

**Table S1** Baseline characteristics of study population and patients in BIOSTAT-CHF index cohort

Factor	Study population (N=2079)	Patients in BIOSTAT- CHF index cohort (N=2516)
Clinical characteristics		
Age, years	69 ± 12	69 ± 12
Sex, Females, n (%)	547 (26.3%)	670 (26.6%)
BMI, kg/m <sup>2</sup>	27.9 ± 5.5	27.9 ± 5.5
NYHA functional class III/IV, n (%)	1237 (59.5%)	1522 (60.5%)
LVEF, %	30 (25–36)	30 (25–36)
Systolic blood pressure, mmHg	124 ± 22	125 ± 22
Heart rate, b.p.m	80 ± 20	80 ± 20
Hospitalization, type of visit, n (%)		
- Outpatient clinic	602 (29.0%)	822 (32.7%)
- Inpatient hospitalisation	1477 (71.0%)	1694 (67.3%)
Previous HF hospitalization in last year, n (%)	646 (31.1%)	794 (31.6%)
Laboratory		
NT-proBNP, ng/L	2696 (1204–5671)	2698 (1178–5755)
Troponin T, µg/L	31.5 (19.2–53.5)	31.3 (19.0–53.8)
Sodium, mmol/L	140 (137–142)	140 (137–142)
Hemoglobin, g/dL	13.2 ± 1.9	13.2 ± 1.9
Potassium, mmol/L	4.2 (3.9–4.6)	4.2 (3.9–4.6)
eGFR, mL/min/1.73 m <sup>2</sup>	60 (44–77)	67.1 (50–86)
BUN, mmol/L	11.1 (7.4–17.9)	11.1 (7.4–17.7)
Medical history		
Atrial fibrillation, n (%)	949 (45.6%)	1143 (45.4%)
Diabetes mellitus, n (%)	660 (31.7%)	819 (32.6%)
COPD, n (%)	353 (17.0%)	436 (17.3%)

Medication, n (%)		
Loop diuretics	2070 (99.6%)	2504 (99.5%)
Beta-blockers	1731 (83.3%)	2093 (83.2%)
ACE-inhibitors/ARB	1490 (71.7%)	1820 (72.3%)
MRA	1097 (52.8%)	1339 (53.2%)

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; BUN: blood urea nitrogen; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; MRA: mineralocorticoid receptor antagonist

**Table S2** Levels of tumor biomarkers: reference values, values in malignancies and values in BIOSTAT-CHF

Tumor biomarkers	Malignancies	Reference value	Median value in BIOSTAT (+ IQR)	Number of measurements in BIOSTAT
CA125 (U/mL)	Ovarian cancer	<35	33.7 (14.4–97.2)	2069
CA15-3 (U/mL)	Breast cancer	<30	19.7 (14.1–26.4)	2073
CA19-9 (U/mL)	Pancreatic cancer	<37	10.2 (5.8–19.1)	2066
CEA (ng/mL)	Colon carcinoma	<5	2.4 (1.6–3.7)	2079
CYFRA 21-1 (ng/mL)	Lung cancer	≤3.3	2.1 (1.5–2.9)	2054
AFP (IU/mL)	Germ cell cancer	<15 or <8.4 ng/ml	1.8 (1.1–2.9)	2078

**Table S3** Differences in median tumor biomarker levels based on history of malignancy

History of malignancy	No (N=1998)	Yes (N=81)	P-value
CA125 (U/mL), median (IQR)	33.0 (14.3–96.2)	53.2 (19.9–113.3)	0.031
CA15-3 (U/mL), median (IQR)	19.7 (14.1–26.4)	20.3 (15.7–26.1)	0.35
CA19-9 (U/mL), median (IQR)	10.2 (5.7–19.0)	10.8 (7.1–20.6)	0.27

CEA (ng/mL), median (IQR)	2.4 (1.6–3.7)	2.5 (1.6–3.8)	0.75
CYFRA 21-1 (ng/mL), median (IQR)	2.0 (1.5–2.9)	2.3 (1.8–3.3)	0.017
AFP (IU/mL), median (IQR)	1.8 (1.1–2.9)	1.9 (1.1–2.6)	0.72

**Table S4** Differences in median tumor biomarker levels based on history of atrial fibrillation

History of atrial fibrillation	No (N=1130)	Yes (N=949)	P-value (Bonferroni corrected)
CA125 (U/mL), median (IQR)	30.4 (13.2 – 93.9)	39.9 (16.3 – 98.6)	0.006
CA15-3 (U/mL), median (IQR)	19.5 (14.1 – 25.8)	20.1 (14.1 – 27.2)	1.00
CYFRA (ng/mL), median (IQR)	2.0 (1.4 – 2.9)	2.1 (1.5 – 2.9)	0.90
CEA (ng/mL), median (IQR)	2.3 (1.6 – 3.6)	2.5 (1.7 – 3.8)	0.12
CA19-9 (U/mL), median (IQR)	9.2 (5.4 – 17.5)	11.3 (6.3 – 21.2)	<0.001
AFP (IU/mL), median (IQR)	1.8 (1.1 – 2.9)	1.8 (1.1 – 2.8)	1.00

**Table S5** Linear regression models for tumor biomarkers

	Univariable		Multivariable	
	Coefficient	P-value	Coefficient	P-value
CA125				
Age	- 0.000	0.845		
Sex	- 0.044	0.488		
BMI	- 0.018	0.000		
Ischemic etiology	- 0.121	0.029	- 0.297	0.017
NYHA class III/IV	+0.552	0.000		
LVEF	- 0.009	0.001		
Oedema	+0.712	0.000	+0.309	0.017
Systolic blood pressure	- 0.006	0.000		
Heart rate	+0.012	0.000		
Previous HF hospitalization in last year	- 0.061	0.301		
Hospitalization, type of visit	+0.470	0.000	+0.238	0.004

NT-proBNP	+0.454	0.000	+0.548	0.000
Troponin T	+0.001	0.985		
Hemoglobin	- 0.043	0.003	+0.079	0.014
Sodium	- 0.053	0.000	- 0.052	0.001
Potassium	- 0.161	0.001		
eGFR	+0.494	0.000		
Albumine	- 0.022	0.000		
BUN	+0.128	0.005		
CRP	+0.219	0.000		
HDL	- 0.536	0.000	- 0.255	0.028
IL-6	+0.364	0.000		
Leucocytes	+0.032	0.001		
ASAT	+0.409	0.000		
ALAT	+0.189	0.000		
γ-GT	+0.459	0.000		
Alkaline phosphatase	+0.488	0.000		
Atrial fibrillation	+0.155	0.005		
Diabetes mellitus	+0.097	0.097		
COPD	+0.046	0.526		
Renal disease	+0.289	0.000		
Smoking	+0.024	0.542		
Malignancy	+0.258	0.072		
Device therapy	- 0.037	0.112		
Loop diuretics	+0.367	0.376		
Beta-blockers	- 0.264	0.000		
ACE-inhibitors/ARB	- 0.156	0.010		
MRA	+0.042	0.437		
Oral anticoagulants	- 0.007	0.907		

CA15-3				
Age	+0.005	0.000	+0.004	0.006
Sex	+0.018	0.466		
BMI	- 0.002	0.341		
Ischemic etiology	+0.063	0.004		
NYHA class III/IV	+0.042	0.060		
LVEF	- 0.000	0.904		
Oedema	+0.026	0.283		
Systolic blood pressure	- 0.001	0.232		
Heart rate	- 0.001	0.038		
Previous HF hospitalization in last year	+0.055	0.017		
Hospitalization, type of visit	+0.000	0.979		
NT-proBNP	+0.009	0.559		
Troponin T	- 0.012	0.483		
Hemoglobin	- 0.014	0.014		
Sodium	- 0.013	0.000	- 0.013	0.001
Potassium	- 0.036	0.061	- 0.082	0.006
eGFR	- 0.000	0.998		
Albumine	- 0.000	0.830		
BUN	+0.080	0.000	+0.120	0.000
CRP	+0.028	0.003		
HDL	- 0.048	0.107		
IL-6	+0.025	0.018		
Leucocytes	- 0.005	0.223		
ASAT	+0.034	0.105		
ALAT	- 0.030	0.063		
$\gamma$ -GT	+0.009	0.601		
Alkaline phosphatase	+0.136	0.000	+0.149	0.000

Atrial fibrillation	+0.021	0.335		
Diabetes mellitus	+0.046	0.045		
COPD	- 0.011	0.704		
Renal disease	+0.117	0.000		
Smoking	- 0.003	0.854		
Malignancy	+0.067	0.228		
Device therapy	+0.020	0.026		
Loop diuretics	- 0.015	0.925		
Beta-blockers	- 0.013	0.648		
ACE-inhibitors/ARB	- 0.055	0.020		
MRA	+0.011	0.593		
Oral anticoagulants	+0.001	0.978		
CA19-9				
Age	+0.008	0.000		
Sex	- 0.034	0.565		
BMI	- 0.001	0.789		
Ischemic etiology	+0.084	0.114		
NYHA class III/IV	+0.177	0.001	+0.253	0.015
LVEF	+0.000	0.979		
Oedema	+0.332	0.000	+0.271	0.006
Systolic blood pressure	- 0.003	0.023		
Heart rate	+0.001	0.386		
Previous HF hospitalization in last year	+0.164	0.003		
Hospitalization, type of visit	+0.102	0.001		
NT-proBNP	+0.117	0.001		
Troponin T	+0.015	0.722		
Hemoglobin	- 0.025	0.076		
Sodium	- 0.024	0.000		

Potassium	- 0.095	0.042		
eGFR	+0.169	0.000	+0.207	0.007
Albumine	- 0.009	0.004		
BUN	+0.144	0.001		
CRP	+0.022	0.351		
HDL	- 0.020	0.783		
IL-6	+0.133	0.000		
Leucocytes	+0.004	0.679		
ASAT	+0.233	0.000	+0.274	0.012
ALAT	+0.044	0.259		
$\gamma$ -GT	+0.176	0.000		
Alkaline phosphatase	+0.215	0.008		
Atrial fibrillation	+0.212	0.000		
Diabetes mellitus	+0.211	0.000		
COPD	+0.061	0.376		
Renal disease	+0.187	0.001		
Smoking	- 0.051	0.179		
Malignancy	+0.145	0.289		
Device therapy	+0.041	0.069		
Loop diuretics	+0.624	0.114		
Beta-blockers	- 0.077	0.269		
ACE-inhibitors/ARB	- 0.081	0.162		
MRA	- 0.012	0.811		
Oral anticoagulants	+0.106	0.048		
CEA				
Age	+0.005	0.000		
Sex	- 0.037	0.279		
BMI	- 0.008	0.006	- 0.012	0.009

Ischemic etiology	+0.083	0.006		
NYHA class III/IV	+0.081	0.009		
LVEF	+0.001	0.579		
Oedema	+0.120	0.000	+0.167	0.004
Systolic blood pressure	- 0.000	0.662		
Heart rate	+0.002	0.030		
Previous HF hospitalization in last year	+0.055	0.088		
Hospitalization, type of visit	+0.033	0.058		
NT-proBNP	+0.049	0.017		
Troponin T	+0.023	0.291		
Hemoglobin	- 0.010	0.201		
Sodium	- 0.010	0.012		
Potassium	+0.024	0.363		
eGFR	+0.043	0.093		
Albumine	- 0.003	0.056		
BUN	+0.082	0.001		
CRP	+0.041	0.002		
HDL	+0.008	0.849		
IL-6	+0.080	0.000		
Leucocytes	+0.015	0.007	+0.017	0.049
ASAT	+0.068	0.022		
ALAT	- 0.006	0.799		
$\gamma$ -GT	+0.061	0.010		
Alkaline phosphatase	+0.047	0.315		
Atrial fibrillation	+0.069	0.022		
Diabetes mellitus	+0.034	0.287		
COPD	+0.194	0.000		
Renal disease	+0.109	0.001	+0.132	0.018



Smoking	+0.155	0.000	+0.127	0.001
Malignancy	+0.022	0.773		
Device therapy	+0.015	0.227		
Loop diuretics	+0.247	0.277		
Beta-blockers	- 0.082	0.040		
ACE-inhibitors/ARB	- 0.050	0.129		
MRA	- 0.016	0.602		
Oral anticoagulants	+0.024	0.430		
CYFRA 21-1				
Age	+0.014	0.000		
Sex	+0.036	0.195		
BMI	- 0.005	0.015	- 0.019	0.000
Ischemic etiology	+0.175	0.000		
NYHA class III/IV	+0.103	0.000		
LVEF	+0.007	0.000		
Oedema	+0.094	0.001		
Systolic blood pressure	+0.001	0.208		
Heart rate	- 0.003	0.000		
Previous HF hospitalization in last year	+0.114	0.000		
Hospitalization, type of visit	+0.013	0.369		
NT-proBNP	+0.077	0.000		
Troponin T	+0.085	0.000		
Hemoglobin	- 0.080	0.000	- 0.052	0.002
Sodium	- 0.005	0.099		
Potassium	+0.071	0.001		
eGFR	- 0.003	0.877		
Albumine	- 0.007	0.000		
BUN	+0.208	0.000	+0.164	0.003

CRP	+0.009	0.414		
HDL	+0.006	0.868		
IL-6	+0.071	0.000		
Leucocytes	+0.014	0.002	+0.024	0.005
ASAT	- 0.053	0.030		
ALAT	- 0.109	0.000		
$\gamma$ -GT	- 0.024	0.231		
Alkaline phosphatase	+0.066	0.084		
Atrial fibrillation	+0.040	0.106		
Diabetes mellitus	+0.194	0.000		
COPD	+0.122	0.000		
Renal disease	+0.330	0.000	+0.175	0.017
Smoking	- 0.049	0.006		
Malignancy	+0.139	0.030	+0.298	0.015
Device therapy	+0.016	0.127		
Loop diuretics	+0.113	0.567		
Beta-blockers	- 0.023	0.482		
ACE-inhibitors/ARB	- 0.108	0.000	- 0.143	0.026
MRA	- 0.060	0.015		
Oral anticoagulants	- 0.015	0.550		
AFP				
Age	- 0.006	0.000		
Sex	+0.218	0.000		
BMI	- 0.018	0.000	- 0.026	0.001
Ischemic etiology	- 0.162	0.000	- 0.266	0.003
NYHA class III/IV	- 0.093	0.004		
LVEF	- 0.005	0.003		
Oedema	- 0.037	0.286		

Systolic blood pressure	- 0.000	0.513		
Heart rate	+0.003	0.001		
Previous HF hospitalization in last year	- 0.166	0.000		
Hospitalization, type of visit	- 0.050	0.005		
NT-proBNP	+0.010	0.655		
Troponin T	- 0.059	0.021		
Hemoglobin	+0.071	0.000	+0.057	0.016
Sodium	+0.001	0.843		
Potassium	- 0.027	0.329		
eGFR	- 0.011	0.688		
Albumine	+0.006	0.000		
BUN	- 0.228	0.000		
CRP	- 0.053	0.000	- 0.099	0.021
HDL	+0.198	0.000		
IL-6	- 0.074	0.000		
Leucocytes	- 0.004	0.465		
ASAT	+0.216	0.000		
ALAT	+0.152	0.000		
$\gamma$ -GT	+0.126	0.000		
Alkaline phosphatase	+0.086	0.075		
Atrial fibrillation	- 0.031	0.325		
Diabetes mellitus	- 0.330	0.000		
COPD	- 0.098	0.018		
Renal disease	- 0.221	0.000		
Smoking	+0.009	0.693		
Malignancy	- 0.009	0.911		
Device therapy	- 0.029	0.028		
Loop diuretics	+0.207	0.384		

Beta-blockers	- 0.041	0.326		
ACE-inhibitors/ARB	+0.051	0.144		
MRA	- 0.016	0.614		
Oral anticoagulants	+0.035	0.276		

ACE: angiotensin converting enzyme; ALAT: alanine transaminase; ARB: angiotensin receptor blocker; ASAT: aspartate transaminase; BMI: body mass index; BUN: blood urea nitrogen; COPD: chronic obstructive pulmonary disease; CRP: c-reactive protein; eGFR: estimated glomerular filtration rate;  $\gamma$ -GT:  $\gamma$ -glutamyl transpeptidase; HDL: High-density lipoprotein; IL-6: Interleukin 6; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; MRA: mineralocorticoid receptor antagonist

**Table S6** Cox regression analysis for secondary outcomes

	Univariable		Multivariable		
	(S)HR* (95% CI)	P-value	(S)HR* (95% CI)	P-value	Harrell's C
<b>CA125</b>					
Composite endpoint	1.20 (1.15 – 1.24)	<0.001	1.13 (1.08 – 1.17)	<0.001	0.69
HF hospitalization	1.13 (1.08 – 1.18)	<0.001	1.10 (1.05 – 1.15)	<0.001	
CV mortality	1.22 (1.16 – 1.28)	<0.001	1.15 (1.08 – 1.22)	<0.001	
Non-CV mortality	1.16 (1.06 – 1.28)	0.002	1.12 (1.00 – 1.25)	0.047	
<b>CA15-3</b>					
Composite endpoint	1.25 (1.13 – 1.38)	<0.001	1.12 (1.02 – 1.24)	0.023	0.69
HF hospitalization	1.17 (1.03 – 1.34)	0.015	1.07 (0.94 – 1.21)	0.339	
CV mortality	1.30 (1.11 – 1.52)	0.001	1.13 (0.96 – 1.33)	0.140	
Non-CV mortality	1.32 (1.00 – 1.75)	0.055	1.19 (0.89 – 1.58)	0.247	
<b>CA19-9</b>					
Composite endpoint	1.12 (1.07 – 1.16)	<0.001	1.05 (1.01 – 1.09)	0.023	0.69
HF hospitalization	1.07 (1.01 – 1.13)	0.019	1.02 (0.96 – 1.07)	0.551	

CV mortality	1.16 (1.08 – 1.26)	<0.001	1.08 (1.01 – 1.16)	0.024	
Non-CV mortality	1.35 (1.18 – 1.54)	<0.001	1.28 (1.12 – 1.46)	<0.001	
CYFRA 21-1					
Composite endpoint	1.64 (1.51 – 1.77)	<0.001	1.36 (1.25 – 1.48)	<0.001	0.69
HF hospitalization	1.29 (1.17 – 1.42)	<0.001	1.08 (0.97 – 1.20)	0.155	
CV mortality	1.62 (1.42 – 1.84)	<0.001	1.26 (1.09 – 1.46)	0.002	
Non-CV mortality	1.72 (1.43 – 2.07)	<0.001	1.48 (1.23 – 1.79)	<0.001	
CEA					
Composite endpoint	1.25 (1.17 – 1.34)	<0.001	1.15 (1.07 – 1.23)	<0.001	0.69
HF hospitalization	1.12 (1.03 – 1.22)	0.012	1.05 (0.96 – 1.15)	0.263	
CV mortality	1.30 (1.17 – 1.45)	<0.001	1.18 (1.06 – 1.32)	0.003	
Non-CV mortality	1.22 (1.00 – 1.49)	0.051	1.12 (0.93 – 1.37)	0.222	
AFP					
Composite endpoint	0.87 (0.82 – 0.93)	<0.001	0.96 (0.89 – 1.02)	0.206	0.69
HF hospitalization	0.90 (0.83 – 0.97)	0.010	0.97 (0.90 – 1.05)	0.492	
CV mortality	0.88 (0.79 – 0.97)	0.010	0.96 (0.88 – 1.07)	0.538	
Non-CV mortality	1.01 (0.81 – 1.28)	0.902	1.16 (0.93 – 1.43)	0.185	

\* Hazard ratio (HR) for the composite endpoint of all-cause mortality and HF hospitalization, subhazard ratio (SHR) for HF hospitalization, CV mortality and non-CV mortality.

Multivariable models corrected as follows:

- Composite endpoint: age, previous hospitalization, presence of oedema, NT-proBNP, systolic blood pressure at baseline, hemoglobin, HDL levels, sodium, beta-blocker
- HF hospitalization: age, previous HF hospitalization, presence of edema at baseline, systolic blood pressure at baseline, and eGFR
- CV mortality: age, BUN, NT-proBNP, troponin T, and sodium
- Non-CV mortality: age, hemoglobin, CRP, and history of malignancy