

Supplementary methods section.

General PPI data resources

Protein-protein interaction (PPI) data was obtained (downloaded on December 3rd 2018) from 6 representative primary human-curated PPI databases. The databases are: The Biomolecular Interaction Network Database (BIND)¹, the Biological General Repository for Interaction Datasets (BIOGRID)², the Database of Interacting Proteins (DIP)³, the Human Protein Reference Database (HPRD)⁴, the IntAct database of molecular interactions (INTACT)⁵ and the database of pdz-domain containing proteins (pdzBase)⁶. For the scope of this study, we focused on tangible, traceable and non-redundant PPIs. As such, only physical and non-self-binary PPI between human-encoded proteins that are documented by at least one publication were used for further analyses.

The databases were integrated using mapping accessions from the following databases (downloaded on December 3rd 2018): the “ID mapping” database of Uniprot⁷ [available at - ftp://ftp.uniprot.org/pub/databases/uniprot/current_release/knowledgebase/idmapping] and the NCBI (The National Center for Biotechnology Information) “gene2refseq” database [available at - <ftp://ftp.ncbi.nlm.nih.gov/gene/DATA/>].

INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 7 (IGFBP-7)							X		
INTEGRIN BETA-2 (ITGB2)				X		X	X	X	
INTERCELLULAR ADHESION MOLECULE 2 (ICAM-2)							X		
INTERLEUKIN-1 RECEPTOR TYPE 1 (IL-1RT1)				X					
INTERLEUKIN-1 RECEPTOR TYPE 2 (IL-1RT2)									X
INTERLEUKIN-17 RECEPTOR A (IL-17RA)				X					
INTERLEUKIN-18 BINDING PROTEIN (IL-18BP)									X
INTERLEUKIN-2 RECEPTOR SUBUNIT ALPHA (IL2-RA)			X	X			X		
INTERLEUKIN			X	X		X			

N-6 RECEPTOR SUBUNIT ALPHA (IL6-RA)									
JUNCTIONAL ADHESION MOLECULE A (JAM-A)									
KALLIKREIN-6 (KLK6)	X		X						X
LOW-DENSITY LIPOPROTEIN RECEPTOR (LDL RECEPTOR)									X
LYMPHOTOXIN-BETA RECEPTOR (LTBR)				X	X				
MATRIX EXTRACELLULAR PHOSPHOGLYCOPROTEIN (MEPE)									X
MATRIX METALLOPROTEINASE-2 (MMP-2)		X	X					X	X
MATRIX METALLOPROTEINASE-3 (MMP-3)			X					X	
MATRIX METALLOPROTEINASE-9 (MMP-9)			X					X	
METALLOPROTEINASE-9 (MMP-9)		X	X					X	

TEINASE INHIBITOR 4 (TIMP4)											
MONOCYTE CHEMOTACTIC PROTEIN 1 (MCP-1)		X	X		X	X		X	X	X	
MYELOBLASTIN (PRTN3)	X										X
MYELOPEROXIDASE (MPO)											X
MYOGLOBIN (MB)			X								
NT-PROBNP											X
NEUROGENIC LOCUS NOTCH HOMOLOG PROTEIN 3 (NOTCH3)										X	
OSTEOPONTIN (OPN)						X			X		
OSTEOPROTEGERIN (OPG)					X						
P-SELECTIN (SELP)	X				X		X		X		
PARAOXNAS E (PON3)											X
PEPTIDOGLYCAN RECOGNITION PROTEIN 1 (PGLYRP1)						X					X
PERLECAN (PLC)									X		X
PLASMINOGEN ACTIVATOR INHIBITOR 1	X			X		X	X	X	X	X	

RICH TYPE 1 PROTEIN M130 (CD163) SECRETOR GLYCOPROTEIN FAMILY 3A MEMBER 2 (SCGB3A2) SPONDIN-1 (SPON1) ST2 PROTEIN (ST2) TARTRATE- RESISTANT ACID PHOSPHATASE TYPE 5 (TR- AP) TISSUE FACTOR PATHWAY INHIBITOR (TFPI) TISSUE-TYPE PLASMINOGEN ACTIVATOR (T-PA) TRANSFERRIN RECEPTOR PROTEIN 1 (TR) TREFOIL FACTOR 3 (TFF3) TREM-LIKE TRANSCRIPT 2 PROTEIN (TLT-2) TUMOR NECROSIS					X		X			X			X
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**FACTOR
 LIGAND
 SUPERFAMIL
 Y MEMBER
 13B
 (TNFSF13B)
 TUMOR
 NECROSIS
 FACTOR
 RECEPTOR 1
 (TNF-R1)
 TUMOR
 NECROSIS
 FACTOR
 RECEPTOR 2
 (TNF-R2)
 TUMOR
 NECROSIS
 FACTOR
 RECEPTOR
 SUPERFAMIL
 Y MEMBER
 10C
 (TNFRSF10C)
 TUMOR
 NECROSIS
 FACTOR
 RECEPTOR
 SUPERFAMIL
 Y MEMBER 14
 (TNFRSF14)
 TUMOR
 NECROSIS
 FACTOR
 RECEPTOR
 SUPERFAMIL
 Y MEMBER 6
 (FAS)
 TYROSINE-
 PROTEIN**

						X						
			X		X	X					X	
					X	X				X		
	X	X	X		X	X				X		
X					X	X	X			X		

KINASE RECEPTOR UFO (AXL) TYROSINE- PROTEIN PHOSPHATAS E NON- RECEPTOR TYPE SUBSTRATE 1 (SHPS-1)							X	
UROKINASE PLASMINOGE N ACTIVATOR SURFACE RECEPTOR (U-PAR)	X		X			X		
UROKINASE- TYPE PLASMINOGE N ACTIVATOR (UPA)	X	X	X			X	X	X
VON WILLEBRAN D FACTOR (VWF)	X			X		X		

Table 2: assay characteristics

TARGET	ANALYTICAL MEASUREMENT				PRECISION	
	LOD	LLO Q	ULO Q	Hook	log10 Rang e	% CV Intr a

TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY MEMBER 14 (TNFRSF14)	0.2	1.0	15625	31250	4.2	7.8	10.3
LOW-DENSITY LIPOPROTEIN RECEPTOR (LDL RECEPTOR)	1.9	1.9	31250	31250	4.2	8.0	9.4
INTEGRIN BETA-2 (ITGB2)	1.9	7.6	62500	62500	3.9	8.4	10.9
INTERLEUKIN-17 RECEPTOR A (IL-17RA)	1.0	1.0	31250	62500	4.5	7.6	10.0
TUMOR NECROSIS FACTOR RECEPTOR 2 (TNF-R2)	1.9	3.8	31250	62500	3.9	7.8	9.7
MATRIX METALLOPROTEINASE-9 (MMP-9)	244.1	244.1	50000	500000	3.3	8.4	12.2
	1		0				
EPHRIN TYPE-B RECEPTOR 4 (EPHB4)	7.6	7.6	62500	125000	3.9	7.9	8.8
INTERLEUKIN-2 RECEPTOR SUBUNIT ALPHA (IL2-RA)	0.1	0.1	1953	7812	4.5	7.6	8.3
OSTEOPROTEGERIN (OPG)	0.5	1.0	15625	31250	4.2	8.1	10.7
CD166 ANTIGEN (ALCAM)	0.2	0.2	7812	15625	4.5	7.0	8.3
TREFOIL FACTOR 3 (TFF3)	0.2	0.2	3906	7812	4.2	7.7	8.8
P-SELECTIN (SELP)	0.1	0.5	15625	15625	4.5	7.8	9.8
CYSTATIN-B (CSTB)	1.0	1.9	7812	15625	3.6	7.6	9.4
MONOCYTE CHEMOTACTIC PROTEIN 1 (MCP-1)	0.1	0.1	1953	3906	4.2	7.9	11.5
SCAVENGER RECEPTOR CYSTEINE-RICH TYPE 1 PROTEIN M130 (CD163)	3.8	7.6	62500	62500	3.9	6.7	8.6
GALECTIN-3 (GAL-3)	30.5	30.5	62500	62500	3.3	7.6	9.2
GRANULINS (GRN)	61.0	61.0	62500	62500	3.0	7.4	10.9
MATRIX EXTRACELLULAR PHOSPHOGLYCOPROTEIN (MEPE)	61.0	61.0	62500	62500	3.0	8.7	11.7
BLEOMYCIN HYDROLASE (BLM HYDROLASE)	7.6	15.3	62500	62500	3.6	7.7	10.8
PERLECAN (PLC)	7.6	15.3	62500	125000	3.6	7.3	9.0
LYMPHOTOXIN-BETA RECEPTOR (LTBR)	0.2	0.5	15625	15625	4.5	7.6	10.5
NEUROGENIC LOCUS NOTCH HOMOLOG PROTEIN 3 (NOTCH 3)	1.9	3.8	62500	62500	4.2	8.7	9.5
METALLOPROTEINASE INHIBITOR 4 (TIMP4)	3.8	7.6	31250	62500	3.6	9.0	12.1
CONTACTIN-1 (CNTN1)	3.8	7.6	31250	62500	3.6	7.5	9.3
CADHERIN-5 (CDH5)	122.1	122.1	12500	125000	3.0	11.0	12.4
	1		0				
TREM-LIKE TRANSCRIPT 2 PROTEIN (TLT-2)	3.8	3.8	15625	31250	3.6	7.9	11.9
FATTY ACID-BINDING PROTEIN, ADIPOCYTE (FABP4)	1.9	1.9	15625	62500	3.9	8.2	9.2
TISSUE FACTOR PATHWAY INHIBITOR (TFPI)	3.8	7.6	31250	62500	3.6	8.8	12.0
PLASMINOGEN ACTIVATOR INHIBITOR 1 (PAI)	1.0	1.0	15625	15625	4.2	7.9	9.9
C-C MOTIF CHEMOKINE 24 (CCL24)	1.0	1.9	7812	15625	3.6	9.2	13.3
TRANSFERRIN RECEPTOR PROTEIN 1 (TR)	30.5	61.0	12500	125000	3.3	6.4	8.6

			0				
TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY MEMBER 10C (TNFRSF10C)	0.1	0.1	3906	7812	4.8	7.4	10.0
GROWTH/DIFFERENTIATION FACTOR 15 (GDF-15)	1.0	1.0	15625	15625	4.2	8.9	11.4
E-SELECTIN (SELE)	3.8	3.8	7812	15625	3.3	6.9	9.5
AZUROCIDIN (AZU1)	7.6	7.6	15625	31250	3.3	7.4	7.8
PROTEIN DELTA HOMOLOG 1 (DLK-1)	3.8	3.8	31250	62500	3.9	8.2	10.7
SPONDIN-1 (SPON1)	122.1	122.1	62500	125000	2.7	8.0	12.0
	1						
MYELOPEROXIDASE (MPO)	7.6	7.6	7812	15625	3.0	6.6	8.2
C-X-C MOTIF CHEMOKINE 16 (CXCL16)	1.9	3.8	31250	62500	3.9	8.6	11.8
INTERLEUKIN-6 RECEPTOR SUBUNIT ALPHA (IL-6RA)	0.1	0.2	7812	15625	4.5	7.7	9.4
RESISTIN (RETN)	0.1	0.1	7812	15625	5.1	7.4	13.0
INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 1 (IGFBP-1)	15.3	15.3	12500	125000	3.9	7.8	9.6
			0				
CHITOTRIOSIDASE-1 (CHIT1)	15.3	15.3	31250	62500	3.3	7.7	10.5
TARTRATE-RESISTANT ACID PHOSPHATASE TYPE 5 (TR-AP)	1.9	7.6	15625	62500	3.3	7.4	10.4
C-C MOTIF CHEMIKINE 22 (CCL22)	61.0	61.0	15625	15625	2.4	8.2	14.9
PULMONARY SURFACTANT-ASSOCIATED PROTEIN D (PSP-D)	15.3	15.3	62500	125000	3.6	9.2	9.1
ELAFIN (PI3)	1.0	15.3	15625	15625	3.0	8.2	12.9
EPITHELIAL CELL ADHESION MOLECULE (EP-CAM)	0.5	1.0	15625	62500	4.2	8.2	11.4
AMINOPEPTIDASE N (AP-N)	61.0	122.1	12500	125000	3.0	7.3	8.0
			0				
TYROSINE-PROTEIN KINASE RECEPTOR UFO (AXL)	0.5	1.0	15625	15625	4.2	7.8	10.7
INTERLEUKIN-1 RECEPTOR TYPE 1 (IL-1RT1)	0.0	0.0	3906	31250	5.1	8.0	10.3
MATRIX METALLOPROTEINASE-2 (MMP-2)	61.0	122.1	62500	125000	2.7	9.2	13.1
TUMOR NECROSIS FACTOR RECEPTOR SUPERFAMILY MEMBER 6 (FAS)	0.5	1.0	15625	62500	4.2	7.7	12.2
MYOGLOBIN (MB)	0.1	0.1	7812	31250	5.1	7.9	14.8
TUMOR NECROSIS FACTOR LIGAND SUPERFAMILY MEMBER 13B (TNFSF13B)	0.2	0.5	15625	31250	4.5	8.0	11.7
MYELOBLASTIN (PRTN3)	0.5	7.6	31250	62500	3.6	8.2	14.2
PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9)	122.1	122.1	12500	100000	3.0	10.0	25.3
	1		0	0			
UROKINASE PLASMINOGEN ACTIVATOR SURFACE RECEPTOR (U-PAR)	0.2	0.2	3906	62500	4.2	7.6	10.2
OSTEOPONTIN (OPN)	122.1	122.1	31250	62500	2.4	7.8	10.5

CATHEPSIN D (CTSD)	1	976.6	62500	125000	1.8	6.6	10.3
PEPTIDOGLYCAN RECOGNITION PROTEIN 1 (PGLYRP1)	6	1.0	15625	15625	4.2	8.4	12.2
CARBOXYPEPTIDASE A1 (CPA1)	1.0	1.0	31250	62500	4.5	7.5	10.0
JUNCTIONAL ADHESION MOLECULE A (JAM-A)	0.1	0.2	3906	31250	4.2	7.6	11.2
GALECTIN-4 (GAL-4)	3.8	7.6	62500	62500	3.9	8.3	10.4
INTERLEUKIN-1 RECEPTOR TYPE 2 (IL-1RT2)	1.0	1.9	15625	62500	3.9	7.9	10.1
TYROSINE-PROTEIN PHOSPHATASE NON-RECEPTOR TYPE SUBSTRATE 1 (SHPS-1)	1.9	1.9	15625	62500	3.9	7.5	8.6
C-C MOTIF CHEMOKINE 15 (CCL15)	7.6	7.6	31250	62500	3.6	9.1	15.1
CASPASE-3 (CASP-3)	1.9	1.9	31250	62500	4.2	9.0	15.7
UROKINASE-TYPE PLASMINOGEN ACTIVATOR (UPA)	0.5	1.0	15625	31250	4.2	8.4	14.4
CARBOXYPEPTIDASE B (CPB1)	1.0	1.0	31250	62500	4.5	7.5	11.7
CHITINASE-3-LIKE PROTEIN 1 (CHI3L1)	1.9	1.9	3906	15625	3.3	7.6	10.1
ST2 PROTEIN (ST2)	7.6	7.6	62500	62500	3.9	7.9	10.5
TISSUE-TYPE PLASMINOGEN ACTIVATOR (T-PA)	1.9	1.9	62500	62500	4.5	9.4	16.1
SECRETOGLOBIN FAMILY 3A MEMBER 2 (SCGB3A2)	61.0	244.1	50000	100000	3.3	10.3	21.7
EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)	30.5	30.5	31250	62500	3.0	6.9	10.2
INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 7 (IGFBP-7)	30.5	61.0	31250	62500	2.7	9.1	13.0
COMPLEMENT COMPONENT C1Q RECEPTOR (CD93)	1.0	1.9	15625	62500	3.9	8.1	11.4
INTERLEUKIN-18-BINDING PROTEIN (IL-18BP)	1.9	1.9	31250	62500	4.2	7.8	10.3
COLLAGEN ALPHA-1(I) CHAIN (COL1A1)	244.1	244.1	62500	62500	2.4	6.4	9.8
PARAOXONASE (PON 3) (PON3)	1	7.6	12500	125000	4.2	9.5	13.3
CATHEPSIN Z (CTSZ)	1.0	1.0	62500	62500	4.8	7.0	8.6
MATRIX METALLOPROTEINASE-3 (MMP-3)	1.0	1.0	15625	62500	4.2	8.7	13.5
RETINOIC ACID RECEPTOR RESPONDER PROTEIN 2 (RARRES2)	7.6	7.6	15625	62500	3.3	8.7	11.5
INTERCELLULAR ADHESION MOLECULE 2 (ICAM-2)	30.5	61.0	12500	125000	3.3	7.8	10.7
KALLIKREIN-6 (KLK6)	1.9	1.9	15625	62500	3.9	8.0	10.6
PLATELET-DERIVED GROWTH FACTOR SUBUNIT A (PDGF SUBUNIT A)	1.0	1.9	15625	31250	3.9	8.7	14.7

TUMOR NECROSIS FACTOR RECEPTOR 1 (TNF-R1)	3.8	7.6	31250	62500	3.6	8.3	12.1
INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 2 (IGFBP-2)	122.1	122.1	62500	62500	2.7	9.0	14.9
VON WILLEBRAND FACTOR (VWF)	1.0	15.3	31250	62500	3.3	8.4	11.8
PLATELET ENDOTHELIAL CELL ADHESION MOLECULE (PECAM-1)	1.0	1.0	15625	62500	4.2	7.2	10.2
N-TERMINAL PROHORMONE BRAIN NATRIURETIC PEPTIDE (NT-PRO BNP)	244.1	244.1	31250	62500	2.1	9.3	18.8
C-C MOTIF CHEMOKINE 16 (CCL16)	15.3	15.3	15625	15625	3.0	9.8	18.3

Table 3: differences in characteristics between the index and validation cohort.

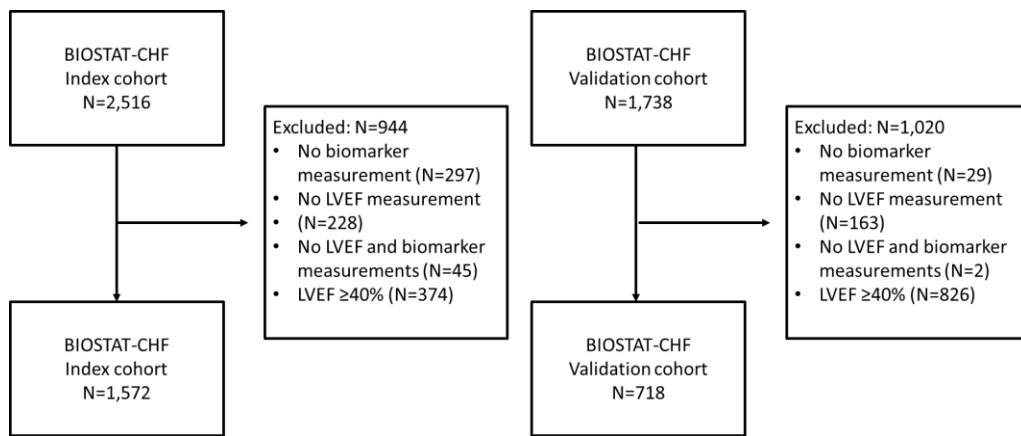
	INDEX COHORT	VALIDATION COHORT
AGE	67 ± 12	72 ± 11
MEN (%)	76%	74%
NYHA CLASS III/IV	61%	52%
DIABETES	31%	30%
ISCHEMIC ETIOLOGY	47%	94%
HYPERTENSION	59%	51%
ATRIAL FIBRILLATION	42%	44%
COPD	17%	15%
ELEVATED JVP	30%	30%
HEPATOMEGALY	15%	4%
EDEMA	55%	57%

Table 4: association of biomarkers with the primary combined outcome after correcting for the BIOSTAT-CHF model

BIOMARKER	HR (95%CI)	P-VALUE
GDF15	1.11 (1.02-1.22)	0.02
PON3	0.99 (0.91-1.07)	0.782

FABP4	1.06 (0.99-1.13)	0.067
GAL4	1.09 (0.98-1.20)	0.105
TFF3	1.08 (0.80-1.19)	0.121
TNFRSF14	1.02 (0.92-1.13)	0.68
TNFR1	1.00 (0.91-1.10)	0.987
TNFR2	1.04 (0.94-1.15)	0.402
CHI3L1	1.05 (0.97-1.13)	0.202

Supplementary figure 1: CONSORT flow chart for final study inclusion



Supplementary figure 2: Kaplan Meier curves for the primary combined outcome of all-cause mortality and HF hospitalizations at 2 years, stratified to diabetic status

