

## **Supplementary materials**

### **Olink biomarkers**

The following Olink biomarker panels were used: Cardiovascular II (CVII), CVD III, Immune response and Oncology II. Across the panels there were several duplicates; B-natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in CVDII and CVDIII panels; amphiregulin (AREG) in the Immune response and Oncology II panel; stem cell factor (SCF) in oncology II and CVDIII; and interleukin 6 in CVDII, Immune response and Oncology II panels.

Detailed information about the 363 biomarkers used in this analysis can be found online(1–4). Figure S1 and S2 show that the biomarker set used encompassed biomarkers from a wide range of biological processes and diseases.

### **Cluster analysis**

The aim of this study was to identify mutually exclusive HFpEF clusters based on biomarker profiles. *Supplementary figure 4* summarises the statistical approach used. Due to the large set of biomarkers, we sought to reduce the dimension of the data using principle component analysis (PCA). PCA was performed on all 363 biomarkers using the *prcomp* package in R. Fifty-nine principle components (PCs) with a minimum eigenvalue of 1 were used as input for the cluster analysis. The optimal number of clusters was determined using the NbClust package in R. NbClust uses 30 indices to determine the optimal cluster number by picking the number of clusters that is calculated in the majority of these indices(5). NbClust determined 6 to be the optimal number of clusters (*Supplementary figure 4*). A hierarchical cluster analysis using complete linkage was performed using the 59 PCs as input.

Cluster 5 and 6 were small clusters and therefore not included in the downstream analyses. Table S1 shows an overview of these patients characteristics.

**Table S1. Characteristics of cluster 5 and 6**

|                          | Cluster 5        | Cluster 6          |
|--------------------------|------------------|--------------------|
| N                        | 3                | 2                  |
| Age > 75 years (%)       | 1 (33.3%)        | 1(50%)             |
| Male (%)                 | 2 (66.7%)        | 2 (100%)           |
| BMI (kg/m <sup>2</sup> ) | 25.2 (3.67)      | 35.0 (3.04)        |
| NYHA, <i>n</i> (%)       |                  |                    |
| I                        | 0 (0%)           | 0 (0%)             |
| II                       | 2 (66.6%)        | 0 (0%)             |
| III                      | 1 (33.3%)        | 1 (50%)            |
| IV                       | 0 (0%)           | 1 (50%)            |
| Haemoglobin, (g/dl)      | 13.7 (2.90)      | 14.2 (1.34)        |
| Creatinine, (μmol/L)     | 113 (13.5)       | 89.0 (4.24)        |
| NT-proBNP, (pg/L)        | 408 [334;1022]   | 3548 [1886;5211]   |
| GDF-15, (pg/mL)          | 3716 [2564;4020] | 11386 [6392;16380] |

**Table S2. Differentially expressed proteins in Cluster 1**

| Protein       | Symbol | Description                                     | logFC        | AveExpr      | t            | P.Value  | adj.P.Val | Up/down-regulated |
|---------------|--------|---|--------------|--------------|--------------|----------|-----------|-------------------|
| <b>O95971</b> | CD160  | CD160 molecule [CD160]                          | 0.8049<br>19 | 7.34782<br>8 | 8.32830<br>2 | 1.14E-15 | 8.96E-15  | Up-regulated      |
| <b>Q8WXI8</b> | CLEC4D | C-type lectin domain family 4 member D [CLEC4D] | 0.9124<br>16 | 4.86834<br>2 | 9.13485<br>8 | 2.69E-18 | 3.48E-17  | Up-regulated      |
| <b>Q9BXN2</b> | CLEC7A | C-type lectin domain containing 7A [CLEC7A]     | 1.0027<br>67 | 4.52783      | 9.40662<br>4 | 3.22E-19 | 5.32E-18  | Up-regulated      |
| <b>P15086</b> | CPB1   | carboxypeptidase B1 [CPB1]                      | 0.8115<br>7  | 3.78332<br>6 | 6.48797<br>6 | 2.42E-10 | 8.22E-10  | Up-regulated      |
| <b>P04080</b> | CSTB   | cystatin B [CSTB]                               | 0.9111<br>33 | 5.19877<br>7 | 7.97962<br>6 | 1.38E-14 | 8.32E-14  | Up-regulated      |
| <b>P78310</b> | CXADR  | CXADR Ig-                                       | 0.8325       | 3.56822      | 8.85513      | 2.28E-   | 2.59E-16  | Up-regulated      |

|               |        |   |          |          |          |          |          |              |
|---------------|--------|---|----------|----------|----------|----------|----------|--------------|
|               |        | like cell adhesion molecule [CXADR]                   | 13       | 9        | 8        | 17       |          |              |
| <b>P15090</b> | FABP4  | fatty acid binding protein 4 [FABP4]                  | 0.938781 | 6.119663 | 6.17449  | 1.55E-09 | 4.69E-09 | Up-regulated |
| <b>Q9NSA1</b> | FGF21  | fibroblast growth factor 21 [FGF21]                   | 1.328739 | 9.065907 | 5.841222 | 1.03E-08 | 2.75E-08 | Up-regulated |
| <b>Q9GZV9</b> | FGF23  | fibroblast growth factor 23 [FGF23]                   | 1.193486 | 6.800046 | 5.491958 | 6.85E-08 | 1.61E-07 | Up-regulated |
| <b>Q99988</b> | GDF15  | growth differentiation factor 15 [GDF15]              | 0.907449 | 5.611699 | 7.915978 | 2.15E-14 | 1.26E-13 | Up-regulated |
| <b>P08833</b> | IGFBP1 | insulin like growth factor binding protein 1 [IGFBP1] | 1.143593 | 4.593692 | 5.912369 | 6.93E-09 | 1.91E-08 | Up-regulated |
| <b>Q16270</b> | IGFBP7 | insulin like growth factor binding protein 7 [IGFBP7] | 0.830434 | 4.198832 | 8.994531 | 7.9E-18  | 9.56E-17 | Up-regulated |
| <b>O95998</b> | IL18BP | interleukin 18 binding protein [IL18BP]               | 0.842736 | 6.449246 | 10.63878 | 1.35E-23 | 9.79E-22 | Up-regulated |
| <b>P01589</b> | IL2RA  | interleukin 2 receptor subunit alpha [IL2RA]          | 0.837103 | 4.354559 | 8.785916 | 3.85E-17 | 3.99E-16 | Up-regulated |
| <b>P18627</b> | LAG3   | lymphocyte activating 3 [LAG3]                        | 0.820326 | 3.699818 | 10.11673 | 1.06E-21 | 4.26E-20 | Up-regulated |
| <b>Q8NHJ6</b> | LILRB4 | leukocyte immunoglobulin like receptor B4 [LILRB4]    | 0.83642  | 4.679224 | 8.53106  | 2.57E-16 | 2.13E-15 | Up-regulated |
| <b>Q8WXI7</b> | MUC16  | mucin 16, cell surface associated [MUC16]             | 0.89825  | 6.841153 | 4.153479 | 3.96E-05 | 6.3E-05  | Up-regulated |
| <b>O76036</b> | NCR1   | natural   | 0.8374   | 4.45856  | 9.53834  | 1.14E-   | 2.29E-18 | Up-regulated |

|               |           |   |              |              |              |          |          |              |
|---------------|-----------|---|--------------|--------------|--------------|----------|----------|--------------|
|               |           | cytotoxicity triggering receptor 1 [NCR1]         | 97           | 6            | 3            | 19       |          |              |
| <b>P19957</b> | PI3       | peptidase inhibitor 3 [PI3]                       | 0.8329<br>41 | 3.77257<br>3 | 6.53699<br>6 | 1.8E-10  | 6.22E-10 | Up-regulated |
| <b>Q03405</b> | PLAUR     | plasminogen activator, urokinase receptor [PLAUR] | 0.8148<br>71 | 4.70634<br>7 | 9.89228<br>8 | 6.63E-21 | 2.19E-19 | Up-regulated |
| <b>Q9BXY4</b> | RSPO3     | R-spondin 3 [RSPO3]                               | 0.8278<br>91 | 6.45588<br>2 | 6.82658      | 3.01E-11 | 1.23E-10 | Up-regulated |
| <b>Q9Y6Q6</b> | TNFRSF11A | TNF receptor superfamily member 11a [TNFRSF11A]   | 1.0444<br>83 | 7.08572<br>5 | 10.6651<br>9 | 1.08E-23 | 9.78E-22 | Up-regulated |
| <b>Q92956</b> | TNFRSF14  | TNF receptor superfamily member 14 [TNFRSF14]     | 0.8579<br>86 | 4.82143<br>4 | 9.17877<br>5 | 1.91E-18 | 2.78E-17 | Up-regulated |
| <b>Q9NS68</b> | TNFRSF19  | TNF receptor superfamily member 19 [TNFRSF19]     | 0.9135<br>89 | 6.04489<br>8 | 8.59774      | 1.57E-16 | 1.36E-15 | Up-regulated |
| <b>P19438</b> | TNFRSF1A  | TNF receptor superfamily member 1A [TNFRSF1A]     | 0.8820<br>84 | 5.63058<br>7 | 9.14973<br>5 | 2.39E-18 | 3.22E-17 | Up-regulated |
| <b>P20333</b> | TNFRSF1B  | TNF receptor superfamily member 1B [TNFRSF1B]     | 0.9869<br>61 | 5.15987<br>9 | 10.3878<br>5 | 1.11E-22 | 5.78E-21 | Up-regulated |
| <b>P43489</b> | TNFRSF4   | TNF receptor superfamily member 4 [TNFRSF4]       | 1.0077<br>05 | 5.73468<br>8 | 11.0032<br>8 | 5.96E-25 | 1.08E-22 | Up-regulated |
| <b>O95407</b> | TNFRSF6B  | TNF receptor superfamily member 6b                | 1.0537<br>24 | 7.30737<br>1 | 9.16504<br>7 | 2.13E-18 | 2.97E-17 | Up-regulated |

|  |  |                |  |  |  |  |  |  |
|--|--|----------------|--|--|--|--|--|--|
|  |  | [TNFRSF6<br>B] |  |  |  |  |  |  |
|--|--|----------------|--|--|--|--|--|--|

**Table S3. Differentially expressed proteins in Cluster 3**

| <b>Protein</b>     | <b>Symbol</b> | <b>Description</b>   | <b>logFC</b>     | <b>AveEx<br/>pr</b> | <b>t</b> | <b>P.value</b> | <b>adj.P.Val</b> | <b>Up/down-<br/>regulated</b> |
|--------------------|---------------|--|------------------|---------------------|----------|----------------|------------------|-------------------------------|
| <b>P36222</b>      | CHI3L1        | chitinase 3<br>like 1<br>[CHI3L1]                                    | -<br>0.8592<br>7 | 6.4501<br>91        | -8.69879 | 7.4E-17        | 2.89E-16         | Down-<br>regulated            |
| <b>Q07065</b>      | CKAP4         | cytoskeleto<br>n associated<br>protein 4<br>[CKAP4]                  | -<br>0.8173<br>2 | 6.5563<br>4         | -15.8032 | 1.36E-<br>44   | 4.94E-43         | Down-<br>regulated            |
| <b>Q9BXN<br/>2</b> | CLEC7<br>A    | C-type<br>lectin<br>domain<br>containing<br>7A<br>[CLEC7A]           | -<br>0.8949      | 4.5278<br>3         | -12.7184 | 1.25E-<br>31   | 1.19E-30         | Down-<br>regulated            |
| <b>P04080</b>      | CSTB          | cystatin B<br>[CSTB]   | -<br>0.9439<br>5 | 5.1987<br>77        | -12.8849 | 2.65E-<br>32   | 2.67E-31         | Down-<br>regulated            |
| <b>P15090</b>      | FABP4         | fatty acid<br>binding<br>protein 4<br>[FABP4]                        | -<br>1.0203<br>9 | 6.1196<br>63        | -10.1573 | 7.57E-<br>22   | 3.77E-21         | Down-<br>regulated            |
| <b>Q9NSA<br/>1</b> | FGF21         | fibroblast<br>growth<br>factor 21<br>[FGF21]                         | -<br>0.9533<br>4 | 9.0659<br>07        | -5.94774 | 5.68E-<br>09   | 1.17E-08         | Down-<br>regulated            |
| <b>Q9GZV<br/>9</b> | FGF23         | fibroblast<br>growth<br>factor 23<br>[FGF23]                         | -<br>1.0416<br>9 | 6.8000<br>46        | -6.9249  | 1.62E-<br>11   | 4.02E-11         | Down-<br>regulated            |
| <b>Q99988</b>      | GDF15         | growth<br>differentiati<br>on factor 15<br>[GDF15]                   | -<br>0.8648<br>2 | 5.6116<br>99        | -11.4077 | 1.75E-<br>26   | 1.22E-25         | Down-<br>regulated            |
| <b>P08833</b>      | IGFBP1        | insulin like<br>growth<br>factor<br>binding<br>protein 1<br>[IGFBP1] | -<br>1.0895<br>3 | 4.5936<br>92        | -8.26778 | 1.76E-<br>15   | 6.14E-15         | Down-<br>regulated            |
| <b>P08727</b>      | KRT19         | keratin 19<br>[KRT19]  | -<br>0.9018<br>4 | 3.0610<br>24        | -10.2735 | 2.89E-<br>22   | 1.52E-21         | Down-<br>regulated            |
| <b>Q8NHJ<br/>6</b> | LILRB4        | leukocyte<br>immunoglo<br>bulin like<br>receptor B4                  | -<br>0.8560<br>3 | 4.6792<br>24        | -13.7411 | 8.13E-<br>36   | 1.23E-34         | Down-<br>regulated            |

|               |           |   |          |          |          |          |          |                |
|---------------|-----------|---|----------|----------|----------|----------|----------|----------------|
|               |           | [LILRB4]  |          |          |          |          |          |                |
| <b>Q8WXI7</b> | MUC16     | mucin 16, cell surface associated [MUC16]       | -0.89228 | 6.841153 | -5.96745 | 5.08E-09 | 1.05E-08 | Down-regulated |
| <b>Q96NY8</b> | NECTIN4   | nectin cell adhesion molecule 4 [NECTIN4]       | -0.84768 | 7.198572 | -15.6614 | 5.61E-44 | 1.45E-42 | Down-regulated |
| <b>P16860</b> | NPPB      | natriuretic peptide B [NPPB]                    | -0.87934 | 3.736958 | -5.55119 | 5E-08    | 9.41E-08 | Down-regulated |
| <b>P19957</b> | PI3       | peptidase inhibitor 3 [PI3]                     | -0.90972 | 3.772573 | -10.9132 | 1.3E-24  | 7.71E-24 | Down-regulated |
| <b>Q9BXY4</b> | RSPO3     | R-spondin 3 [RSPO3]                             | -0.99358 | 6.455882 | -13.043  | 6.05E-33 | 6.65E-32 | Down-regulated |
| <b>Q07654</b> | TFF3      | trefoil factor 3 [TFF3]                         | -0.97307 | 5.92917  | -13.8915 | 1.92E-36 | 3.17E-35 | Down-regulated |
| <b>O14763</b> | TNFRSF10B | TNF receptor superfamily member 10b [TNFRSF10B] | -0.83932 | 7.354225 | -15.2089 | 5.03E-42 | 1.14E-40 | Down-regulated |
| <b>Q9Y6Q6</b> | TNFRSF11A | TNF receptor superfamily member 11a [TNFRSF11A] | -0.99141 | 7.085725 | -16.2108 | 2.29E-46 | 1.66E-44 | Down-regulated |
| <b>Q92956</b> | TNFRSF14  | TNF receptor superfamily member 14 [TNFRSF14]   | -0.90848 | 4.821434 | -15.8857 | 5.97E-45 | 2.41E-43 | Down-regulated |
| <b>Q9NS68</b> | TNFRSF19  | TNF receptor superfamily member 19 [TNFRSF19]   | -1.04204 | 6.044898 | -16.3847 | 3.97E-47 | 3.6E-45  | Down-regulated |
| <b>P19438</b> | TNFRSF1A  | TNF receptor superfamily member 1A [TNFRSF1A]   | -0.9397  | 5.630587 | -15.9731 | 2.49E-45 | 1.29E-43 | Down-regulated |
| <b>P20333</b> | TNFRSF1B  | TNF receptor                                    | -0.9287  | 5.159879 | -15.4661 | 3.92E-43 | 9.49E-42 | Down-regulated |

|               |          |   |          |          |          |          |          |                |
|---------------|----------|---|----------|----------|----------|----------|----------|----------------|
|               |          | superfamily member 1B [TNFRSF1B]              | 1        |          |          |          |          |                |
| <b>P43489</b> | TNFRSF4  | TNF receptor superfamily member 4 [TNFRSF4]   | -0.83662 | 5.734688 | -13.7211 | 9.84E-36 | 1.43E-34 | Down-regulated |
| <b>O95407</b> | TNFRSF6B | TNF receptor superfamily member 6b [TNFRSF6B] | -0.97736 | 7.307371 | -13.0209 | 7.43E-33 | 7.94E-32 | Down-regulated |

**Table S4. Differentially expressed proteins in Cluster 4**

| <b>Protein</b> | <b>Symbol</b> | <b>Description</b>  | <b>logFC</b> | <b>AveExpr</b> | <b>t</b> | <b>P.Value</b> | <b>adj.P.Val</b> | <b>Up/down-regulated</b> |
|----------------|---------------|---|--------------|----------------|----------|----------------|------------------|--------------------------|
| <b>Q15389</b>  | ANGPT1        | angiopoietin 1 [ANGPT1]   | 1.043379     | 7.301649       | 6.445598 | 3.13E-10       | 2.22E-09         | Up-regulated             |
| <b>P42574</b>  | CASP3         | caspase 3 [CASP3]   | 1.504064     | 6.353016       | 10.31929 | 1.97E-22       | 3.58E-21         | Up-regulated             |
| <b>P29965</b>  | CD40LG        | CD40 ligand [CD40LG]  | 1.312199     | 4.347495       | 10.06801 | 1.58E-21       | 2.72E-20         | Up-regulated             |
| <b>P38936</b>  | CDKN1A        | cyclin dependent kinase inhibitor 1A [CDKN1A]                     | 1.1699       | 3.849987       | 9.526949 | 1.24E-19       | 1.81E-18         | Up-regulated             |
| <b>P09341</b>  | CXCL1         | C-X-C motif chemokine ligand 1 [CXCL1]                            | 1.147292     | 8.80211        | 7.696225 | 9.88E-14       | 9.43E-13         | Up-regulated             |
| <b>Q9UN19</b>  | DAPP1         | dual adaptor of phosphotyrosine and 3-phosphoinositides 1 [DAPP1] | 2.154514     | 4.624869       | 10.42786 | 7.97E-23       | 1.61E-21         | Up-regulated             |
| <b>Q14203</b>  | DCTN1         | dynactin subunit 1 [DCTN1]  | 0.832109     | 4.670096       | 8.463549 | 4.23E-16       | 4.65E-15         | Up-regulated             |
| <b>Q16698</b>  | DECR1         | 2,4-dienoyl-CoA reductase 1 [DECR1]                               | 1.761809     | 5.472935       | 12.47673 | 1.16E-30       | 1.4E-28          | Up-regulated             |

|               |          |   |          |          |          |          |          |              |
|---------------|----------|---|----------|----------|----------|----------|----------|--------------|
| <b>O94907</b> | DKK1     | dickkopf WNT signaling pathway inhibitor 1 [DKK1]                           | 0.827601 | 9.126566 | 7.45335  | 5.13E-13 | 4.54E-12 | Up-regulated |
| <b>P01133</b> | EGF      | epidermal growth factor [EGF]   | 1.616315 | 6.922769 | 8.53557  | 2.49E-16 | 2.82E-15 | Up-regulated |
| <b>Q04637</b> | EIF4G1   | eukaryotic translation initiation factor 4 gamma 1 [EIF4G1]                 | 1.53699  | 4.461354 | 11.89389 | 2.32E-28 | 1.2E-26  | Up-regulated |
| <b>P09038</b> | FGF2     | fibroblast growth factor 2 [FGF2]   | 0.883794 | 1.437425 | 11.21686 | 9.32E-26 | 3.08E-24 | Up-regulated |
| <b>P14317</b> | HCLS1    | hematopoietic cell-specific Lyn substrate 1 [HCLS1]                         | 1.230829 | 5.939195 | 10.71722 | 6.92E-24 | 1.65E-22 | Up-regulated |
| <b>O94992</b> | HEXIM1   | HEXIM P-TEFb complex subunit 1 [HEXIM1]                                     | 1.185035 | 5.583211 | 11.47112 | 1E-26    | 4.04E-25 | Up-regulated |
| <b>Q9Y6K9</b> | IKBKG    | inhibitor of nuclear factor kappa B kinase regulatory subunit gamma [IKBKG] | 1.131863 | 4.520584 | 12.00782 | 8.3E-29  | 5.02E-27 | Up-regulated |
| <b>Q9NWZ3</b> | IRAK4    | interleukin 1 receptor associated kinase 4 [IRAK4]                          | 1.616846 | 3.002674 | 12.13242 | 2.69E-29 | 2.44E-27 | Up-regulated |
| <b>Q9UKP3</b> | ITGB1BP2 | integrin subunit beta 1 binding protein 2 [ITGB1BP2]                        | 1.66077  | 4.635337 | 11.5811  | 3.78E-27 | 1.72E-25 | Up-regulated |
| <b>P07948</b> | LYN      | LYN proto-oncogene, Src family  | 0.920128 | 4.566285 | 10.76699 | 4.52E-24 | 1.17E-22 | Up-regulated |



|               |         |   |          |          |          |          |          |              |
|---------------|---------|---|----------|----------|----------|----------|----------|--------------|
|               |         | tyrosine kinase [LYN]                                 |          |          |          |          |          |              |
| <b>P16455</b> | MGMT    | O-6-methylguanine-DNA methyltransferase [MGMT]        | 1.442209 | 4.685031 | 9.509785 | 1.43E-19 | 1.99E-18 | Up-regulated |
| <b>P35240</b> | NF2     | neurofibromin 2 [NF2]                                 | 1.22294  | 0.168852 | 12.91393 | 2.02E-32 | 3.66E-30 | Up-regulated |
| <b>P04085</b> | PDGFA   | platelet derived growth factor subunit A [PDGFA]      | 0.834112 | 1.25921  | 6.484704 | 2.47E-10 | 1.83E-09 | Up-regulated |
| <b>P01127</b> | PDGFB   | platelet derived growth factor subunit B [PDGFB]      | 1.562135 | 8.596332 | 7.454131 | 5.11E-13 | 4.54E-12 | Up-regulated |
| <b>Q9HCM2</b> | PLXNA4  | plexin A4 [PLXNA4]                                    | 1.343607 | 5.065251 | 9.691782 | 3.34E-20 | 5.05E-19 | Up-regulated |
| <b>Q96SB3</b> | PPP1R9B | protein phosphatase 1 regulatory subunit 9B [PPP1R9B] | 1.304569 | 3.718838 | 9.953883 | 4.01E-21 | 6.62E-20 | Up-regulated |
| <b>P30044</b> | PRDX5   | peroxiredoxin 5 [PRDX5]                               | 1.234463 | 5.969949 | 10.71159 | 7.26E-24 | 1.65E-22 | Up-regulated |
| <b>O14828</b> | SCAMP3  | secretory carrier membrane protein 3 [SCAMP3]         | 1.469799 | 5.539404 | 10.48494 | 4.93E-23 | 1.05E-21 | Up-regulated |
| <b>Q9UQQ2</b> | SH2B3   | SH2B adaptor protein 3 [SH2B3]                        | 1.400395 | 3.897667 | 9.454795 | 2.2E-19  | 2.96E-18 | Up-regulated |
| <b>O43597</b> | SPRY2   | sprouty RTK signaling antagonist 2 [SPRY2]            | 1.313251 | 3.427296 | 10.3648  | 1.35E-22 | 2.58E-21 | Up-regulated |
| <b>P12931</b> | SRC     | SRC proto-oncogene, non-receptor tyrosine kinase      | 1.23053  | 6.712173 | 7.968705 | 1.49E-14 | 1.46E-13 | Up-regulated |

|               |        |   |          |          |          |          |          |                |
|---------------|--------|---|----------|----------|----------|----------|----------|----------------|
|               |        | [SRC]   |          |          |          |          |          |                |
| <b>P78362</b> | SRPK2  | SRSF protein kinase 2 [SRPK2]                     | 1.074254 | 1.741313 | 12.08928 | 3.97E-29 | 2.88E-27 | Up-regulated   |
| <b>Q13043</b> | STK4   | serine/threonine kinase 4 [STK4]                  | 1.387621 | 4.126016 | 9.080406 | 4.08E-18 | 4.78E-17 | Up-regulated   |
| <b>P40222</b> | TXLNA  | taxilin alpha [TXLNA]                             | 1.311471 | 5.605138 | 11.24859 | 7.07E-26 | 2.57E-24 | Up-regulated   |
| <b>Q05516</b> | ZBTB16 | zinc finger and BTB domain containing 16 [ZBTB16] | 1.365525 | 1.997167 | 15.08115 | 1.77E-41 | 6.42E-39 | Up-regulated   |
| <b>P27352</b> | CBLIF  | cobalamin binding intrinsic factor [CBLIF]        | -0.80701 | 8.500153 | -3.67944 | 0.000264 | 0.001029 | Down-regulated |

**Table S5. Survival all-cause mortality and/or hospitalisation at 2 years**

|  | Cluster 1                   | Cluster 2                   | Cluster 3                     | Cluster 4                   |
|--|-----------------------------|-----------------------------|-------------------------------|-----------------------------|
| <i>All-cause mortality and/or hospitalisation at 24 months</i> |                             |                             |                               |                             |
|  | HR (95% CI) <i>p</i> -value | HR (95% CI) <i>p</i> -value | HR (95% CI) <i>p</i> -value   | HR (95% CI) <i>p</i> -value |
| Univariate   | Reference                   | 0.64 (0.43 – 0.95) 0.026*   | 0.27 (0.17 – 0.42) < 0.001*** | 0.92 (0.56 – 1.52) 0.745    |
| Model 1  | Reference                   | 0.61 (0.41 – 0.90) 0.014*   | 0.31 (0.20 – 0.49) < 0.001*** | 0.93 (0.56 – 1.53) 0.777    |

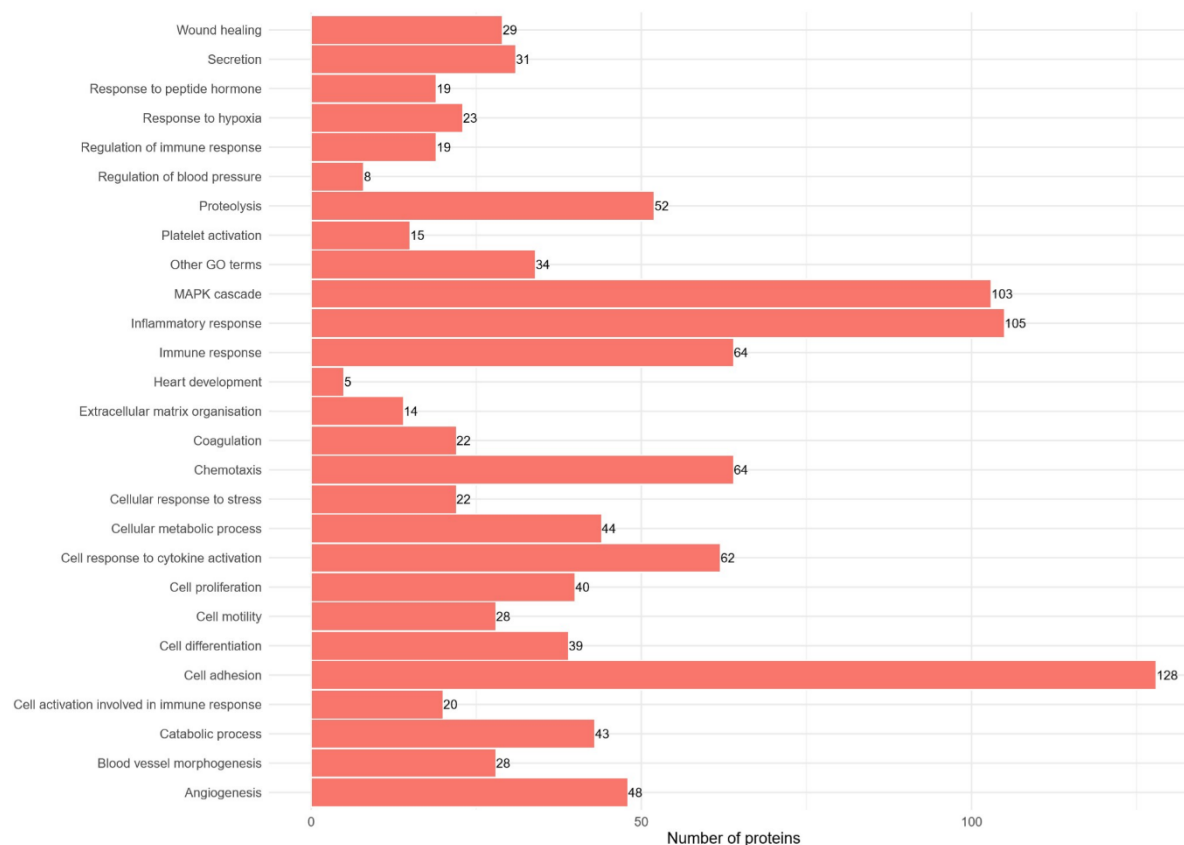
|         |           |                               |                                 |                             |
|---------|-----------|-------------------------------|---------------------------------|-----------------------------|
| Model 2 | Reference | 0.59 (0.39 – 0.89) 0.011*     | 0.31 (0.20 – 0.49)<br><0.001*** | 0.94 (0.57-1.55)<br>0.795   |
| Model 3 | Reference | 0.58 (0.39 – 0.87)<br>0.008** | 0.30 (0.19 – 0.48)<br><0.001*** | 0.84 (0.51 – 1.40)<br>0.501 |

*Model 1 = adjusts for Age and Sex*

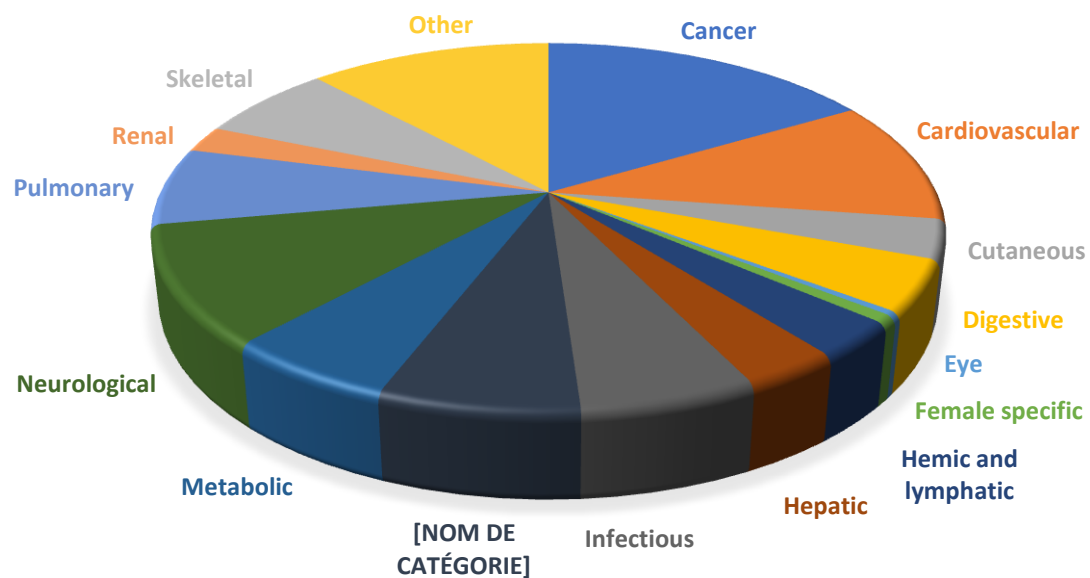
*Model 2 = Model 1 + adjusts HF hospitalisation in the previous year*

*Model 3 = Model 2 + adjusts for NYHA class*

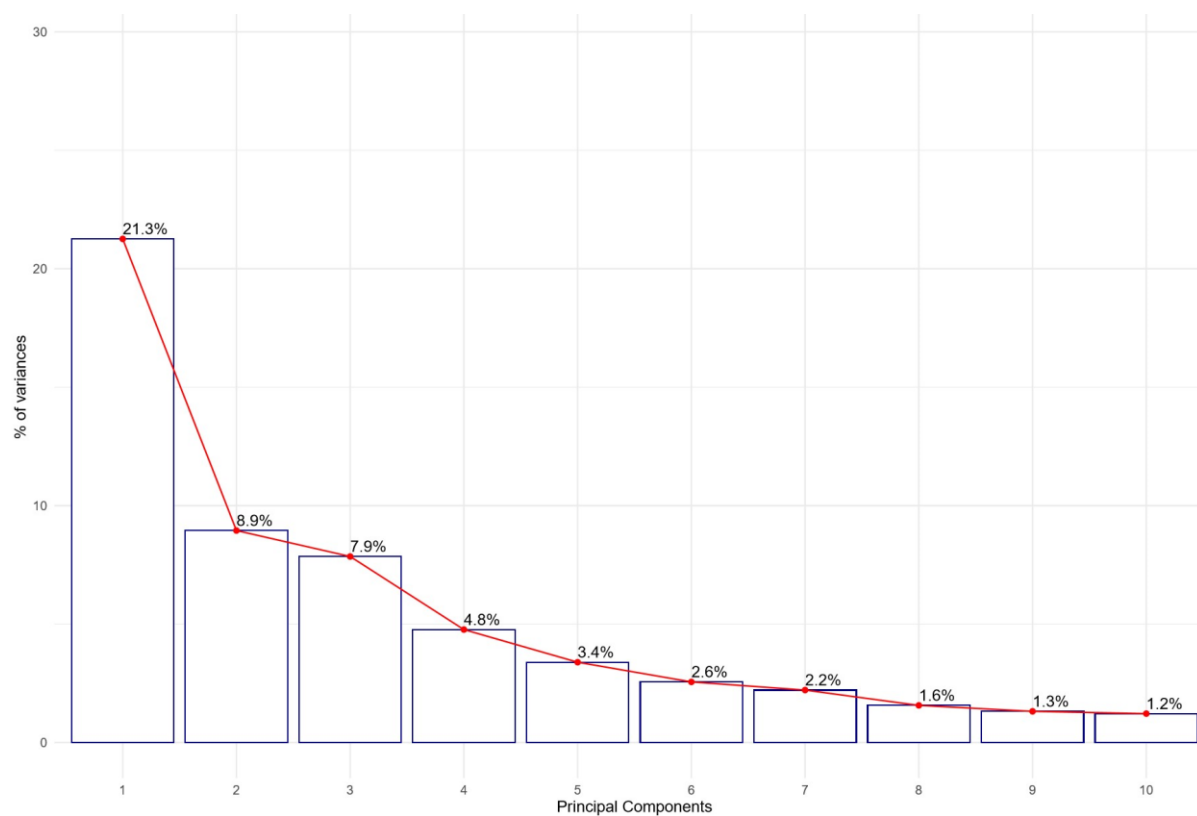
**Figure S1. Overview of GO biological processes of Olink biomarker proteins**



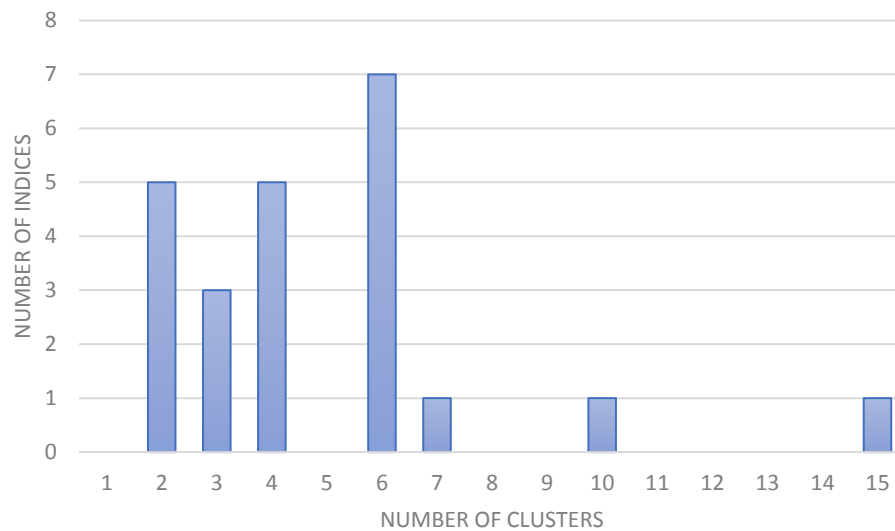
**Figure S2. Pie chart depicting the proportion of Olink biomarkers involved in each disease area.**



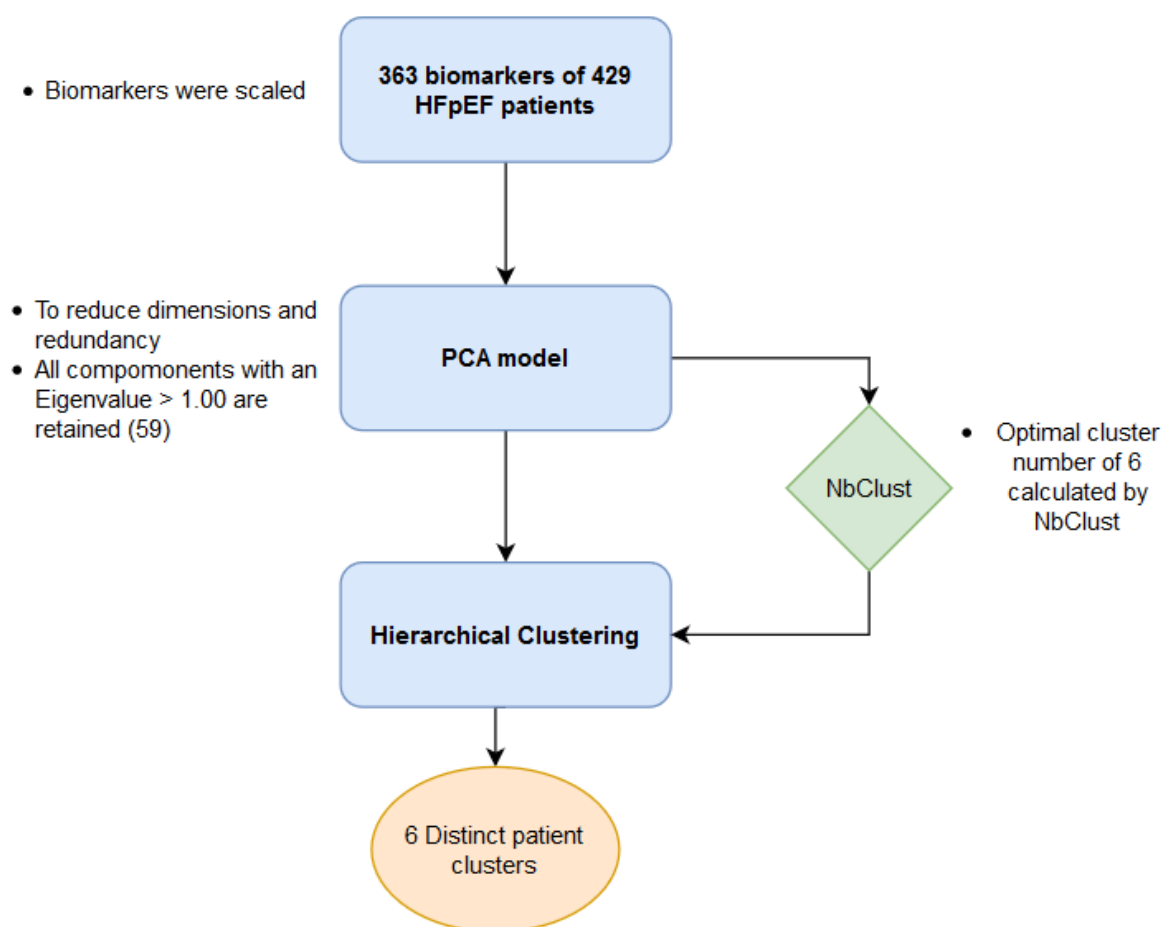
**Figure S3: Variance explained for the top 10 principle components.**



**Figure S4. NbClust: optimal number of clusters according to indices.**



**Figure S5. Flow chart of cluster analysis**



**Table S6. Overview of cluster analyses studies and their findings**

| Article/reference                | Year | Cohort size | Based on                      | Validation group | Phenotypes/clusters  |
|----------------------------------|------|-------------|-------------------------------|------------------|--|
| <b>Shah <i>et al.</i> (6)</b>    | 2015 | 397         | Clinical features             | Yes              | <ol style="list-style-type: none"> <li>1. Younger patients with moderate diastolic dysfunction, relatively normal BNP.</li> <li>2. Obese, diabetic with high prevalence of sleep apnoea.</li> <li>3. Older patients with CKD, RV dysfunction, poorest outcomes.</li> </ol> |
| <b>Segar <i>et al.</i> (7)</b>   | 2019 | 654         | Clinical features & echo data | Yes              | <ol style="list-style-type: none"> <li>1. Higher BNP, severe symptoms, DM and increased creatinine.</li> <li>2. Lower prevalence of DM &amp; HF symptoms</li> <li>3. Low BMI, intermediate risk</li> </ol>   |
| <b>Kao <i>et al.</i> (8)</b>     | 2015 | 3023        | Clinical features             | Yes              | Multiple clusters. Subgroup C & E clusters of patients with poor renal function and poorest outcomes.  |
| <b>Tromp <i>et al.</i> (9)</b>   | 2018 | 6480        | Clinical features             | Yes              | 3 HFpEF clusters <ol style="list-style-type: none"> <li>1. Elderly/AF cluster</li> <li>2. Metabolic cluster: Obese, hypertension, diabetes</li> <li>3. Lean diabetic: DM &amp; low BMI</li> </ol>  |
| <b>Hedman <i>et al.</i> (10)</b> | 2020 | 320         | Biomarkers & echo data        | No               | 2 worse faring clusters <ol style="list-style-type: none"> <li>1. Hypertension, coronary artery disease, CKD, diabetes, anaemia</li> <li>2. AF, COPD, old age, CKD</li> </ol>  |
| <b>Cohen <i>et al.</i> (11)</b>  | 2020 | 3442        | Clinical features             | No               | <ol style="list-style-type: none"> <li>1. Younger higher prevalence smoking, best prognosis</li> <li>2. Older, AF</li> <li>3. Obesity, DM, CKD, worst prognosis.</li> </ol>  |

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