

Impact of disease duration on proteomic bioprofile and prognosis in rheumatoid arthritis patients

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Supplementary material

Supplementary Table S1. Protein names sorted in alphabetical order.

Protein full name	Entry name	Olink® Panel*	Uniprot ID**
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 antigen related 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	IGGFCRECEPTORII	CVD II	P31994
Pro-interleukin-16	IL16	CVD II	Q14005
Interleukin-17D	IL17D	CVD II	Q8TAD2
Interleukin-18 (CVD2)	IL18	CVD II	Q14116
Interleukin-1 receptor antagonist protein	IL1RA	CVD II	P18510
Interleukin-1 receptor-like 2	IL1RL2	CVD II	Q9HB29
Interleukin-27	IL27	CVD II	Q8NEV9
Interleukin-4 receptor subunit alpha	IL4RA	CVD II	P24394
Interleukin-6 (CVD2)	IL6	CVD II	P05231
Melusin	ITGB1BP2	CVD II	Q9UKP3
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	Q9UEW3
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	PDGFSUBUNITB	CVD II	P01127
Programmed cell death 1 ligand 2	PDL2	CVD II	Q9BQ51
Polymeric immunoglobulin receptor	PIGR	CVD II	P01833
Placenta growth factor	PLGF	CVD II	P49763
Prolargin	PRELP	CVD II	P51888
Brother of CDO	PROTEINBOC	CVD II	Q9BWV1
Serine protease 27	PRSS27	CVD II	Q9BQR3
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
Tumour necrosis factor receptor superfamily member 10A	TNFRSF10A	CVD II	O00220
Tumour necrosis factor receptor superfamily member 11A	TNFRSF11A	CVD II	Q9Y6Q6
Tumour 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

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

Supplementary Table S2. Biological process, abbreviation, and full names of Cardiovascular II Olink® multiplex panel of the studied proteins.

Angiogenesis	GDF-2; VEGFD; TIE2; HO-1; DCN; STK4; PGF; IL-6; LEP; HSP 27; THBS2; IL-18; ADM; ANGPT-1; BNP; TF;
Blood vessel morphogenesis	THBS2; TIE2; IL18; LEP; ADM; HO-1; ANGPT-1; PGF; GDF-2; BNP; TF; VEGFD; DCN; STK4; IL6; HSP27;
Catabolic process	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;
Cell adhesion	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;
Coagulation	PAR-1; TF; HSP27; MERTK; TM; PDGF subunit B; CD40-L; SRC; ADAM-TS30;
Heart development	PDGF subunit B; Dkk-1; TIE2; ADM; STK4;
Immune response	TNFRSF13B; IL1RL2; NEMO; CD4; XCL1; IL6; IgG Fc receptor II-b; 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;
Inflammatory response	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;
MAPK cascade	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;
Platelet activation	HSP 27; MERTK; IL-6; TM; PDGF subunit B; PAR-1; CD40-L; SRC; ADAM-TS30;
Proteolysis	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;
Regulation of blood pressure	ACE2; PAR-1; PDGF subunit B; BNP; REN; SOD2; HO-1; LEP;
Response to hypoxia	VEGFD; PDGF subunit B; SRC; TIE2; ADM; HO-1; PGF; LEP;

Response to peptide hormone	SERPINA12; SRC; GH; LEP; AGRP; PDGF subunit B; TIE2; PARP-1; SORT1; ADM; IL6;
Wound healing	TM; HB-EGF; PAR-1; PDGF subunit B; TF; MMP-12; CD40-L; SRC; ADAM-TS30; HO-1; HSP-27; MERTK; IL6; DCN;
Other gene	FS; GIF; CA5A; GLO1; PAPP; PRSS8; KIM1; VSIG2; PRSS27;
Ontology terms	ITGB1BP2;

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: Lymphotoxin; 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: Lymphotoxin; IgG Fc receptor II-b: Low affinity immunoglobulin gamma Fc region receptor II-b; CCL3: C-C motif chemokine 3; CEACAM8: Carcinoembryonic antigen related cell adhesion molecule 8; PlgR: Polymeric immunoglobulin receptor; TNFRSF10A: Tumor necrosis factor receptor superfamily member 10A; TNFRSF11A: Tumour 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; CTSC: 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; PAPP: Pappalysin-1; PRSS8: Proctasin; KIM1: Kidney Injury Molecule; VSIG2: Kidney Injury Molecule; PRSS27: Serine protease 27; ITGB1BP2: Melusin;

Supplementary Table S3. Full list of association between circulating biomarkers and rheumatoid arthritis disease duration.

Biomarker	Beta	LCI	UCI	P	FDR
NT-pro BNP (log)	0.32	0.15	0.5	0.0003	0.026
CTSL1	0.7	0.29	1.11	0.0008	0.026
Gal9	0.93	0.38	1.49	0.001	0.026
BNP	0.27	0.11	0.43	0.0011	0.026
MMP12	0.37	0.13	0.6	0.0023	0.040
ADM	0.62	0.22	1.03	0.0025	0.040
TNFRSF11A	0.58	0.19	0.98	0.0035	0.048
CD4	0.77	0.23	1.32	0.0054	0.064
PGF	0.71	0.2	1.23	0.0066	0.067
HAOX1	-0.17	-0.3	-0.05	0.0072	0.067
IL16	0.49	0.13	0.86	0.0077	0.067
TM	0.73	0.17	1.29	0.0106	0.084
IL17D	0.8	0.17	1.43	0.0126	0.092
CEACAM8	0.38	0.07	0.69	0.0162	0.110
ACE2	-0.33	-0.62	-0.04	0.0265	0.163
ADAMTS13	-1.48	-2.81	-0.15	0.0291	0.163
Troponin T (log)	0.33	0.03	0.63	0.0292	0.163
IL6	0.15	0.01	0.28	0.0366	0.193
CA5A	-0.23	-0.45	-0.01	0.0414	0.207
FGF23	0.21	0	0.43	0.0468	0.213
TRAILR2	0.42	0	0.84	0.0493	0.213
hOSCAR	0.69	0	1.37	0.0493	0.213
LPL	0.42	0	0.84	0.052	0.215
PDL2	0.53	-0.02	1.07	0.0586	0.232
TF	0.52	-0.03	1.07	0.0633	0.235
HO1	0.39	-0.02	0.8	0.0644	0.235
VSIG2	0.25	-0.02	0.52	0.0741	0.261
IL1RL2	0.33	-0.04	0.71	0.0831	0.282
KIM1	0.2	-0.04	0.44	0.0979	0.321
HBEGF	-0.23	-0.51	0.05	0.1041	0.330
PAPPA	0.2	-0.04	0.43	0.1095	0.336
AMBP	0.71	-0.17	1.6	0.1146	0.340
GH	-0.07	-0.17	0.02	0.1222	0.352
IL18	0.25	-0.08	0.57	0.1416	0.396
SLAMF7	0.18	-0.08	0.44	0.1761	0.478
PDGFsubunitB	-0.15	-0.38	0.08	0.2025	0.531
IDUA	-0.24	-0.6	0.13	0.2068	0.531
IL4RA	0.33	-0.2	0.87	0.2207	0.552
TNFRSF10A	0.3	-0.21	0.8	0.2543	0.604
GIF	0.08	-0.06	0.22	0.2604	0.604
CTRC	0.14	-0.11	0.39	0.2606	0.604
CRP (log)	0.07	-0.06	0.21	0.2733	0.618
Dkk1	-0.15	-0.44	0.13	0.2919	0.645
ANGPT1	-0.11	-0.33	0.11	0.3244	0.673

SOD2	-0.82	-2.48	0.83	0.3283	0.673
TGM2	0.14	-0.14	0.43	0.3318	0.673
MARCO	0.41	-0.42	1.24	0.3331	0.673
IL1ra	0.13	-0.17	0.43	0.3889	0.770
REN	0.09	-0.12	0.3	0.4039	0.778
PRSS27	0.16	-0.22	0.54	0.4095	0.778
THPO	-0.18	-0.64	0.27	0.435	0.810
SPON2	0.32	-0.56	1.2	0.4713	0.859
MMP7	0.12	-0.21	0.45	0.4811	0.859
VEGFD	-0.19	-0.73	0.35	0.4882	0.859
AGRP	-0.15	-0.58	0.28	0.4971	0.859
ITGB1BP2	-0.05	-0.21	0.1	0.5134	0.863
FS	0.1	-0.21	0.41	0.5243	0.863
LOX1	0.1	-0.22	0.43	0.535	0.863
LEP	0.06	-0.13	0.26	0.5365	0.863
FABP2	0.06	-0.14	0.26	0.5504	0.863
PSGL1	-0.22	-0.95	0.51	0.5542	0.863
DCN	0.2	-0.48	0.88	0.5669	0.869
THBS2	-0.22	-0.99	0.55	0.5773	0.871
SERPINA12	-0.04	-0.19	0.11	0.5907	0.877
FGF21	-0.03	-0.13	0.08	0.6017	0.877
PRSS8	0.12	-0.35	0.6	0.6094	0.877
DECR1	-0.04	-0.2	0.12	0.6235	0.877
PRELP	0.2	-0.66	1.07	0.642	0.877
TIE2	-0.18	-0.95	0.59	0.6437	0.877
PTX3	0.08	-0.25	0.4	0.6498	0.877
GT	0.06	-0.22	0.35	0.6555	0.877
CD40L	-0.04	-0.21	0.14	0.6667	0.880
BOC	-0.13	-0.78	0.52	0.6888	0.894
PAR1	-0.09	-0.55	0.37	0.7046	0.894
CXCL1	0.04	-0.16	0.24	0.7123	0.894
CCL3	0.04	-0.19	0.27	0.7177	0.894
STK4	-0.05	-0.33	0.23	0.7244	0.894
IgGFcreceptorIIb	-0.03	-0.22	0.16	0.7625	0.908
MERTK	-0.06	-0.48	0.35	0.7723	0.908
SRC	-0.07	-0.55	0.41	0.7756	0.908
XCL1	0.04	-0.22	0.3	0.7802	0.908
GLO1	-0.04	-0.31	0.24	0.8026	0.908
SORT1	-0.07	-0.67	0.53	0.8174	0.908
BMP6	-0.05	-0.45	0.36	0.8239	0.908
HSP27	0.09	-0.69	0.87	0.8243	0.908
IL27	0.05	-0.38	0.47	0.8314	0.908
GDF2	-0.03	-0.35	0.28	0.8317	0.908
CCL17	-0.01	-0.2	0.18	0.885	0.955
TNFRSF13B	0.02	-0.34	0.38	0.8999	0.960
PARP1	0.02	-0.32	0.36	0.9161	0.960
RAGE	-0.02	-0.45	0.41	0.9199	0.960

CD84	-0.02	-0.46	0.42	0.9333	0.964
NEMO	0	-0.19	0.2	0.9756	0.984
PIgR	0.02	-1.28	1.31	0.9809	0.984
SCF	0	-0.42	0.43	0.9836	0.984

The biomarkers are ordered by strength of the association (p -value).

A positive beta coefficient means that the expression of the biomarker is increased with longer rheumatoid arthritis duration in an ordered logistic regression model. FDR: false discovery rate.