365 ± 276.8	0.6221 ^a
Flt-3 Ligand	1508 ± 413.3	1288 ± 297.9	0.5825 ^a
Fractalkine	1231 ± 307.9	936.7 ± 193.7	0.0737 ^a
GCP-2	1084 ± 300	839.2 ± 175.9	0.1294 ^a
GDNF	1316 ± 248.2	1151 ± 131.8	0.4697 ^a
HGF	850.9 ± 184.9	754.4 ± 119.8	0.6772 ^a
IGFBP-1	3923 ± 931.2	3596 ± 625	0.4532 ^b
IGFBP-2	8487 ± 1119	8859 ± 722.3	0.5876 ^b
IGFBP-3	1495 ± 436.8	1715 ± 383.7	0.2334 ^a
IGFBP-4	3087 ± 1180	3126 ± 1185	0.9097 ^a
IL-16	990.5 ± 233.6	929.9 ± 190	0.9097 ^a
IP-10	1773 ± 313.4	1428 ± 201.4	0.021 ^a
LIF	1165 ± 296.3	954.9 ± 201.5	0.1763 ^a
LIGHT	1126 ± 251.6	898.6 ± 157	0.1099 ^a
MCP-4	793.6 ± 207.5	645 ± 121.9	0.5044 ^a
MIF	1282 ± 357.6	1124 ± 313	0.6221 ^a
MIP-3-alpha	675.3 ± 126.5	609.2 ± 103.8	0.3577 ^b
NAP-2	5909 ± 837.7	5354 ± 723.8	0.1011 ^b
NT-3	1418 ± 200.8	1383 ± 147.3	0.9097 ^a
NT-4	932.8 ± 238.5	952.5 ± 218.2	0.7183 ^a
Osteopontin	11,903 ± 1633	12,746 ± 1223	0.255 ^b
Osteoprotegerin	1083 ± 286.4	1014 ± 201.2	0.7334 ^a
PARC	3490 ± 961.7	3390 ± 863	0.6221 ^a
PIGF	681.2 ± 160	573.5 ± 115.9	0.1699 ^a
TGF- b 2	1124 ± 421.6	867.2 ± 293.2	0.3804 ^a
TGF- b 3	1084 ± 252.6	851.8 ± 125.3	0.2661 ^a
TIMP-1	7015 ± 963.2	6121 ± 766.6	0.2451 ^b
TIMP-2	12,102 ± 856.8	12,010 ± 702.8	>0.999 ^a

Supplementary File S2. Data as mean ± standard error of mean (SEM), and p-values of the 80 inflammatory mediators analyzed in plasma human samples. a paired t test, b Wilcoxon test.

IL-6				TNF-α			
SPPB\Marker	Up	Down	Total %	SPPB\Marker	Up	Down	Total %
Improved	2/12	6/12	67%	Improved	2/12	6/12	67%
Worsen	2/12	2/12		Worsen	2/12	2/12	
CXCL-1				IL-7			
SPPB\Marker	Up	Down	Total %	SPPB\Marker	Up	Down	Total %
Improved	1/12	7/12	58%	Improved	2/12	6/12	58%
Worsen	-	4/12		Worsen	1/12	3/12	
MCP-1				GM-CSF			
SPPB\Marker	Up	Down	Total %	SPPB\Marker	Up	Down	Total %
Improved	4/12	4/12	50%	Improved	1/12	7/12	67%
Worsen	2/12	2/12		Worsen	1/12	3/12	
CXCL-10				IL-4			
SPPB\Marker	Up	Down	Total %	SPPB\Marker	Up	Down	Total %
Improved	1/12	7/12	83%	Improved	6/12	2/12	58%
Worsen	3/12	1/12		Worsen	3/12	1/12	
IL-1β				p21			
SPPB\Marker	Up	Down	Total %	SPPB\Marker	Up	Down	Total %
Improved	-	8/12	92%	Improved	1/12	7/12	67%
Worsen	3/12	1/12		Worsen	1/12	3/12	
IL-10				p16			
SPPB\Marker	Up	Down	Total %	SPPB\Marker	Up	Down	Total %
Improved	5/12	3/12	50%	Improved	2/12	6/12	67%
Worsen	3/12	1/12		Worsen	2/12	2/12	
RANTES							
SPPB\Marker	Up	Down	Total %				
Improved	7/12	1/12	58%				
Worsen	4/12	-					

Supplementary File S3. Association analysis comparing functional (improve/worsen) and biomarkers (increase/decrease) changes in Primary Care cohort.



Supplementary File S4. ROC curves of inflammatory and senescence markers analyzed in Primary Care setting cohort.

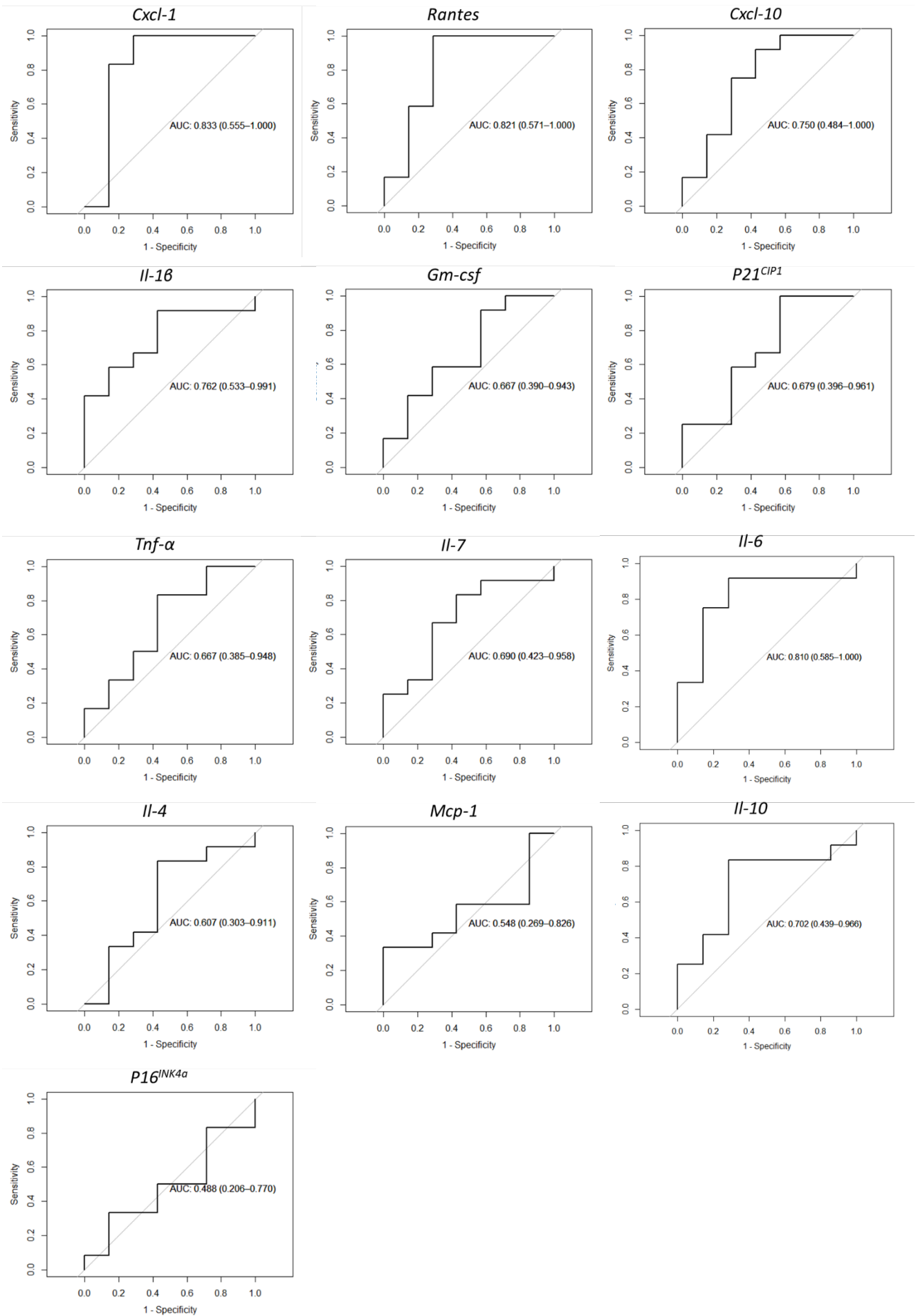
A

Variable	Rest (Mean ± SD)	Trained (Mean ± SD)	<i>p</i> -value
Body weight	36.99 ± 4.66	36.30 ± 4.57	0.8506
Grip strength	4.12 ± 0.94	4.31 ± 0.70	0.6217
Motor coordination	2.21 ± 0.77	2.07 ± 0.67	0.6917
Endurance	427.75 ± 111.24	427.83 ± 121.85	0.9988

B

Variable	Pre (Mean ± SD)	Post (Mean ± SD)	<i>p</i> -value
Body weight	36.99 ± 4.66	35.89 ± 4.07	0.3663
Grip strength	4.12 ± 0.94	3.49 ± 0.97	<i>0.0967</i>
Motor coordination	2.21 ± 0.77	1.22 ± 0.30	0.0027
Endurance	427.75 ± 111.24	335.38 ± 89.59	0.0038

Supplementary File S5. Analysis of clinical data in mice cohort. **(A)** Comparison of functional parameters before the intervention in trained vs rest group. **(B)** Comparison of functional parameters in rest mice before and after the intervention. Bold numbers represent statistical significance ($p < 0.05$), and italic numbers represents a tendency ($p < 0.1$).



Supplementary File S6. ROC curves of inflammatory and senescence markers analyzed in mice cohort.