

**Supplemental Table 1** Association of GDF-15 with comorbidities

	<b>Correlation coefficient (R<sup>2</sup>)</b>	<b>p-value</b>
eGFR, mL/min/1.73 m <sup>2</sup>	0.204	<0.001
Hemoglobin, g/L	0.051	<0.001
HbA <sub>1c</sub> , mmol/mol	0.047	<0.001
Systolic blood pressure, mmHg	0.012	0.047
BW change in the last 6 months, kg	0.083	<0.001

**Abbreviations:** BW, body weight; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; HbA<sub>1c</sub>, glycated hemoglobin.

**Supplemental Table 2** Assessment of available I-NEED-HELP markers in the study population

<b>Acronym</b>		<b>Definition</b>	<b>Study population</b>
<b>I</b>	<b>Inotropes</b>	Previous or ongoing requirement for dobutamine, milrinone, dopamine, or levosimendan	Not available
<b>N</b>	<b>NYHA class/ natriuretic peptide</b>	Persisting NYHA class III or IV and/or persistently high BNP or NT-proBNP	73% of the population in NYHA class III/IV; median BNP concentration: 568 ng/L
<b>E</b>	<b>End-organ dysfunction</b>	Worsening renal or liver dysfunction in the setting of heart failure	15% of the population with an eGFR < 45 ml/min/m <sup>2</sup>
<b>E</b>	<b>Ejection fraction</b>	Very low ejection fraction <20%	24% of the population with a LVEF < 20%
<b>D</b>	<b>Defibrillator shocks</b>	Recurrent appropriate defibrillator shocks	Not available
<b>H</b>	<b>Hospitalizations</b>	More than 1 hospitalization with heart failure in the last 12 months	99.9% of the population had more than 2 hospitalizations due to HF over the course of their condition (not available specific data within the last 12 months)
<b>E</b>	<b>Edema/escalating diuretics</b>	Persisting fluid overload and/or increasing diuretic requirement	Mean daily oral dose of furosemide: 96 mg
<b>L</b>	<b>Low blood pressure</b>	Consistently low BP with systolic <90 to 100 mmHg	17% of the population had systolic BP < 100 mmHg
<b>P</b>	<b>Prognostic medication</b>	Inability to up-titrate (or need to decrease/cease) ACEi, beta-blockers, ARNIs, or MRAs	56% and 62% of the population treated with < 50% of the recommended target dose of ACEi/ARB and betablocker, respectively

**Abbreviations:** ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNIs, angiotensin receptor-neprilysin inhibitors; BNP, brain natriuretic peptide; BP, blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

**Supplemental Table 3** Association between circulating GDF-15 and the presence and severity of HF signs or symptoms (none to mild [0-2] vs. moderate to severe [3-5]) at MLHFQ questions

	<b><math>\beta \pm</math> standard error</b>	<b>p-value</b>
MLHFQ, Q-1 (congestion)	0.210 $\pm$ 0.033	<b>&lt;0.001</b>
MLHFQ, Q-2 (need of rest)	-0.013 $\pm$ 0.036	0.721
MLHFQ, Q-3 (mobility impairment)	0.089 $\pm$ 0.039	<b>0.022</b>
MLHFQ, Q-4 (impact on household chores)	0.047 $\pm$ 0.035	0.178
MLHFQ, Q-5 (home confinement)	0.073 $\pm$ 0.034	<b>0.034</b>
MLHFQ, Q-6 (sleeping disorders)	0.064 $\pm$ 0.034	0.064
MLHFQ, Q-7 (social interactions)	-0.027 $\pm$ 0.042	0.513
MLHFQ, Q-8 (working)	-0.018 $\pm$ 0.035	0.600
MLHFQ, Q-9 (recreational limitations)	0.043 $\pm$ 0.036	0.229
MLHFQ, Q-10 (sexual activities)	0.069 $\pm$ 0.035	<b>0.048</b>
MLHFQ, Q-11 (anorexia)	0.156 $\pm$ 0.034	<b>&lt;0.001</b>
MLHFQ, Q-12 (breathing difficulties)	0.066 $\pm$ 0.038	0.084
MLHFQ, Q-13 (fatigue)	0.065 $\pm$ 0.041	0.112
MLHFQ, Q-14 (hospitalization)	0.132 $\pm$ 0.034	<b>&lt;0.001</b>
MLHFQ, Q-15 (financial impact)	0.132 $\pm$ 0.034	<b>&lt;0.001</b>
MLHFQ, Q-16 (treatment side effects)	0.106 $\pm$ 0.038	<b>0.006</b>
MLHFQ, Q-17 (emotional impact)	0.053 $\pm$ 0.037	0.155
MLHFQ, Q-18 (loss of control)	0.015 $\pm$ 0.039	0.691
MLHFQ, Q-19 (anxiety)	0.118 $\pm$ 0.034	<b>&lt;0.001</b>
MLHFQ, Q-20 (cognitive functions)	0.002 $\pm$ 0.039	0.945
MLHFQ, Q-21 (depression)	0.023 $\pm$ 0.028	0.528

**Abbreviations:** GDF-15, growth differentiation factor-15; HF, heart failure; MLHFQ, Minnesota living with heart failure questionnaire; Q, question.

**Supplemental Table 4** Univariate and multivariate logistic regression analysis of circulating GDF-15 and MLHFQ question 11 score (anorexia severity in heart failure)

	Age- and sex- adjusted		Multivariable	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
<b>Clinical characteristics</b>				
NYHA class, III/IV vs. II	1.396 (1.115; 1.709)	<b>0.004</b>	-	-
Diabetes mellitus (yes vs. no)	1.267 (1.034; 1.554)	<b>0.022</b>	1.025 (0.804; 1.306)	0.837
Hypertension (yes vs. no)	1.126 (0.917; 1.385)	0.255		
Atrial fibrillation (yes vs. no)	0.854 (0.656; 1.112)	0.244		
CKD (yes vs. no)	0.837 (0.670; 1.05)	0.116		
Body mass index, kg/m <sup>2</sup>	0.969 (0.931; 1.008)	0.130		
Body weight, Kg	0.988 (0.977; 1.001)	0.075		
Body fat (skinfold method), %	0.996 (0.974; 1.018)	0.738		
<b>Laboratory values</b>				
Albumin, g/L	0.978 (0.929; 1.029)	0.380		
eGFR, per 10 mL/min/1.73 m <sup>2</sup> increase	0.872 (0.781; 0.977)	<b>0.013</b>	0.947 (0.831; 1.079)	0.413
HbA <sub>1c</sub> , mmol/mol	1.142 (1.009; 1.305)	<b>0.046</b>	-	-
HOMA-IR index	0.996 (0.934; 1.062)	0.908		
Insulin/glucagon ratio	0.151 (0.017; 1.210)	0.909		
BNP, per 100 ng/L increase	1.058 (1.033; 1.085)	<b>&lt;0.001</b>	1.025 (0.992; 1.060)	0.116
Total cholesterol, mmol/L	0.844 (0.696; 1.022)	0.083		
Free fatty acids, mmol/L	0.597 (0.116; 3.022)	0.509		
β-hydroxybutyrate, per 10 μmol/L increase	1.014 (1.000; 1.327)	<b>0.037</b>	1.001 (0.984; 1.017)	0.894
GDF-15, per 100 ng/L increase	1.044 (1.027; 1.063)	<b>&lt;0.001</b>	1.029 (1.004; 1.055)	0.019
<b>Echocardiography</b>				
LV end-diastolic diameter, per 5 mm increase	0.917 (0.822; 1.021)	0.126		
LV ejection fraction, per 5% increase	0.885 (0.729; 1.071)	0.216		
E/Em ratio	0.997 (0.966; 1.029)	0.872		
RV dysfunction, (yes vs. no)	1.668 (1.220; 2.307)	<b>0.002</b>	1.390 (1.105; 1.754)	0.005
RV dysfunction grade, 2-3 vs. 0-1*	1.484 (1.191; 1.857)	<b>&lt;0.001</b>	-	-
<b>Hemodynamic</b>				
RAP, mmHg	1.003 (0.957; 1.051)	0.884		
PA mean pressure, mmHg	0.992 (0.968; 1.017)	0.544		
PAWP, mmHg	0.986 (0.954; 1.019)	0.419		
RAP/PAWP ratio	1.426 (0.489; 4.128)	0.530		
PVR, Wood's unit	1.015 (0.858; 1.206)	0.867		

In the multivariable model, dashes stand for variables not tested because of possible collinearity.

\*Since right ventricular dysfunction grades 0-1 and grades 2-3 have similar prognostic impact, they were aggregated for dichotomized analyses.

**Abbreviations:** BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; HbA<sub>1c</sub>, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; MLHFQ, Minnesota living with heart failure questionnaire; NYHA, New York Heart Association; LV, left ventricle; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

**Supplemental Table 5** Univariate and multivariate logistic regression analysis of circulating GDF-15 and cachexia status (unintentional oedema-free body weight loss >5% in the past 6 months)

	Age- and sex- adjusted		Multivariable			
			Model 1		Model 2	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
<b>Clinical characteristics</b>						
NYHA class, III/IV vs. II	1.492 (0.856; 2.601)	0.158				
Diabetes mellitus (yes vs. no)	0.919 (0.553; 1.528)	0.747				
Hypertension (yes vs. no)	1.024 (0.630; 1.667)	0.283				
Atrial fibrillation (yes vs. no)	1.129 (0.825; 1.534)	0.437				
CKD (yes vs. no)	1.232 (0.950; 1.599)	0.114				
Body mass index, <25 kg/m <sup>2</sup>	4.237 (2.553; 7.032)	<0.001	3.868 (1.686; 8.872)	0.001	-	-
Body weight, Kg	0.972 (0.957; 0.989)	<0.001	1.010 (0.984; 1.036)	0.429	-	-
Body fat (skinfold method), %	0.942 (0.915; 0.969)	<0.001	0.967 (0.930; 1.007)	0.106	-	-
<b>Laboratory values</b>						
Albumin, g/L	0.915 (0.861; 0.973)	<b>0.005</b>	0.913 (0.847; 0.983)	0.015	0.915 (0.854; 0.980)	0.012
eGFR, per 10 mL/min/1.73 m <sup>2</sup> increase	0.899 (0.789; 1.022)	0.106				
HbA <sub>1c</sub> , mmol/mol	0.948 (0.812; 1.107)	0.503				
HOMA-IR index	0.972 (0.897; 1.052)	0.483				
Insulin/glucagon ratio	0.072 (0.004; 1.424)	0.084				
BNP, ≥ 2000 ng/L	2.763 (1.369; 5.774)	<b>0.005</b>	1.228 (0.463; 3.259)	0.678	2.099 (0.901; 4.890)	0.086
Total cholesterol, mmol/L	0.896 (0.715; 1.121)	0.337				
Free fatty acids, mmol/L	1.002 (0.180; 5.576)	0.998				
β-hydroxybutyrate, per 10 μmol/L increase	1.000 (0.985; 1.016)	0.917				
GDF-15, per 100 ng/L increase	1.038 (1.018; 1.059)	<0.001	1.027 (1.001; 1.055)	0.044	1.027 (1.003; 1.051)	0.025
<b>Echocardiography</b>						
LV end-diastolic diameter, per 5 mm increase	0.970 (0.844; 1.115)	0.671				
LV ejection fraction, per 5% increase	0.795 (0.628; 1.006)	0.056				
E/Em ratio	1.004 (0.967; 1.042)	0.820				

RV dysfunction, (yes vs. no)	1.775 (0.824; 3.823)	0.142				
RV dysfunction grade, 2-3 vs. 0-1*	1.934 (1.153; 3.341)	<b>0.012</b>	1.628 (0.891; 2.974)	0.113	1.969 (1.135; 3.418)	0.015
<b>Hemodynamic</b>						
RAP, mmHg	1.005 (0.952; 1.062)	0.843				
PA mean pressure, mmHg	1.004 (0.975; 1.033)	0.773				
PAWP, mmHg	1.019 (0.981; 1.060)	0.327				
RAP/PAWP ratio	0.835 (0.219; 3.189)	0.793				
PVR, Wood's unit	0.963 (0.785; 1.179)	0.714				

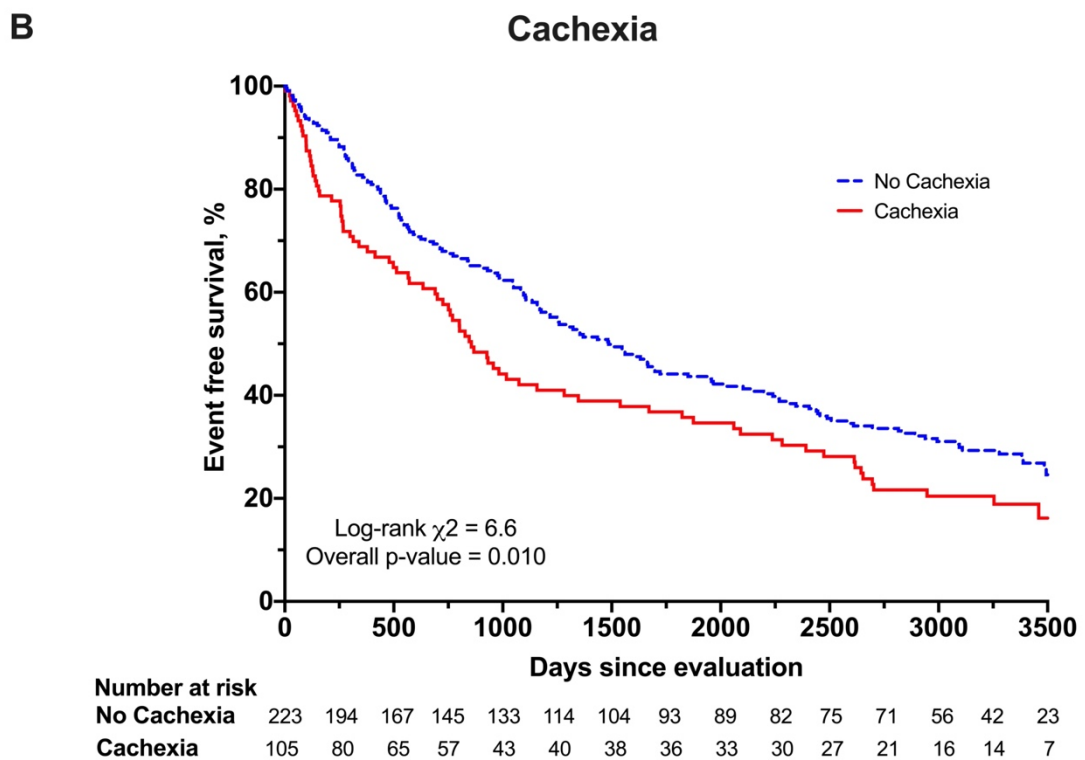
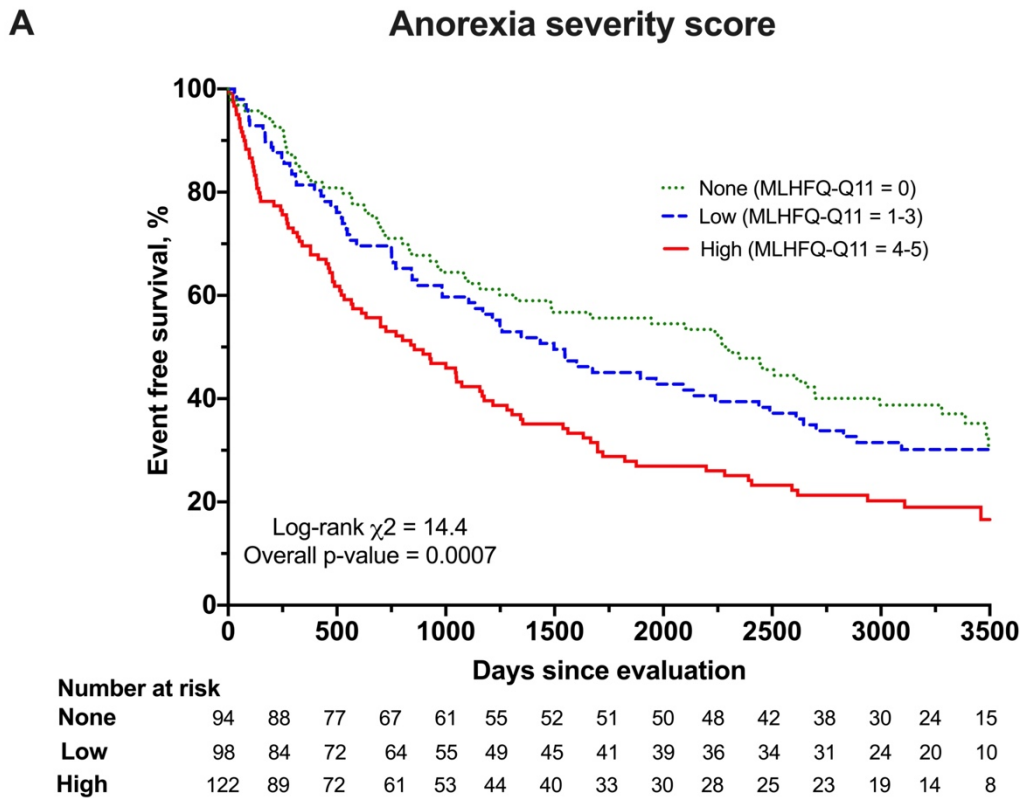
Multivariable Model 1: body mass index (BMI), body weight (BW), fat mass by skinfold method, albumin, BNP, GDF-15, RV dysfunction severity.

Multivariable Model 2: albumin, BNP, GDF-15, RV dysfunction severity.

\*Since right ventricular dysfunction grades 0-1 and grades 2-3 have similar prognostic impact, they were aggregated for dichotomized analyses.

**Abbreviations:** BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; HbA<sub>1c</sub>, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; MLHFQ, Minnesota living with heart failure questionnaire; NYHA, New York Heart Association; LV, left ventricle; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

Supplemental Figure 1



Supplemental Figure 2

## HYPOTHETICAL MECHANISMS

