

## Supplemental Material

**Supplement Table 1** - Protein names sorted in alphabetical order

<b>Protein full name</b>	<b>Entry name</b>	<b>Olink® Panel*</b>	<b>Uniprot ID**</b>
Angiotensin-converting enzyme 2	ACE2	CVD II	Q9BYF1
Adisintegrin and metalloproteinase with thrombospondin motifs 13	ADAMTS13	CVD II	Q76LX8
ADM	ADM	CVD II	P35318
Agouti-related protein	AGRP	CVD II	O00253
Protein AMBP	AMBP	CVD II	P02760
Angiopoietin-1	ANG1	CVD II	Q15389
Bone morphogenetic protein 6	BMP6	CVD II	P22004
Natriuretic peptides B	BNP	CVD II	P16860
Carbonic anhydrase 5A, mitochondrial	CA5A	CVD II	P35218
C-C motif chemokine 17	CCL17	CVD II	Q92583
C-C motif chemokine 3	CCL3	CVD II	P10147
T-cell surface glycoprotein CD4	CD4	CVD II	P01730
CD40 ligand	CD40L	CVD II	P29965
SLAM family member 5	CD84	CVD II	Q9UIB8
Carcinoembryonic antigenrelated cell adhesion molecule 8	CEACAM8	CVD II	P31997
Chymotrypsin C	CTRC	CVD II	Q99895
Cathepsin L1	CTSL1	CVD II	P07711
C-X-C motif chemokine 1 (CVD2)	CXCL1	CVD II	P09341
Decorin	DCN	CVD II	P07585
2,4-dienoyl-CoA reductase, mitochondrial	DECR1	CVD II	Q16698
Dickkopf-related protein 1	DKK1	CVD II	O94907
Fatty acid-binding protein, intestinal	FABP2	CVD II	P12104
Fibroblast growth factor 21 (CVD2)	FGF21	CVD II	Q9NSA1
Fibroblast growth factor 23 (CVD2)	FGF23	CVD II	Q9GZV9
Follistatin	FS	CVD II	P19883
Galectin-9	GAL9	CVD II	O00182
Growth/differentiation factor 2	GDF2	CVD II	Q9UK05
Growth hormone	GH	CVD II	P01241
Gastric intrinsic factor	GIF	CVD II	P27352
Lactoylglutathione lyase	GLO1	CVD II	Q04760
Gastrotropin	GT	CVD II	P51161
Hydroxyacid oxidase 1	HAOX1	CVD II	Q9UJM8
Proheparin-binding EGF-like growth factor	HBEGF	CVD II	Q99075
Heme oxygenase 1	HO1	CVD II	P09601
Osteoclast-associated immunoglobulin-like receptor	HOSCAR	CVD II	Q8IYS5

Heat shock 27 kDa protein	HSP27	CVD II	P04792
Alpha-L-iduronidase	IDUA	CVD II	P35475
Low affinity immunoglobulin gamma Fc region receptor II-b	IGGFCREC EPTORIIB	CVD II	P31994
Pro-interleukin-16	IL16	CVD II	Q14005
Interleukin-17D	IL17D	CVD II	Q8TAD 2
Interleukin-18 (CVD2)	IL18	CVD II	Q14116
Interleukin-1 receptor antagonist protein	IL1RA	CVD II	P18510
Interleukin-1 receptor-like 2	IL1RL2	CVD II	Q9HB2 9
Interleukin-27	IL27	CVD II	Q8NEV 9
Interleukin-4 receptor subunit alpha	IL4RA	CVD II	P24394
Interleukin-6 (CVD2)	IL6	CVD II	P05231
Melusin	ITGB1BP2	CVD II	Q9UKP 3
Kidney injury molecule 1	KIM1	CVD II	Q96D42
Leptin	LEP	CVD II	P41159
Lectin-like oxidized LDL receptor 1	LOX1	CVD II	P78380
Lipoprotein lipase	LPL	CVD II	P06858
Macrophage receptor MARCO	MARCO	CVD II	Q9UEW 3
Tyrosine-protein kinase Mer	MERTK	CVD II	Q12866
Matrix metalloproteinase-12	MMP12	CVD II	P39900
Matrix metalloproteinase-7	MMP7	CVD II	P09237
NF-kappa-B essential modulator	NEMO	CVD II	Q9Y6K9
Pappalysin-1	PAPPA	CVD II	Q13219
Proteinase-activated receptor 1	PAR1	CVD II	P25116
Poly [ADP-ribose] polymerase 1	PARP1	CVD II	P09874
Platelet-derived growth factor subunit B	PDGFSUBU NITB	CVD II	P01127
Programmed cell death 1 ligand 2	PDL2	CVD II	Q9BQ5 1
Polymeric immunoglobulin receptor	PIGR	CVD II	P01833
Placenta growth factor	PLGF	CVD II	P49763
Prolargin	PRELP	CVD II	P51888
Brother of CDO	PROTEINB OC	CVD II	Q9BWW 1
Serine protease 27	PRSS27	CVD II	Q9BQR 3
Prostasin	PRSS8	CVD II	Q16651
P-selectin glycoprotein ligand 1	PSGL1	CVD II	Q14242
Pentraxin-related protein PTX3	PTX3	CVD II	P26022
Receptor for advanced glycosylation end products	RAGE	CVD II	Q15109
Renin	REN	CVD II	P00797
Stem cell factor (CVD2)	SCF	CVD II	P21583
Serpin A12	SERPINA12	CVD II	Q8IW75

SLAM family member 7	SLAMF7	CVD II	Q9NQ25
Superoxide dismutase [Mn], mitochondrial	SOD2	CVD II	P04179
Sortilin	SORT1	CVD II	Q99523
Spondin-2	SPON2	CVD II	Q9BUD6
Proto-oncogene tyrosine-protein kinase Src	SRC	CVD II	P12931
Serine/threonine-protein kinase 4	STK4	CVD II	Q13043
Tissue factor	TF	CVD II	P13726
Protein-glutamine gamma-glutamyltransferase 2	TGM2	CVD II	P21980
Thrombospondin-2	THBS2	CVD II	P35442
Thrombopoietin	THPO	CVD II	P40225
Angiopoietin-1 receptor	TIE2	CVD II	Q02763
Thrombomodulin	TM	CVD II	P07204
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A	CVD II	O00220
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	CVD II	Q9Y6Q6
Tumor necrosis factor receptor superfamily member 13B	TNFRSF13B	CVD II	O14836
TNF-related apoptosis-inducing ligand receptor 2	TRAILR2	CVD II	O14763
Vascular endothelial growth factor D	VEGFD	CVD II	O43915
V-set and immunoglobulin domain-containing protein 2	VSIG2	CVD II	Q96IQ7
Lymphotactin	XCL1	CVD II	P47992

Legend: \*CVDII: cardiovascular II panel; \*\*UniProt ID from UniProt Knowledgebase

**Supplement Table 2** - Biological process, abbreviation, and full names of Cardiovascular II Olink® multiplex panel of the studied proteins.

<b>Angiogenesis</b>	GDF-2; VEGFD; TIE2; HO-1; DCN; STK4; PGF; IL-6; LEP; HSP 27; THBS2; IL-18; ADM; ANGPT-1; BNP; TF;
<b>Blood vessel morphogenesis</b>	THBS2; TIE2; IL18; LEP; ADM; HO-1; ANGPT-1; PGF; GDF-2; BNP; TF; VEGFD; DCN; STK4; IL6; HSP27;
<b>Catabolic process</b>	MMP-7; IDUA; DCN; AMBP; FABP2; HO-1; DECR1; CTSL1; BOC; GT; FGF-23; HAOX1; RAGE; LEP; ADAM- TS30; HSP27; ACE2; MMP-12; LPL; PRELP;
<b>Cell adhesion</b>	RAGE; CD4; IL6; CD40-L; SRC; TGM2; TIE2; IL-18; LEP; XCL1; SLAMF7; PD-L2; IL-27; PSGL-1; IL-1ra; SCF; ADAM-TS30; HSP27; LOX-1; IL-4RA; IL1RL2; ANGPT-1; AMBP; MERTK; SPON2; BOC; CD84; THBS2;
<b>Coagulation</b>	PAR-1; TF; HSP27; MERTK; TM; PDGF subunit B; CD40-L; SRC; ADAM-TS30;
<b>Heart development</b>	PDGF subunit B; Dkk-1; TIE2; ADM; STK4;
<b>Immune response</b>	<a href="#">TNFRSF13B</a> ; IL1RL2; NEMO; CD4; XCL1; IL6; <a href="#">IgG Fc receptor II-b</a> ; CCL3; SRC; IL-18; CEACAM8; Gal-9; HO-1; PlgR; IL-4RA; SLAMF7; TNFRSF10A; IL-27; LEP; CTSL1; TNFRSF11A; ANGPT-1; AMBP; SPON2; MARCO; CD84; ADM; CCL17; CD40-L; CXCL1; ADAM-TS30; RAGE; BMP-6; PD-L2; hOSCAR; PTX3; IL-16; TRAIL-R2;
<b>Inflammatory response</b>	CXCL1; XCL1; IL1RL2; IL-4RA; BMP-6; IL-6; LPL; PTX3; TIE2; CD40-L; LEP; TRAIL-R2; RAGE; IL-18; LOX-1; PAR-1; CCL3; TF; TNFRSF11A; IL-27; TNFRSF10A; Gal-9; IL-17D; NEMO; CCL17; IL-1ra; HO-1; ACE2;
<b>MAPK cascade</b>	NEMO; HB-EGF; SCF; PDGF subunit B; GDF-2; ANGPT-1; CCL3; TIE2; PAR-1; LEP; REN; TNFRSF11A; THPO; FGF21; Gal-9; SRC; GH; XCL1; FGF-23; CCL17;IL-18; BMP-6; IL-6; AMBP; CD40-L;
<b>Platelet activation</b>	HSP 27; MERTK; IL-6; TM; PDGF subunit B; PAR-1; CD40-L; SRC; ADAM-TS30;
<b>Proteolysis</b>	SRC; PARP-1; ADAM-TS30; TF; LOX-1; MMP-12; CTRC; TNFRSF10A; REN; IL-6; PAR-1; CTSL1; TRAIL-R2; MMP-7; ACE2; Gal-9;
<b>Regulation of blood pressure</b>	ACE2; PAR-1; PDGF subunit B; BNP; REN; SOD2; HO-1; LEP;
<b>Response to hypoxia</b>	VEGFD; PDGF subunit B; SRC; TIE2; ADM; HO-1; PGF; LEP;
<b>Response to peptide hormone</b>	SERPINA12; SRC; GH; LEP; AGRP; PDGF subunit B; TIE2; PARP-1; SORT1; ADM; IL6;
<b>Wound healing</b>	TM; HB-EGF; PAR-1; PDGF subunit B; TF; MMP-12; CD40-L; SRC; ADAM-TS30; HO-1; HSP-27; MERTK; IL6; DCN;
<b>Other Gene Ontology terms</b>	FS; GIF; CA5A; GLO1; PAPPA; PRSS8; KIM1; VSIG2; PRSS27; <a href="#">ITGB1BP2</a> ;

Legend: GDF-2 indicates Growth/differentiation factor 2 ; VEGFD: Vascular endothelial growth factor D; TIE2: Angiopoietin-1 receptor; HO-1:Heme oxygenase 1;

DCN:Decorin;STK4: Serine/threonine-protein kinase 4; PGF: Placenta growth factor; IL-6: Interleukin-6; LEP: Leptin; HSP 27: Heat shock 27 kDa protein; THBS2: Thrombospondin-2 ;IL-18: Interleukin-18; ADM: Adrenomedullin; ANGPT-1:Angiopoietin-1;BNP: Natriuretic peptides B; TF: Tissue factor; HSP27: Heat shock 27 kDa protein; MMP-7: Matrix metalloproteinase-7; IDUA: Alpha-L-iduronidase; DCN: Decorin; AMBP: Protein AMBP; FABP2: DECR1: 2,4-dienoyl-CoA reductase, mitochondrial; CTSL1: Cathepsin L1; BOC: Brother of CDO; GT:Gastrotropin; FGF-23: Fibroblast growth factor 23; HAOX1: Hydroxyacid oxidase 1; RAGE: Receptor for advanced glycosylation end products; ADAM-TS30: A disintegrin and metalloproteinase with thrombospondin motifs 13; ACE2: Angiotensin-converting enzyme 2; MMP-12: Matrix metalloproteinase-12; LPL: Lipoprotein lipase; PRELP: Prolargin; CD4: T-cell surface glycoprotein CD4; CD40-L: CD40 ligand; Gal-9: Galectin-9; SRC: Proto-oncogene tyrosine-protein kinase Src; TGM2: Protein-glutamine gamma-glutamyltransferase 2; XCL-1: Lymphotoctin; SLAMF7: SLAM family member 7; PD-L2: Programmed cell death 1 ligand 2; IL-27: Interleukin-27; PSGL-1: P-selectin glycoprotein ligand 1; IL-1ra: interleukin-1 receptor antagonist protein; SCF: Stem cell factor; LOX-1: Lectin-like oxidized LDL receptor 1; IL-4RA:Interleukin-4 receptor subunit alpha; IL1RL2: Interleukin-1 receptor-like 2; MERTK: Tyrosine-protein kinase Mer; SPON2: Spondin-2; CD84: SLAM family member 5; PAR-1: Proteinase-activated receptor 1; TF: Tissue factor; TM:Thrombomodulin; PDGF subunit B: Platelet-derived growth factor subunit B; Dkk-1: Dickkopf-related protein 1; STK4:Serine/threonine-protein kinase 4;TNFRSF13B: Tumor necrosis factor receptor superfamily member 13B; NEMO: NFkappa-B essential modulator; XCL1: Lymphotoctin; IgG Fc receptor II-b: Low affinity immunoglobulin gamma Fc region receptor II-b; CCL3: C-C motif chemokine 3; CEACAM8: Carcinoembryonic antigenrelated cell adhesion molecule 8; PlgR: Polymeric immunoglobulin receptor; TNFRSF10A: Tumor necrosis factor receptor superfamily member 10A;TNFRSF11A: Tumor necrosis factor receptor superfamily member 11A; MARCO: Macrophage receptor MARCO; CCL17: C-C motif chemokine 17; CXCL1: C-X-C motif chemokine 1; BMP-6: Bone morphogenetic protein 6; hOSCAR:Osteoclast-associated immunoglobulin-like receptor; PTX3: Pentraxin-related protein PTX3; IL-16: Interleukin-16; TRAIL-R2: TNF-related apoptosis-inducing ligand receptor 2; IL-17D: Interleukin -17D; HB-EGF: Proheparin-binding EGF-like growth factor; REN:Renin; THPO: Thrombopoietin; FGF21: Fibroblast growth factor 21; GH: Growth hormone; CTRC: Chymotrypsin C; CTSL1: Cathepsin L1; SOD2: Superoxide dismutase [Mn], mitochondrial (SOD2); SERPINA12: Serpin A12; AGRP: Agouti-related protein; SORT1: Sortilin; FS: Follistatin; GIF: Gastric intrinsic factor; CA5A: Carbonic anhydrase 5A, mitochondrial; GLO1: Lactoylglutathione lyase; PAPPA: Pappalysin-1; PRSS8: Prostasin; KIM1: Kidney Injury Molecule; VSIG2: Kidney Injury Molecule; PRSS27: Serine protease 27; ITGB1BP2: Melusin;

**Supplement Table 3.** Circulating proteins according to identified clusters.

Characteristic	Overall, N = 399 <sup>1</sup>	1, N = 223 <sup>1</sup>	2, N = 176 <sup>1</sup>	p-value <sup>2</sup>
<b>Olink protein biomarkers</b>				
BMP-6	5.71 (5.44, 6.02)	5.57 (5.35, 5.87)	5.94 (5.59, 6.18)	<0.001
ANGPT1	9.46 (8.89, 9.95)	9.28 (8.73, 9.78)	9.69 (9.14, 10.10)	<0.001
ADM	7.23 (6.91, 7.66)	7.02 (6.70, 7.26)	7.68 (7.34, 8.04)	<0.001
CD40-L	7.27 (6.70, 7.82)	7.10 (6.43, 7.67)	7.52 (6.90, 8.03)	<0.001
SLAMF7	3.98 (3.59, 4.39)	3.80 (3.49, 4.20)	4.16 (3.81, 4.70)	<0.001
PGF	8.11 (7.87, 8.41)	7.90 (7.74, 8.10)	8.44 (8.22, 8.68)	<0.001
ADAM-TS13	6.35 (6.26, 6.43)	6.36 (6.27, 6.43)	6.35 (6.26, 6.43)	0.6
BOC	4.26 (4.08, 4.48)	4.21 (4.04, 4.42)	4.36 (4.14, 4.54)	<0.001
IL-4RA	2.02 (1.83, 2.23)	1.90 (1.78, 2.07)	2.14 (2.01, 2.36)	<0.001
SRC	8.15 (7.99, 8.26)	8.17 (7.99, 8.26)	8.13 (8.00, 8.25)	0.4
IL-1ra	5.01 (4.64, 5.47)	4.82 (4.50, 5.16)	5.31 (4.94, 5.70)	<0.001
IL6	3.52 (2.97, 4.43)	3.21 (2.83, 4.03)	3.94 (3.35, 4.99)	<0.001
TNFRSF10A	3.86 (3.64, 4.10)	3.70 (3.55, 3.90)	4.06 (3.89, 4.30)	<0.001
STK4	6.62 (6.28, 6.81)	6.58 (6.19, 6.78)	6.66 (6.38, 6.86)	0.003
IDUA	6.20 (5.92, 6.50)	6.10 (5.86, 6.38)	6.34 (6.00, 6.58)	<0.001
TNFRSF11A	5.58 (5.30, 6.03)	5.37 (5.15, 5.60)	6.07 (5.71, 6.37)	<0.001
PAR-1	9.56 (9.31, 9.78)	9.42 (9.13, 9.64)	9.73 (9.53, 9.91)	<0.001
TRAIL-R2	5.91 (5.62, 6.28)	5.70 (5.49, 5.88)	6.31 (6.05, 6.66)	<0.001
PRSS27	8.75 (8.43, 9.05)	8.62 (8.31, 8.90)	8.95 (8.70, 9.22)	<0.001
TIE2	7.56 (7.43, 7.71)	7.50 (7.37, 7.64)	7.65 (7.51, 7.79)	<0.001
TF	5.40 (5.15, 5.69)	5.23 (5.03, 5.43)	5.63 (5.44, 5.88)	<0.001
IL1RL2	4.78 (4.49, 5.08)	4.73 (4.39, 4.98)	4.85 (4.59, 5.18)	<0.001
PDGF subunit B	10.77 (10.24, 11.14)	10.57 (9.98, 11.04)	10.90 (10.52, 11.27)	<0.001
IL-27	6.23 (5.95, 6.49)	6.08 (5.79, 6.34)	6.39 (6.14, 6.67)	<0.001
IL-17D	2.91 (2.72, 3.08)	2.79 (2.63, 2.99)	3.02 (2.86, 3.22)	<0.001
CXCL1	10.22 (9.71, 10.69)	10.12 (9.53, 10.58)	10.30 (9.91, 10.82)	0.002
LOX-1	6.77 (6.41, 7.17)	6.65 (6.31, 6.97)	6.97 (6.59, 7.30)	<0.001
Gal-9	8.18 (7.96, 8.46)	8.04 (7.80, 8.16)	8.45 (8.26, 8.68)	<0.001
GIF	8.40 (7.65, 8.99)	8.26 (7.60, 8.80)	8.61 (7.75, 9.36)	0.002
SCF	8.90 (8.64, 9.16)	8.85 (8.63, 9.09)	8.97 (8.67, 9.28)	0.003
IL18	9.05 (8.72, 9.42)	8.95 (8.63, 9.24)	9.22 (8.88, 9.62)	<0.001
FGF-21	7.01 (5.91, 8.28)	6.38 (5.38, 7.60)	7.64 (6.62, 9.43)	<0.001
PIgR	6.81 (6.73, 6.90)	6.75 (6.68, 6.84)	6.88 (6.81, 6.98)	<0.001
RAGE	13.50 (13.25, 13.80)	13.44 (13.17, 13.69)	13.62 (13.33, 13.94)	<0.001
SOD2	9.95 (9.90, 10.01)	9.95 (9.89, 9.99)	9.97 (9.92, 10.02)	<0.001
CTRC	10.68 (10.16, 11.14)	10.61 (10.13, 11.05)	10.77 (10.22, 11.29)	0.021
FGF-23	4.43 (4.10, 4.89)	4.24 (3.97, 4.56)	4.76 (4.41, 5.24)	<0.001
SPON2	8.33 (8.18, 8.50)	8.22 (8.10, 8.33)	8.51 (8.37, 8.63)	<0.001
GH	7.32 (5.91, 8.99)	7.07 (5.79, 8.89)	7.62 (6.14, 9.22)	0.080
FS	11.46 (11.12, 11.93)	11.37 (10.96, 11.76)	11.63 (11.29, 12.07)	<0.001
GLO1	6.42 (6.09, 6.92)	6.35 (5.99, 6.77)	6.56 (6.20, 7.00)	<0.001
CD84	5.24 (4.93, 5.48)	5.08 (4.85, 5.40)	5.40 (5.14, 5.62)	<0.001
PAPPA	3.68 (3.31, 3.99)	3.50 (3.16, 3.84)	3.89 (3.55, 4.22)	<0.001
SERPINA12	2.95 (2.31, 3.77)	3.11 (2.33, 3.77)	2.90 (2.29, 3.76)	0.4
REN	6.95 (6.44, 7.59)	6.65 (6.21, 7.15)	7.38 (6.84, 8.27)	<0.001
DECR1	8.73 (7.94, 9.45)	8.61 (7.81, 9.35)	8.87 (8.21, 9.61)	0.009
MERTK	6.26 (5.93, 6.52)	6.03 (5.78, 6.32)	6.44 (6.26, 6.72)	<0.001
KIM1	7.18 (6.69, 7.80)	6.98 (6.46, 7.47)	7.58 (7.05, 8.14)	<0.001

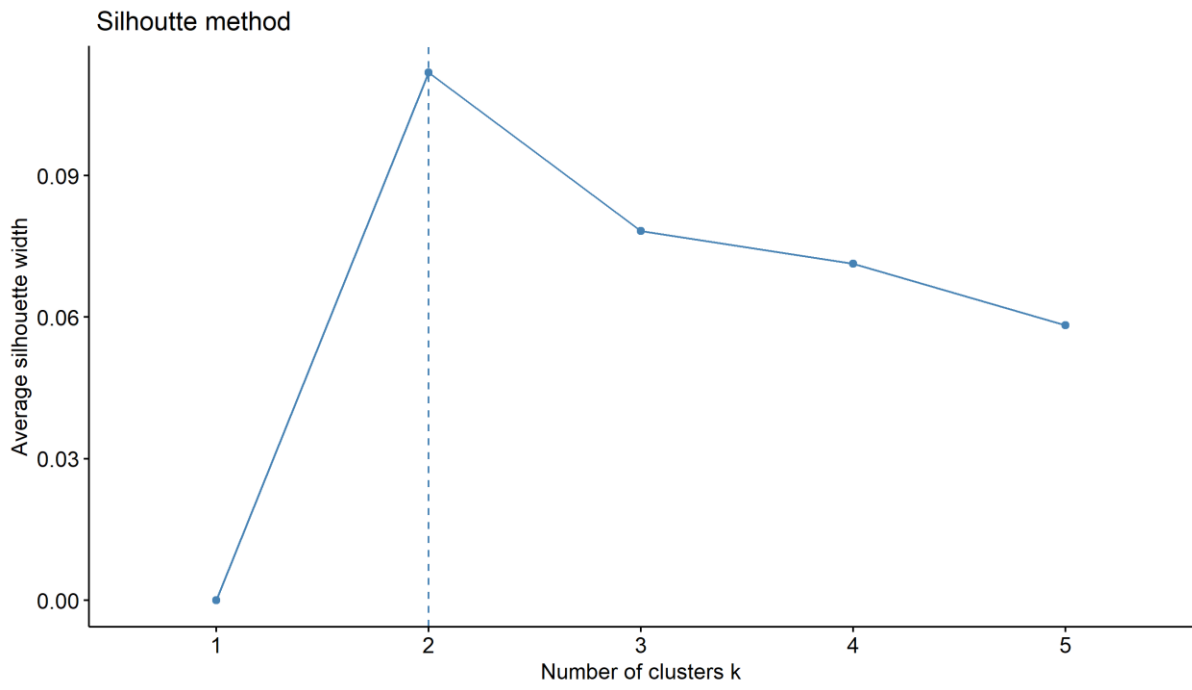
THBS2	5.81 (5.68, 5.93)	5.75 (5.63, 5.84)	5.87 (5.76, 6.00)	<0.001
TM	10.83 (10.60, 11.08)	10.66 (10.46, 10.82)	11.07 (10.92, 11.30)	<0.001
VSIG2	4.92 (4.50, 5.50)	4.69 (4.33, 5.09)	5.35 (4.88, 5.84)	<0.001
AMBP	7.94 (7.82, 8.07)	7.84 (7.73, 7.96)	8.06 (7.95, 8.19)	<0.001
PRELP	8.61 (8.47, 8.74)	8.51 (8.40, 8.63)	8.72 (8.62, 8.89)	<0.001
HO-1	11.72 (11.46, 12.03)	11.62 (11.36, 11.89)	11.86 (11.60, 12.12)	<0.001
XCL1	5.09 (4.72, 5.55)	4.96 (4.63, 5.28)	5.34 (4.93, 5.69)	<0.001
IL16	6.97 (6.69, 7.32)	6.83 (6.51, 7.06)	7.20 (6.94, 7.50)	<0.001
SORT1	8.94 (8.76, 9.15)	8.84 (8.65, 8.98)	9.09 (8.92, 9.32)	<0.001
CEACAM8	4.57 (4.20, 4.99)	4.36 (4.04, 4.66)	4.89 (4.56, 5.32)	<0.001
PTX3	5.07 (4.75, 5.45)	4.96 (4.63, 5.33)	5.21 (4.88, 5.57)	<0.001
PSGL-1	4.25 (4.11, 4.38)	4.24 (4.12, 4.35)	4.25 (4.11, 4.41)	0.3
CCL17	9.28 (8.68, 10.00)	9.17 (8.45, 9.72)	9.52 (8.94, 10.47)	<0.001
CCL3	6.49 (6.06, 6.89)	6.23 (5.89, 6.62)	6.83 (6.48, 7.21)	<0.001
MMP7	10.43 (10.10, 10.75)	10.24 (9.85, 10.50)	10.69 (10.37, 10.99)	<0.001
IgG Fc receptor II-b	4.56 (3.74, 5.14)	4.43 (3.44, 4.98)	4.73 (3.97, 5.35)	<0.001
ITGB1BP2	7.24 (6.64, 7.91)	7.10 (6.44, 7.72)	7.45 (6.90, 8.10)	<0.001
DCN	4.90 (4.73, 5.08)	4.81 (4.67, 4.95)	5.06 (4.90, 5.24)	<0.001
Dkk-1	9.42 (9.04, 9.84)	9.26 (8.87, 9.64)	9.66 (9.29, 10.08)	<0.001
LPL	10.27 (9.94, 10.52)	10.20 (9.91, 10.47)	10.34 (9.96, 10.57)	0.018
PRSS8	8.65 (8.30, 8.94)	8.36 (8.17, 8.66)	8.92 (8.69, 9.13)	<0.001
AGRP	5.66 (5.39, 5.94)	5.54 (5.25, 5.74)	5.83 (5.57, 6.13)	<0.001
HB-EGF	6.66 (6.31, 7.11)	6.54 (6.19, 6.93)	6.85 (6.52, 7.30)	<0.001
GDF-2	9.49 (9.12, 9.96)	9.44 (9.06, 9.91)	9.51 (9.19, 9.99)	0.2
FABP2	8.28 (7.63, 8.87)	8.03 (7.40, 8.65)	8.55 (7.85, 9.12)	<0.001
THPO	3.37 (3.13, 3.63)	3.26 (3.06, 3.48)	3.52 (3.28, 3.75)	<0.001
MARCO	6.66 (6.52, 6.81)	6.58 (6.43, 6.72)	6.74 (6.64, 6.88)	<0.001
GT	1.89 (1.62, 2.27)	1.84 (1.54, 2.13)	2.03 (1.75, 2.36)	<0.001
BNP	2.18 (1.69, 2.94)	1.96 (1.62, 2.58)	2.60 (1.97, 3.74)	<0.001
MMP12	6.65 (6.16, 7.22)	6.42 (6.00, 6.86)	7.05 (6.52, 7.55)	<0.001
ACE2	4.00 (3.63, 4.43)	3.77 (3.51, 4.09)	4.33 (3.98, 4.75)	<0.001
PD-L2	3.65 (3.44, 3.89)	3.55 (3.32, 3.72)	3.84 (3.59, 4.05)	<0.001
CTSL1	7.13 (6.87, 7.44)	6.96 (6.75, 7.20)	7.32 (7.09, 7.67)	<0.001
hOSCAR	10.89 (10.70, 11.05)	10.76 (10.61, 10.91)	11.04 (10.89, 11.15)	<0.001
TNFRSF13B	10.08 (9.79, 10.36)	10.00 (9.68, 10.22)	10.24 (9.91, 10.61)	<0.001
TGM2	9.88 (9.44, 10.24)	9.86 (9.33, 10.23)	9.92 (9.55, 10.27)	0.13
LEP	7.87 (7.16, 8.57)	7.86 (7.10, 8.40)	7.93 (7.25, 8.74)	0.029
CA5A	2.27 (1.87, 2.90)	2.08 (1.72, 2.47)	2.63 (2.19, 3.13)	<0.001
HSP 27	10.40 (10.29, 10.51)	10.38 (10.29, 10.49)	10.42 (10.29, 10.53)	0.2
CD4	5.61 (5.40, 5.83)	5.48 (5.31, 5.63)	5.79 (5.62, 6.00)	<0.001
NEMO	7.53 (7.00, 8.00)	7.45 (6.93, 7.89)	7.61 (7.18, 8.15)	<0.001
VEGFD	8.10 (7.89, 8.31)	8.06 (7.86, 8.29)	8.13 (7.94, 8.35)	0.015
PARP-1	3.46 (3.21, 3.77)	3.32 (3.12, 3.63)	3.66 (3.38, 3.99)	<0.001
HAOX1	5.40 (4.55, 6.47)	5.24 (4.31, 6.07)	5.69 (4.70, 7.05)	<0.001

Legend: BMP-6: Bone morphogenetic protein 6; ANGPT-1:Angiopoietin-1; ADM: Adrenomedullin; CD40-L: CD40 ligand; SLAMF7: SLAM family member 7; PGF: Placenta growth factor; ADAM-TS30: A disintegrin and metalloproteinase with thrombospondin motifs 13; BOC: Brother of CDO; IL- 4RA:Interleukin-4 receptor subunit alpha; SRC: Proto-oncogene tyrosine-protein kinase Src; IL-1ra: interleukin-1 receptor antagonist protein; IL-6: Interleukin-6; TNFRSF10A: Tumor necrosis factor receptor superfamily member 10A; STK4:Serine/threonine-protein kinase 4; IDUA: Alpha-L-iduronidase; TNFRSF11A: Tumor necrosis factor receptor superfamily member 11A; PAR-1: Proteinase-activated receptor 1; TRAIL-R2: TNF-related apoptosis-inducing ligand receptor 2; PRSS27: Serine protease 27; TIE2: Angiopoietin-1 receptor; TF: Tissue factor; IL1RL2: Interleukin-1 receptor-like 2; PDGF subunit B: Platelet-derived growth factor subunit B;IL -27: Interleukin-27; IL-17D: Interleukin -17D; CXCL1: C-X-C motif chemokine 1; LOX-1: Lectin-like oxidized LDL receptor 1; Gal-9: Galectin-9; GIF: Gastric intrinsic factor; SCF: Stem cell factor; IL-18: Interleukin-18; FGF21: Fibroblast growth factor 21; PlgR: Polymeric immunoglobulin receptor; RAGE: Receptor

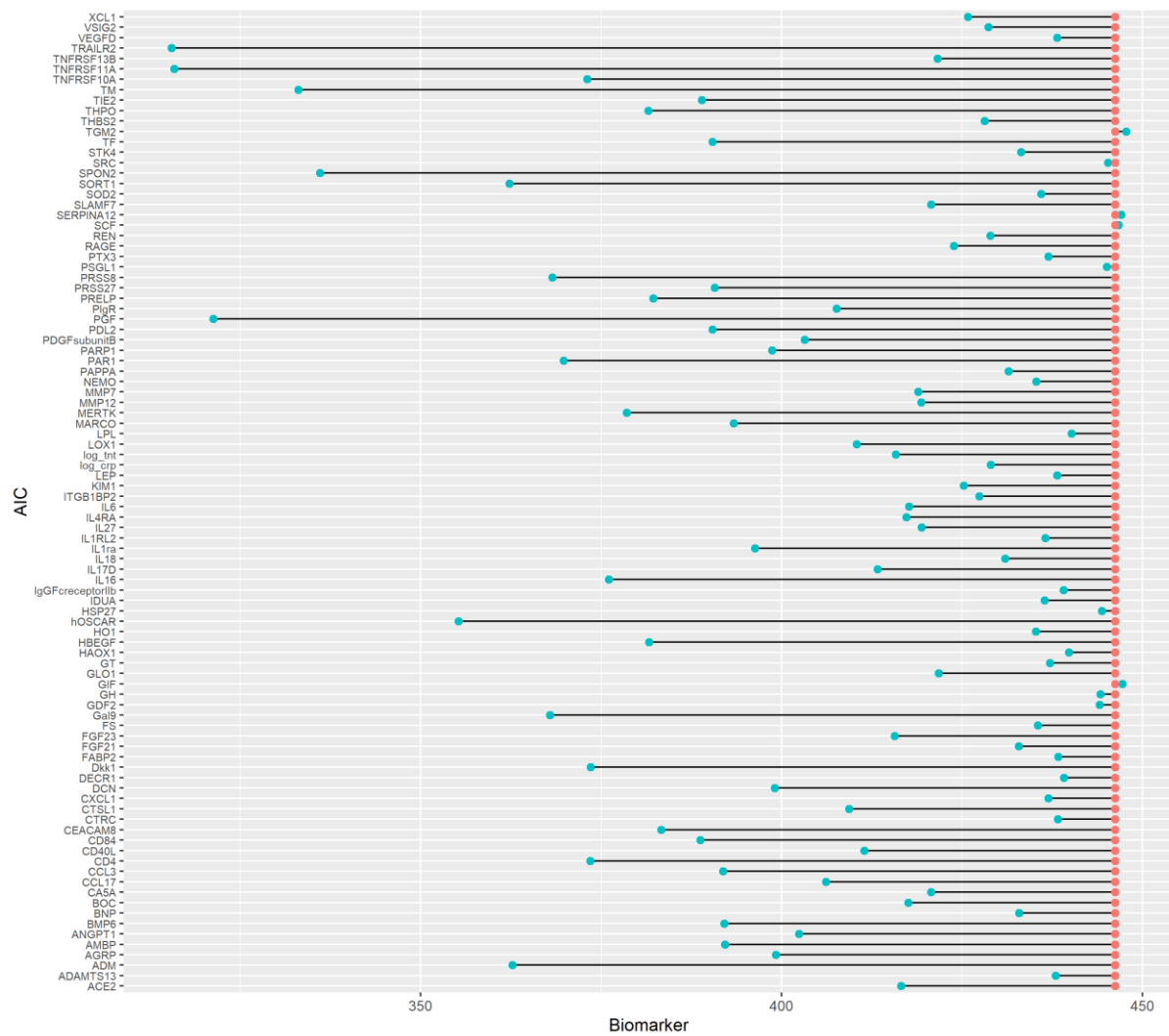


for advanced glycosylation end products; SOD2: Superoxide dismutase [Mn], mitochondrial (SOD2); CTSC: Chymotrypsin C; FGF-23: Fibroblast growth factor 23; SPON2: Spondin-2; GH: Growth hormone; FS: Follistatin; GLO1: Lactoylglutathione lyase; CD84: SLAM family member 5; PAPP-A: Pappalysin-1; SERPINA12: Serpin A12; REN: Renin; DECR1: 2,4-dienoyl-CoA reductase, mitochondrial; MERTK: Tyrosine-protein kinase Mer; KIM1: Kidney Injury Molecule; THBS2: Thrombospondin-2; TM: Thrombomodulin; VSIG2: Kidney Injury Molecule; AMBP: Protein AMBP; PRELP: Prolargin; HO-1: Heme oxygenase 1; XCL1: Lymphotactin; IL-16: Interleukin-16; SORT1: Sortilin; CEACAM8: Carcinoembryonic antigen-related cell adhesion molecule 8; PTX3: Pentraxin-related protein PTX3; PSGL-1: P-selectin glycoprotein ligand 1; CCL17: C-C motif chemokine 17; CCL3: C-C motif chemokine 3; MMP-7: Matrix metalloproteinase-7; IgG Fc receptor II-b: Low affinity immunoglobulin gamma Fc region receptor II-b; ITGB1BP2: Melusin; DCN: Decorin; Dkk-1: Dickkopf-related protein 1; LPL: Lipoprotein lipase; PRSS8: Prostatic; AGRP: Agouti-related protein; HB-EGF: Proheparin-binding EGF-like growth factor; GDF2: Growth/differentiation factor 2; FABP2: Fatty Acid Binding Protein 2; THPO: Thrombopoietin; MARCO: Macrophage receptor MARCO; GT: Gastrotropin; BNP: Natriuretic peptides B; MMP-12: Matrix metalloproteinase-12; ACE2: Angiotensin-converting enzyme 2; PD-L2: Programmed cell death 1 ligand 2; CTSL1: Cathepsin L1; hOSCAR: Osteoclast-associated immunoglobulin-like receptor; TNFRSF13B: Tumor necrosis factor receptor superfamily member 13B; TGM2: Protein-glutamine gamma-glutamyltransferase 2; LEP: Leptin; CA5A: Carbonic anhydrase 5A, mitochondrial; HSP 27: Heat shock 27 kDa protein; CD4: T-cell surface glycoprotein CD4; NEMO: NFkappa-B essential modulator; VEGFD: Vascular endothelial growth factor D; PARP-1: Poly [ADP-ribose] polymerase 1; HAOX1: Hydroxyacid oxidase 1;

**Supplement Figure 1** - Average silhouette statistics profile suggests the presence of 2 clusters

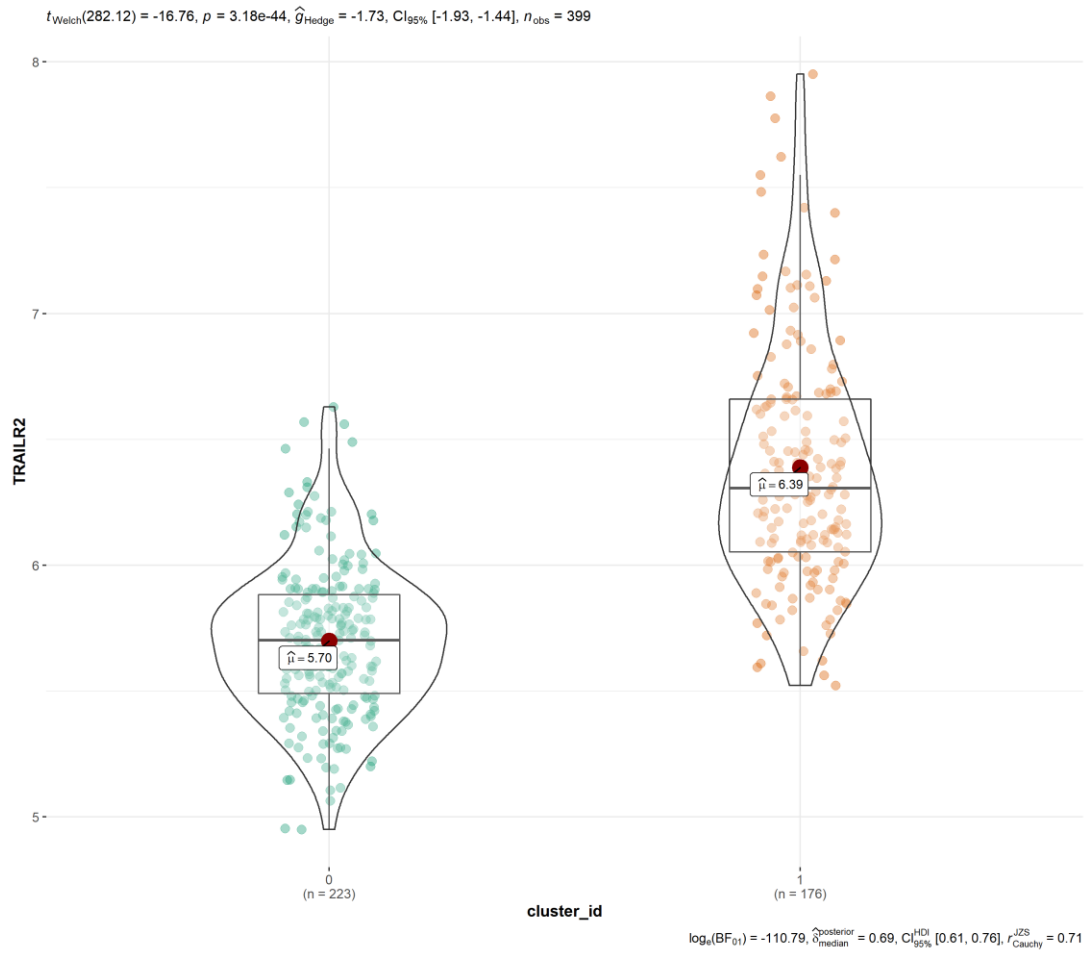


**Supplement Figure 2 - Akaike information criterion (AIC) values for each model biomarker**



Each model was adjusted for age, sex, diabetes, hypertension, dyspnea, RA duration, hemoglobin, and renal function (estimated glomerular filtration rate). Red dots represent the baseline model (adjusted variables), blue dots signify the impact of each biomarker on the AIC (the lower, the better).

### Supplement Figure 3a - Violin-plot showing the most relevant biomarker (TRAILR2) according to clustering.



### Supplement Figure 3b - Violin-plot showing the second most relevant biomarker (TNFRSF11A) according to clustering.

