

**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 diameter	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.

Model	Hospitalization		All-cause mortality		Combined	
	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/1.73m <sup>2</sup> ), 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/1.73m <sup>2</sup> ), 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 [TGFR2]
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]
GNPMB	glycoprotein nmb [GNPMB]
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 metalloproteinase 2
PGF	placental growth factor [PGF]