**Supplement table 1.** Spearman correlation of IGFBP7 and clinical parameters.

|  |  |  |
| --- | --- | --- |
| Parameter | Coefficient | P- value |
| Age | 0.29 | <0.001 |
| Gender | -0.07 | <0.001 |
| BMI | -0.03 | 0.098 |
| SBP | -0.03 | 0.064 |
| NT-proBNP | 0.37 | <0.001 |
| hsTnT | 0.37 | <0.001 |
| GDF-15 | 0.43 | <0.001 |
| Hemoglobin | -0.23 | <0.001 |
| Urea | 0.34 | <0.001 |
| eGFR | -0.49 | <0.001 |
| Sodium | -0.09 | <0.001 |
| HDL | -0.21 | <0.001 |
| Betablocker at baseline | -0.06 | 0.003 |
| HF hospitalisation in last year | 0.13 | <0.001 |
| Extent of peripheral oedema | 0.36 | <0.001 |
| Atrial fibrillation | 0.25 | <0.001 |
| Diabetes Mellitus | 0.12 | <0.001 |
| LVEF | 0.02 | 0.336 |
| LVESD | -0.03 | 0.262 |
| LVEDD | -0.06 | 0.005 |
| Mitral valve regurgitation | 0.09 | <0.001 |
| Septal e' | -0.08 | 0.054 |
| Posterior wall thickness | 0.09 | <0.001 |
| Intraventricular wall thickness | 0.08 | <0.001 |
| E/A ratio | 0.23 | <0.001 |
| LA diameterre | 0.24 | <0.001 |

BMI, body mass index**;** SBP, systolic blood pressure; NTproBNP, N-terminal prohormone of brain natriuretic peptide; hsTnT, high-sensitive troponin T; GDF15, growth differentiation factor 15; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD left ventricular end systolic diameter; LVEDD, left ventricular end diastolic diameter; LA, left atrium.

**Supplement table 2**. Hospitalization and mortality incidence by IGFBP7 tertiles, during the study follow-up.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | N | IGFBP7-1 | IGFBP7-2 | IGFBP7-3 | P- value |
| HF rehospitalization, N(%) | 527 | 104 (13.9%) | 159 (21.2%) | 264 (35.2%) | <0.001 |
| Mortality, N(%) | 526 | 83 (11.1%) | 147 (19.6%) | 297(39.6%) | <0.001 |
| Mortality or HF rehospitalization, N(%) | 869 | 165 (22.0%) | 262 (34.9%) | 442 (58.9%) | <0.001 |

IGFBP7, insulin-like growth factor binding protein 7; N, number; HF, heart failure.

**Supplement table 3.** Cox regression models for the prediction of hospitalization, all-cause mortality and combined outcome in BIOSTAT-CHF Validation cohort, by each doubling of IGFBP7.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Hospitalization |  | All-cause mortality |  | Combined |  |
| Model | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| A | 2.38 (1.95 - 2.91) | <0.001 | 2.66 (2.19 - 3.22) | <0.001 | 2.37 (2.03 - 2.79) | <0.001 |
| B | 1.60 (1.28 - 2.00) | <0.001 | 2.44 (2.03 - 2.94) | <0.001 | 1.34 (1.12 - 1.61) | 0.001 |
| C | 1.37 (1.06 - 1.77) | 0.013 | 1.37 (1.09 - 1.73) | 0.006 | 1.23 (1.01 - 1.50) | 0.03 |

IGFBP7: Insulin- like growth factor binding protein, HF: hazard ratio, CI: confidence interval.

Model A: Age, sex

Model B: Hospitalization: age, hospitalization in a year previous to inclusion, the extent of peripheral oedema, SBP, and eGFR. All-cause mortality: age, blood urea nitrogen, NT-proBNP, Hb and beta-blocker use at the baseline. Combined: age, NT-proBNP, Hb, beta-blocker use at baseline, HF hospitalization in a year prior to inclusion, extent of peripheral oedema, SBP, HDL and serum sodium levels.

Model C: Hospitalization: age, HF hospitalisation in previous year, extent of peripheral edema, SBP, eGFR, gender, atrial fibrillation, diabetes mellitus, GDF15, Hb, NTProBNP and BMI. All-cause mortality: age, BUN, NTproBNP, Hb, beta-blocker at baseline, gender, atrial fibrillation, diabetes mellitus, GDF15, BMI. Combined: age, NTproBNP, Hb, beta-blocker at baseline, hospitalisation in previous year, extent of peripheral oedema, SBP, HDL, sodium, gender, atrial fibrillation, diabetes mellitus, GDF15 and BMI.

**Supplement table 4.** Baseline characteristics of subjects with LVEF <40%, by IGFBP7 tertiles.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Factor | Level | triIGFBP7= 1 | triIGFBP7= 2 | triIGFBP7= 3 | P-value |
| N |  | 585 | 528 | 517 |  |
| IGFBP7 [ng/mL], median (IQR) |  | 99.18 (89.9, 106.9) | 133.1 (124.6, 143.7) | 194.1 (169.4, 235.1) | <0.001 |
| Age, median (IQR) |  | 72.6 (64.8, 80.7) | 80.3 (72.6, 87.1) | 82 (73.4, 88.6) | <0.001 |
| Male gender (%) |  | 423 (72.3%) | 417 (79.0%) | 413 (79.9%) | 0.004 |
| BMI, median (IQR) |  | 27.1 (24.3, 30.8) | 27.1 (24.0, 30.2) | 26.4 (23.8, 29.3) | 0.036 |
| SBP (mmHg), median IQR |  | 120 (110, 135) | 120 (110, 140) | 120 (107, 130) | 0.001 |
| NT-proBNP (pg/mL), median (IQR) |  | 1365 (582.9, 2840) | 2866.5 (1423, 5196) | 4851.5 (2560, 10335) | <0.001 |
| Troponin T (pg/mL), median (IQR) |  | 20.3 (12.9, 36.9) | 31.3 (20.0, 48.5) | 42.8 (27.9, 65.6) | <0.001 |
| GDF-15 (ng/ml), median (IQR) |  | 2.8 (2.3, 3.5 | 3.3 (2.7, 3.9) | 4.0 (3.2, 5.1) | <0.001 |
| Hemoglobin (g/dL), median (IQR) |  | 13.8 (12.7, 14.9) | 13.6 (12.3, 14.8) | 12.8 (11.4, 14.2) | <0.001 |
| Urea (mmol/L), median (IQR) |  | 9.5 (6.8, 14.9) | 11.3 (7.7, 17.4) | 16 (9.9, 26.0) | <0.001 |
| eGFR (ml/min/1.73m2), median IQR |  | 75.4 (61.36 88.6) | 58.3 (45.8, 72.9) | 48.4(34.1, 64.7) | <0.001 |
| Sodium (mmol/L), median (IQR) |  | 140 (138, 142) | 140 (138, 142) | 139 (136, 141) | <0.001 |
| HDL (mmol/L), median (IQR) |  | 1.1 (.9, 1.41) | 1.04 (.85, 1.3) | .931 (.745, 1.171) | <0.001 |
| Use of betablocker at baseline (%) |  | 503 (86.0%) | 456 (86.4%) | 423 (81.8%) | 0.074 |
| HF hospitalisation in previous year (%) |  | 164 (28.0%) | 166 (31.4%) | 216 (41.8%) | <0.001 |
| Extent of peripheral oedema (%) | Not Present | 288 (61.3%) | 178 (42.5%) | 134 (29.7%) | <0.001 |
|  | Ankle | 133 (28.3%) | 134 (32.0%) | 117 (25.9%) |  |
|  | Below Knee | 45 (9.6%) | 89 (21.2%) | 147 (32.6%) |  |
|  | Above Knee | 4 (0.9%) | 18 (4.3%) | 53 (11.8%) |  |
| Atrial fibrillation (%) |  | 168 (28.7%) | 234 (44.3%) | 286 (55.3%) | <0.001 |
| Diabetes Mellitus (%) |  | 147 (25.1%) | 170 (32.2%) | 202 (39.1%) | <0.001 |

N, number; IGFBP7, insulin-like growth factor binding protein 7; BMI, body mass index; SBP, systolic blood pressure; NTproBNP, N-terminal pro–B-type natriuretic peptide; hsTnT, high-sensitive troponin T; GDF-15, growth/differentiation factor 15; eGFR, Estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure.

**Supplement table 5.** Baseline characteristics of subjects with LVEF > 40%, by IGFBP7 tertiles.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Factor | Level | triIGFBP7 = 1 | triIGFBP7 = 2 | triIGFBP7 = 3 | p-value |
| NTproBNP (pg/mL), median IQR |  | 149 | 192 | 205 |  |
| IGFBP7 (ng/mL), median IQR |  | 101.2 (89.6, 108.0) | 134.0 (125.0, 143.9) | 198.1 (176.3, 240.2) | <0.001 |
| Age, median (IQR) |  | 78.6 (70.7, 87.1) | 85.7 (77.0, 91.1) | 87.3 (79.9, 92.5) | <0.001 |
| Male gender (%) |  | 87 (58.4%) | 118 (61.5%) | 144 (70.2%) | 0.049 |
| BMI, median (IQR) |  | 27.3(24.8, 31.6) | 27.7 (24.2, 31.1) | 27.9 (24.1, 31.91) | 0.98 |
| SBP (mm/Hg), median IQR |  | 129 (115, 140) | 130 (115.5, 144) | 125 (110, 140) | 0.33 |
| NTproBNP (pg/mL), median IQR |  | 1157.5 (338.0, 2707.5) | 2056 (1196.5, 5027) | 4825 (2696, 9292) | <0.001 |
| hsTnT (pg/mL), median IQR |  | 21.0 (13.4, 39.1) | 29.6 (21.5, 53.4) | 46.8 (30.4, 79.6) | <0.001 |
| GDF-15 (ng/mL), median IQR |  | 3.1 (2.4, 3.8) | 3.5 (3.0, 4.3) | 4.3 (3.5, 5.2) | <0.001 |
| Hemoglobin (g/dL), median IQR |  | 13.3(12.0, 14.3) | 12.7 (11.277, 13.9) | 12.083 (10.6, 13.3) | <0.001 |
| Urea (mmol/L), median (IQR) |  | 7.1 (5.3, 10.353) | 10.5 (7.2, 14.9) | 13.4 (9.0, 19.8) | <0.001 |
| eGFR (ml/min/1.73m2), median IQR |  | 73.7 (57.9, 87.3) | 56.5 (41.3, 73.1) | 42.9 (28.3, 58.2) | <0.001 |
| Sodium (mmol/L), median IQR |  | 140 (137, 142) | 140 (137, 142) | 138 (136, 141) | 0.004 |
| HDL (mmol/L) median IQR |  | 1.1 (.92, 1.3) | 1.1 (0.9, 1.3) | 1.0 (0.8, 1.3) | 0.11 |
| Use of betablocker at baseline (%) |  | 21 (14.1%) | 42 (21.9%) | 49 (23.9%) | 0.066 |
| HF hospitalisation in previous year (%) | | 31 (20.8%) | 44 (22.9%) | 79 (38.5%) | <0.001 |
| Extent of peripheral edema (%) | Not present | 54 (43.9%) | 60 (37.0%) | 21 (11.5%) | <0.001 |
|  | Ankle | 40 (32.5%) | 51 (31.5%) | 55 (30.1%) |  |
|  | Bellow knee | 25 (20.3%) | 35 (21.6%) | 68 (37.2%) |  |
|  | Above knee | 4 (3.3%) | 16 (9.9%) | 39 (21.3%) |  |
| Atrial Fibrillation present (%) |  | 56 (37.6%) | 113 (58.9%) | 134 (65.4%) | <0.001 |
| Diabetes Mellitus present (%) |  | 42 (28.2%) | 76 (39.6%) | 75 (36.6%) | 0.083 |

N, number; IGFBP7, insulin-like growth factor binding protein 7; BMI, body mass index; SBP, systolic blood pressure; NTproBNP, N-terminal pro–B-type natriuretic peptide; hsTnT, high-sensitive troponin T; GDF-15, growth/differentiation factor 15; eGFR, Estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure.

**Supplement table 6.** Biomarkers correlated with IGFBP7 in HF population.

|  |  |
| --- | --- |
| Marker | Full name |
| WISP-1 | cellular communication network factor 4 [CCN4] |
| FGF-23 | fibroblast growth factor 23 [FGF23] |
| PRELP | proline and arginine rich end leucine rich repeat protein [PRELP] |
| GDF-15 | growth differentiation factor 15 [GDF15] |
| hK11 | kallikrein related peptidase 11 [KLK11] |
| CXADR | CXADR Ig-like cell adhesion molecule [CXADR] |
| IFN-gamma-R1 | interferon gamma receptor 1 [IFNGR1] |
| EPHA2 | EPH receptor A2 [EPHA2] |
| TNFRSF19 | TNF receptor superfamily member 19 [TNFRSF19] |
| TRAIL-R2 | TNF receptor superfamily member 10b [TNFRSF10B] |
| WFDC2 | WAP four-disulfide core domain 2 [WFDC2] |
| IL-4RA | interleukin 4 receptor [IL4R] |
| TGFR-2 | transforming growth factor beta receptor 2 [TGFBR2] |
| PLC | heparan sulfate proteoglycan 2 [HSPG2] |
| IGF1R | insulin like growth factor 1 receptor [IGF1R] |
| IGFBP-2 | insulin like growth factor binding protein 2 [IGFBP2] |
| SPON2 | spondin 2 [SPON2] |
| LILRB4 | leukocyte immunoglobulin like receptor B4 [LILRB4] |
| TNFSF13 | TNF superfamily member 13 [TNFSF13] |
| TNFRSF11A | TNF receptor superfamily member 11a [TNFRSF11A] |
| IGFBP-1 | insulin like growth factor binding protein 1 [IGFBP1] |
| CKAP4 | cytoskeleton associated protein 4 [CKAP4] |
| TFF3 | trefoil factor 3 [TFF3] |
| TREM1 | triggering receptor expressed on myeloid cells 1 [TREM1] |
| TNFRSF6B | TNF receptor superfamily member 6b [TNFRSF6B] |
| LTBR | lymphotoxin beta receptor [LTBR] |
| CD4 | CD4 molecule [CD4] |
| VSIG2 | V-set and immunoglobulin domain containing 2 [VSIG2] |
| DCN | decorin [DCN] |
| PAR-1 | coagulation factor II thrombin receptor [F2R] |
| DLL1 | delta like canonical Notch ligand 1 [DLL1] |
| TNF-R2 | TNF receptor superfamily member 1B [TNFRSF1B] |
| BNP | natriuretic peptide B |
| U-PAR | plasminogen activator, urokinase receptor [PLAUR] |
| PVRL4 | nectin cell adhesion molecule 4 [NECTIN4 |
| AREG | amphiregulin [AREG] |
| WIF-1 | WNT inhibitory factor 1 [WIF1] |
| CD27 | CD27 molecule [CD27] |
| TGF-alpha | transforming growth factor alpha [TGFA] |
| CAIX | carbonic anhydrase 9 [CA9] |
| MILR1 | mast cell immunoglobulin like receptor 1 [MILR1] |

**Continuation of the Supplement table 6.**

|  |  |
| --- | --- |
| Marker | Full name |
| TNFRSF14 | TNF receptor superfamily member 14 [TNFRSF14] |
| TNF-R1 | TNF receptor superfamily member 1A [TNFRSF1A] |
| CD160 | CD160 molecule [CD160] |
| BOC | BOC cell adhesion associated, oncogene regulated [BOC] |
| SPON1 | spondin 1 [SPON1] |
| ADM | adrenomedullin [ADM] |
| ST2 | interleukin 1 receptor like 1 [IL1RL1] |
| TNFRSF4 | TNF receptor superfamily member 4 [TNFRSF4] |
| CD93 | CD93 molecule [CD93] |
| PD-L2 | programmed cell death 1 ligand 2 [PDCD1LG2] |
| Notch 3 | NA |
| RSPO3 | R-spondin 3 [RSPO3] |
| TNFRSF10A | TNF receptor superfamily member 10a [TNFRSF10A] |
| LAG3 | lymphocyte activating 3 [LAG3] |
| IL-18BP | interleukin 18 binding protein [IL18BP] |
| AGRP | agouti related neuropeptide [AGRP] |
| ITGB5 | integrin subunit beta 5 [ITGB5] |
| CLEC7A | C-type lectin domain containing 7A [CLEC7A] |
| TF | coagulation factor III, tissue factor [F |
| GPNMB | glycoprotein nmb [GPNMB] |
| EPHB4 | EPH receptor B4 [EPHB4] |
| DPP10 | dipeptidyl peptidase like 10 [DPP10] |
| IL-1RT1 | interleukin 1 receptor type 1 [IL1R1] |
| CDSN | corneodesmosin [CDSN] |
| FABP4 | fatty acid binding protein 4 [FABP4] |
| RAGE | advanced glycosylation end-product specific receptor [AGER] |
| FR-alpha | folate receptor alpha [FOLR1] |
| CSTB | cystatin B [CSTB] |
| NCR1 | natural cytotoxicity triggering receptor 1 [NCR1] |
| Gal-9 | galectin 9 [LGALS9 |
| GPC1 | glypican 1 [GPC1] |
| MMP-2 | matrix metallopeptidase 2 |
| PGF | placental growth factor [PGF] |