

Supplementary Material

Heart failure with improved versus persistently reduced left ventricular ejection fraction: a comparison of the BIOSTAT-CHF (European) and ASIAN-HF Registry

Authors

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Supplementary Table S1: Baseline characteristics of patients with HF that were included and excluded in BIOSTAT-CHF.

Characteristics	Baseline		
	Included (n = 826)	Excluded (n = 1690)	P value
Age (years)	65.8 ± 11.9	70.5 ± 11.7	<0.001
Male sex, n (%)	647 (78.3)	1199 (70.9)	<0.001
Medical history			
Hypertension, n (%)	501 (60.7)	1068 (63.2)	0.217
Ischemic heart disease, n (%)	350 (42.4)	781 (46.2)	0.069
Valvular surgery, n (%)	57 (6.9)	122 (7.2)	0.771
Atrial fibrillation, n (%)	303 (36.7)	840 (49.7)	<0.001
Diabetes mellitus, n (%)	232 (28.1)	587 (34.7)	<0.001
Stroke, n (%)	64 (7.7)	169 (10.0)	0.067
Peripheral arterial disease, n (%)	66 (8.0)	207 (12.2)	0.001
COPD, n (%)	125 (15.1)	311 (18.4)	0.042
HF hospitalisation in last year, n (%)	251 (30.4)	543 (32.1)	0.377
Clinical profile			
Heart rate (bpm)	79.0 ± 18.9	80.4 ± 19.8	0.047
Systolic blood pressure (mm Hg)	124.5 ± 20.5	124.8 ± 22.6	0.385
Diastolic blood pressure (mm Hg)	76.8 ± 12.3	74.0 ± 13.8	<0.001
BMI (kg/m ²)	27.7 ± 5.0	28.0 ± 5.7	0.082
NYHA class III/IV, n (%)	417 (51.1)	1105 (67.8)	<0.001
Orthopnoea, n (%)	191 (23.2)	688 (40.8)	<0.001
Pulmonary rales, n (%)	357 (44.2)	934 (57.1)	<0.001
Peripheral oedema, n (%)	329 (49.8)	927 (64.4)	<0.001
Jugular venous pressure, n (%)	141 (24.9)	413 (38.0)	<0.001
Third heart sound, n (%)	80 (9.7)	167 (9.9)	0.895
Hepatomegaly, n (%)	124 (15.0)	234 (13.9)	0.445
Echocardiography			
LVEF (%)	28.2 ± 7.1	32.7 ± 11.9	<0.001
LVED diameter (mm)	63.4 ± 8.4	59.8 ± 10.3	<0.001

LVES diameter (mm)	51.9 ± 9.6	48.7 ± 12.3	<0.001
Left atrial diameter (mm)	47.0 ± 7.9	47.6 ± 8.1	0.077
ECG			
LBBB (%)	181 (22.2)	373 (22.3)	0.919
RBBB (%)	56 (6.9)	154 (9.2)	0.046
LVH (%)	103 (12.6)	250 (15.0)	0.109
Laboratory			
Serum creatinine (µmol/L)	97.2 (80.2-23.0)	105.0 (86.0-133.0)	<0.001
Blood urea (mmol/L)	10.8 (7.4-16.8)	11.7 (7.7-18.9)	0.007
eGFR (ml/min ⁻¹)	139.7 ± 3.8	138.9 ± 4.1	<0.001
Sodium (mEq/L)	4.3 ± 0.5	4.3 ± 0.6	<0.001
Potassium (mEq/L)	6.8 ± 2.7	7.4 ± 3.2	0.180
Glucose (mg/dL)	6.5 ± 1.5	6.7 ± 1.4	<0.001
HbA1c (%)	4.5 ± 1.3	4.1 ± 1.3	0.180
Total cholesterol (mmol/L)	1.1 ± 0.4	1.1 ± 0.4	<0.001
LDL cholesterol (mmol/L)	2.7 ± 1.0	2.5 ± 1.1	0.002
HDL cholesterol (mmol/L)	1.5 ± 1.0	1.4 ± 1.1	0.074
Triglycerides	13.5 ± 1.8	13 ± 1.9	0.112
Hemoglobin (g/dL)	4.5 ± 0.7	4.4 ± 0.7	<0.001
Red blood cell count (million per mm ³)	8.1 ± 2.8	8.4 ± 3.0	<0.001
White blood cell count (1000 per mm ³)	227.2 ± 83.2	226.3 ± 92.3	0.039
Platelet count (1000 per mm ³)	139.7 ± 3.8	138.9 ± 4.1	0.826
Total bilirubin (µmol/L)	12.9 (9.2-18.6)	15.0 (10.1-23.0)	<0.001
ASAT (U/L)	24.0 (18.0-34.0)	26.0 (20.0-36.0)	<0.001
ALAT (U/L)	25.0 (17.6-39.0)	25.0 (16.0-37.0)	0.227
Gamma GT (U/L)	44.0 (26.0-84.0)	63.0 (30.0-123.0)	<0.001
Alkaline phosphatase (µg/L)	80.0 (62.0-116.0)	87.0 (68.8-119.0)	0.011
TSH (mU/L)	1.8 (1.1-2.9)	1.9 (1.2-3.1)	0.159
FT4 (pmol/L)	15.6 ± 6.9	17.8 ± 7.9	<0.001
Troponin I (µg/L)	0.03 (0.01-0.10)	0.04 (0.02-0.11)	0.009
Troponin T (µg/L)	0.03 (0.02-0.05)	0.03 (0.02-0.06)	0.110
NT-proBNP (pg/mL)	3561 (1771.3-	4448 (2547.8-	<0.001

	7328.8)	8845.3)	
Medication			
ACEi/ARB, n (%)	656 (79.4)	1164 (68.9)	<0.001
Beta-blocker, n (%)	705 (85.4)	1388 (82.1)	0.042
MRA, n (%)	464 (56.2)	875 (51.8)	0.038
Loop diuretics, n (%)	823 (99.6)	1681 (99.5)	0.563
Digoxin, n (%)	141 (17.1)	350 (20.7)	0.031

ACEi, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **AST**, aspartate transaminase; **ALT**, alanine transaminase; **BMI**, body mass index; **BNP**, brain natriuretic peptide; **COPD**, chronic obstructive pulmonary disease; **ECG**:

Electrocardiography; **eGFR**, estimated glomerular filtration rate; **FT4**, free thyroxine;

HbA1c, glycated hemoglobin; **HDL**, high density lipoprotein; **HFimpEF**, heart failure with improved ejection fraction; **HFrefEF**, heart failure with reduced ejection fraction; **IHD**:

ischemic heart disease; **LBBB**, left bundle branch block; **LDL**, low density lipoprotein;

LVED, left ventricular end diastolic; **LVEF**, left ventricular ejection fraction; **LVES**, left

ventricular end systolic; **MRA**, mineralocorticoid receptor antagonist; **NT-proBNP**, NT-pro brain natriuretic peptide; **NYHA**, New York Heart Association; **RBBB**, right bundle branch

block; **TSH**, thyroid stimulating hormone; **LVH**, left ventricular hypertrophy.

Values are means \pm standard deviations (SD), medians (IQR, interquartile range [25th to 75th percentile range]) or numbers (percentages).

Supplementary Table S2: Baseline characteristics of patients with HF that were included and excluded in ASIAN-HF.

Characteristics	Baseline		
	Included (n =499)	Excluded (n =3803)	P value
Age (years)	62.1 ± 13.6	60.3 ± 13.0	0.003
Male sex, n (%)	373 (74.7)	2941 (77.3)	0.200
Medical history			
Hypertension, n (%)	245 (49.1)	1953 (51.4)	0.340
Ischemic heart disease, n (%)	192 (38.5)	1973 (51.9)	<0.001
Atrial fibrillation, n (%)	149 (29.9)	609 (16.0)	<0.001
Diabetes mellitus, n (%)	174 (34.9)	1559 (41.0)	0.009
Stroke, n (%)	42 (8.4)	225 (5.9)	0.030
Peripheral arterial disease, n (%)	13 (2.6)	106 (2.8)	0.820
COPD, n (%)	51 (10.2)	283 (7.4)	0.029
HF hospitalisation in last year, n (%)	334 (66.9)	2231 (58.7)	0.002
Clinical profile			
BMI (kg/m ²)	23.9 ± 4.7	25.1 ± 5.5	<0.001
NYHA class III/IV, n (%)	129 (29.5)	1098 (32.0)	0.270
Heart rate (bpm)	77.8 ± 15.7	80.2 ± 16.3	0.002
Systolic blood pressure (mm Hg)	115.3 ± 19.3	119.0 ± 20.3	<0.001
Diastolic blood pressure (mm Hg)	68.9 ± 12.1	73.0 ± 12.7	<0.001
Orthopnoea, n (%)	73 (14.8)	783 (20.8)	0.002
Pulmonary rales, n (%)	47 (9.4)	610 (16.0)	<0.001
Peripheral oedema, n (%)	102 (20.4)	863 (22.7)	0.260
Jugular venous pressure, n (%)	54 (10.8)	588 (15.5)	0.006
Third heart sound, n (%)	56 (11.2)	394 (10.4)	0.550
Hepatomegaly, n (%)	30 (6.0)	193 (5.1)	0.370
Echocardiography			
LVEF (%)	27.3 ± 7.1	27.3 ± 7.1	0.900
LVED diameter (mm)	62.3 ± 9.7	60.8 ± 10.1	0.003
LVES diameter (mm)	53.3 ± 10.6	51.7 ± 11.1	0.006
Left atrial volume (ml)	97.0 ± 67.4	64.8 ± 38.4	<0.001

ECG			
LBBB (%)	47 (9.7)	520 (14.5)	0.004
RBBB (%)	31 (6.4)	335 (9.4)	0.033
LVH (%)	97 (20.1)	918 (25.6)	0.009
Laboratory			
eGFR (ml/min ⁻¹)	66.0 (46.1-82.8)	62.4 (43.6-82.7)	0.210
Sodium (mEq/L)	139.0 (137.0-141.0)	138 (136.0-141.0)	<0.001
Potassium (mEq/L)	4.3 (3.9-4.6)	4.2 (3.9-4.6)	0.200
Hemoglobin (g/dL)	13.3 (11.7-14.6)	13.0 (11.5-14.4)	0.009
Medication			
ACEi/ARB, n (%)	410 (82.2)	2860 (76.2)	0.003
Beta-blocker, n (%)	446 (89.4)	2839 (75.7)	<0.001
MRA, n (%)	313 (62.7)	2170 (57.8)	0.037
Loop diuretics, n (%)	375 (77.8)	2913 (80.7)	0.130
Digoxin, n (%)	103 (21.4)	941 (26.1)	0.026

ACEi, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **BMI**, body mass index; **COPD**, chronic obstructive pulmonary disease; **ECG**:

Electrocardiography: **eGFR**, estimated glomerular filtration rate; **HFimpEF**, heart failure with improved ejection fraction; **HF_rEF**, heart failure with reduced ejection fraction; **LBBB**, left bundle branch block; **LVED**, left ventricular end diastolic; **LVEF**, left ventricular ejection fraction; **LVES**, left ventricular end systolic; **MRA**, mineralocorticoid receptor antagonist; New York Heart Association; **RBBB**, right bundle branch block; **LVH**, left ventricular hypertrophy.

Values are means ± standard deviations (SD), medians (IQR, interquartile range [25th to 75th percentile range]) or numbers (percentages).

Supplementary Table S3: Cardiovascular and non-cardiovascular mortality rates in patients with HFimpEF and persistent HFrefEF in BIOSTAT-CHF and ASIAN-HF.

Event	HFimpEF	HFrefEF	P value
BIOSTAT-CHF			
CV death	7 (4.6%)	70 (10.4%)	<0.001
Non-CV death	4 (2.6%)	27 (4.0%)	<0.001
ASIAN-HF			
CV death	7 (4.9%)	39 (10.9%)	0.037
Non-CV death	0 (0%)	9 (2.5%)	0.056

Supplementary Table S4: Baseline characteristics of patients with HF in comparisons between HFimpEF and persistent HFrEF in ASIAN-HF.

Characteristics	Baseline		
	HFimpEF (n =142)	Persistent HFrEF (n =357)	P value
Age (years)	60.5 (15.0)	62.8 (13.0)	0.091
Male sex, n (%)	96 (67.6)	277 (77.6)	0.021
Medical history			
Hypertension, n (%)	85 (59.9)	160 (44.8)	0.002
Ischemic heart disease, n (%)	38 (26.8)	154 (43.1)	<0.001
Atrial fibrillation, n (%)	35 (24.6)	114 (31.9)	0.110
Diabetes mellitus, n (%)	41 (28.9)	133 (37.3)	0.076
Stroke, n (%)	9 (6.3)	33 (9.2)	0.290
Peripheral arterial disease, n (%)	5 (3.5)	8 (2.2)	0.420
COPD, n (%)	17 (12.0)	34 (9.5)	0.420
HF hospitalisation in last year, n (%)	73 (51.4)	261 (73.1)	<0.001
Clinical profile			
BMI (kg/m ²)	24.1 (4.8)	23.8 (4.7)	0.580
NYHA class III/IV, n (%)	31 (24.0)	98 (31.7)	0.110
Heart rate (bpm)	79.7 (16.3)	77.1 (15.4)	0.089
Systolic blood pressure (mm Hg)	119.6 (20.0)	113.6 (18.7)	0.002
Diastolic blood pressure (mm Hg)	71.4 (12.8)	67.9 (11.7)	0.004
Orthopnoea, n (%)	16 (11.3)	57 (16.2)	0.170
Pulmonary rales, n (%)	9 (6.3)	38 (10.6)	0.140
Peripheral oedema, n (%)	26 (18.3)	76 (21.3)	0.460
Jugular venous pressure, n (%)	9 (6.3)	45 (12.6)	0.042
Third heart sound, n (%)	13 (9.2)	43 (12.0)	0.360
Hepatomegaly, n (%)	7 (4.9)	23 (6.4)	0.520
Echocardiography			
LVEF (%)	29.1 (6.7)	26.6 (7.2)	<0.001
LVED diameter (mm)	59.0 (9.2)	63.7 (9.6)	<0.001
LVES diameter (mm)	49.1 (10.0)	55.0 (10.3)	<0.001
Left atrial volume (ml)	92.1 (63.6)	98.2 (68.3)	0.580

ECG			
LBBB (%)	9 (6.5)	38 (10.9)	0.140
RBBB (%)	5 (3.6)	26 (7.5)	0.120
LVH (%)	35 (25.4)	62 (18.0)	0.069
Laboratory			
eGFR (ml/min ⁻¹)	69.8 (54.1-85.0)	63.0 (43.6-81.9)	0.031
Sodium (mEq/L)	139.0 (138.0-141.0)	139.0 (137.0-141.0)	0.890
Potassium (mEq/L)	4.3 (3.9-4.6)	4.3 (4.0-4.6)	0.910
Hemoglobin (g/dL)	13.4 (11.6-15.0)	13.3 (11.8-14.6)	0.240
Medication			
ACEi/ARB, n (%)	122 (85.9)	288 (80.7)	0.170
Beta-blocker, n (%)	126 (88.7)	320 (89.6)	0.770
MRA, n (%)	77 (54.2)	236 (66.1)	0.013
Loop diuretics, n (%)	88 (66.2)	287 (82.2)	<0.001
Digoxin, n (%)	17 (12.8)	86 (24.6)	0.005

ACEi, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **BMI**, body mass index; **COPD**, chronic obstructive pulmonary disease; **ECG**:

Electrocardiography: **eGFR**, estimated glomerular filtration rate; **HFimpEF**, heart failure with improved ejection fraction; **HF_rEF**, heart failure with reduced ejection fraction; **LBBB**, left bundle branch block; **LVED**, left ventricular end diastolic; **LVEF**, left ventricular ejection fraction; **LVES**, left ventricular end systolic; **MRA**, mineralocorticoid receptor antagonist; New York Heart Association; **RBBB**, right bundle branch block; **LVH**, left ventricular hypertrophy.

Values are means ± standard deviations (SD), medians (IQR, interquartile range [25th to 75th percentile range]) or numbers (percentages).

Supplementary Table S5: Predictors of HFimpEF in patients with HFrEF at baseline in ASIAN-HF.

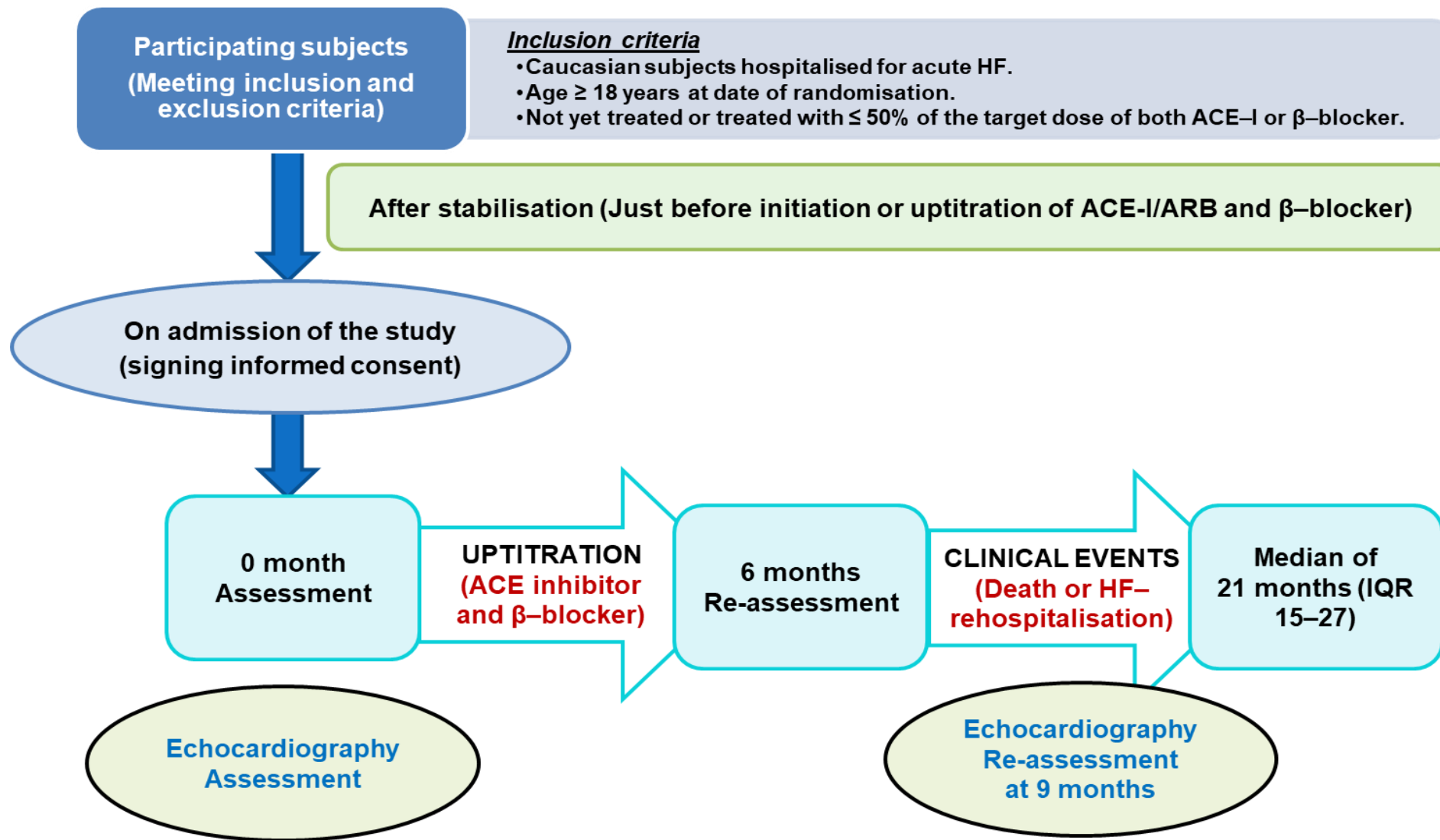
Predictors	OR	95% CI	P value*
Sex (Female) [#]	1.986	1.244 - 3.170	0.004
Hypertension	2.512	1.590 - 3.967	<0.001
Ischemic heart disease [#]	0.508	0.308 - 0.838	0.008
HF hospitalisation in last year	0.363	0.232 - 0.567	<0.001
Systolic blood pressure	1.020	1.009 - 1.031	<0.001
Diastolic blood pressure	1.025	1.007 - 1.043	0.006
LVEF [#]	1.050	1.017 - 1.084	0.003
LVED diameter [#]	0.941	0.914 - 0.968	<0.001
LVES diameter [#]	0.933	0.908 - 0.959	<0.001
MRA [#]	0.548	0.350 - 0.856	0.008
Loop diuretics	0.446	0.275 - 0.723	0.001
Digoxin	0.401	0.217 - 0.741	0.004

CI, 95% confidence interval; **LVED**, left ventricular end diastolic; **LVEF**, left ventricular ejection fraction; **LVES**, left ventricular end systolic;

MRA, mineralocorticoid receptor antagonist; **OR**, odds ratio.

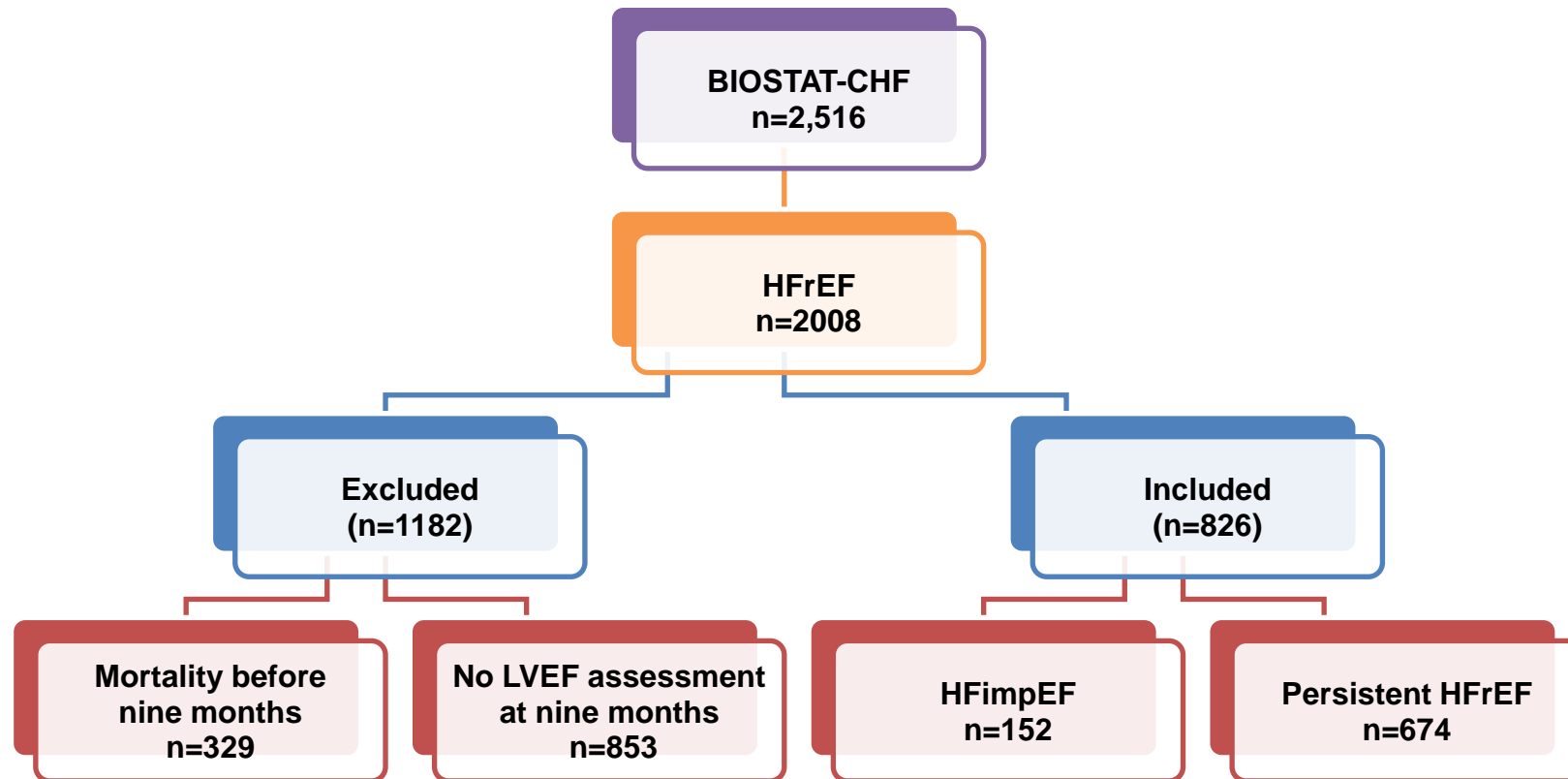
*Multivariable model: adjusted for age, sex, ischemic heart disease, systolic blood pressure, diabetes mellitus and eGFR.

[#]Predictors presented in the BIOSTAT-CHF cohort. **Supplementary Figure S1: Overall study design of BIOSTAT-CHF.**



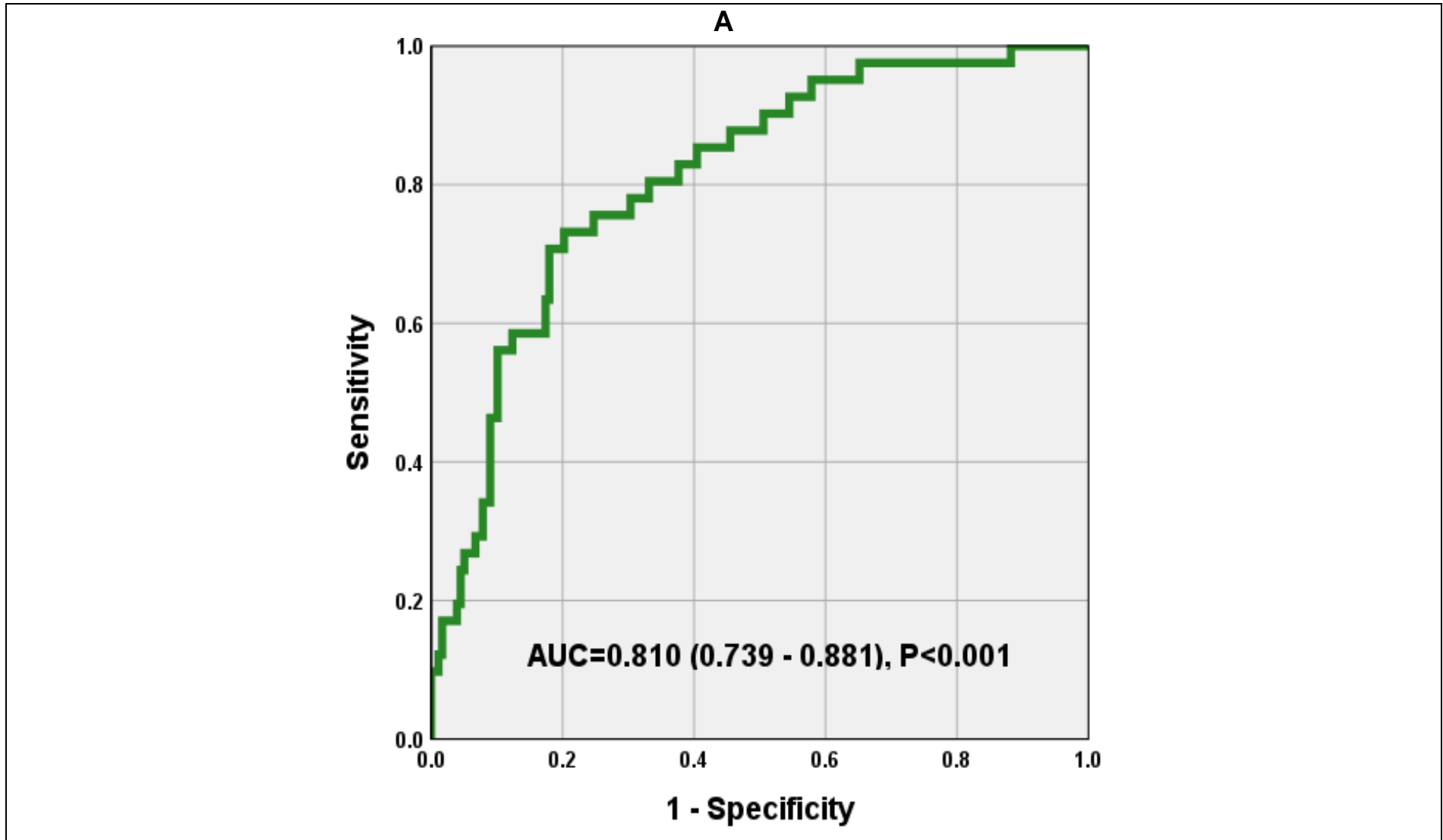
ACEi, angiotensin converting enzyme inhibitor; **ARB**, angiotensin receptor blocker; **BIOSTAT-CHF**, the BIOlogy Study to TAilored Treatment in Chronic Heart Failure; **HF**, heart failure.

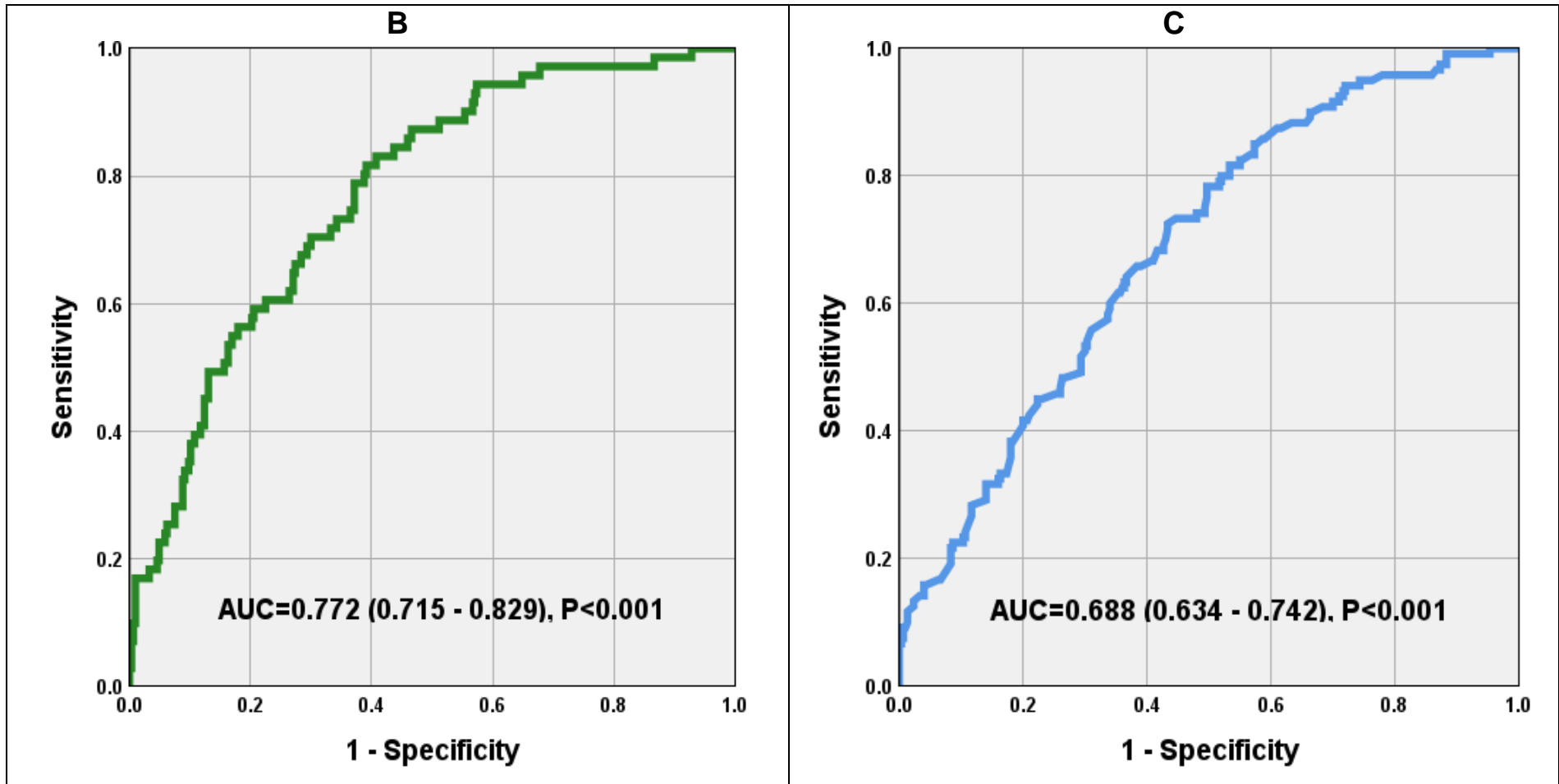
Supplementary Figure S2: Flow diagram of selected patients.

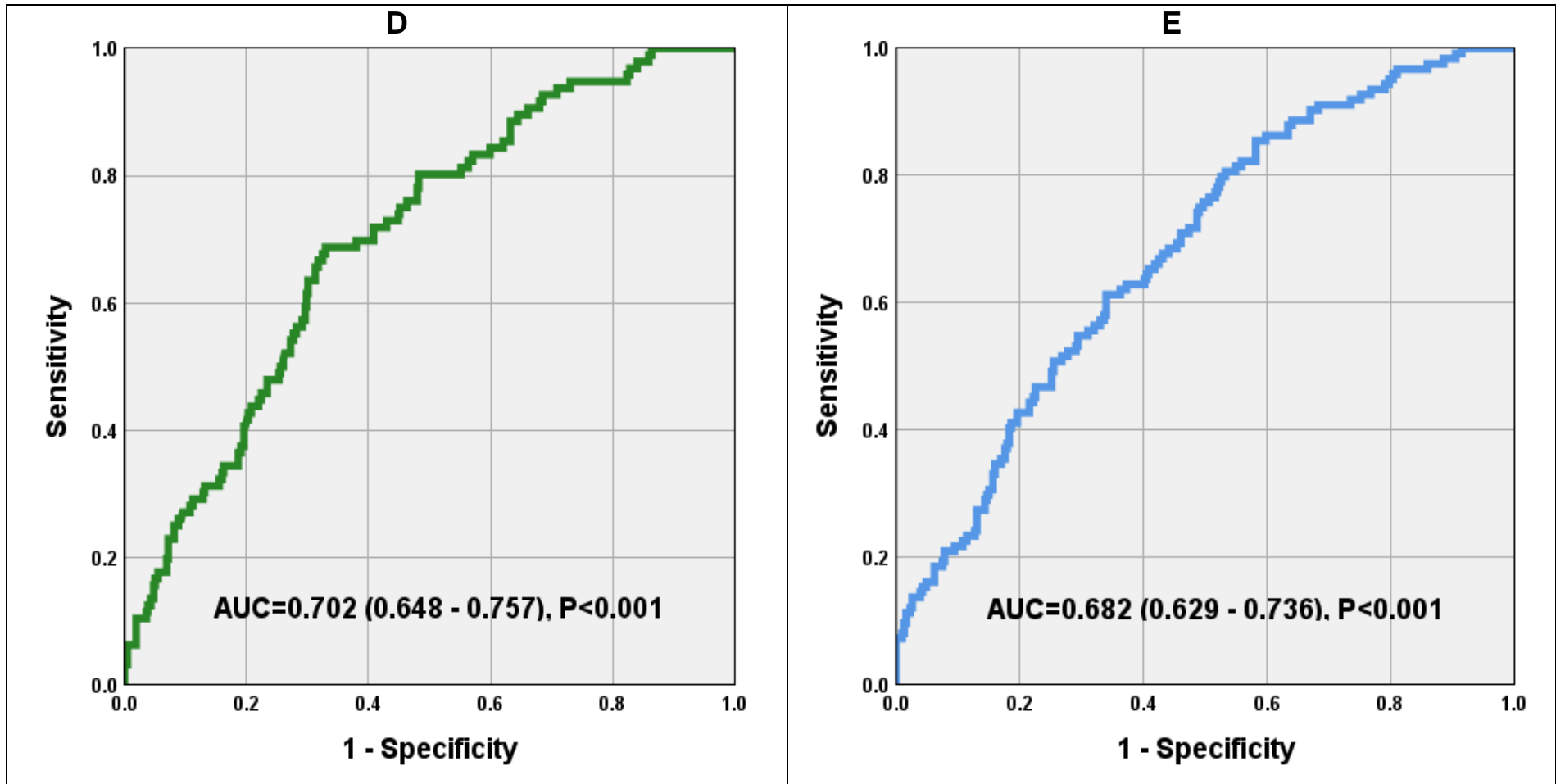


BIostat-CHF, the BIOlogy Study to Tailored Treatment in Chronic Heart Failure; **LVEF**, left ventricular ejection fraction; **HFimpEF**, heart failure with improved ejection fraction; **HFrEF**, heart failure with reduced ejection fraction.

Supplementary Figure S3: Predictive models of HFimpEF in patients who had HF rEF at baseline in BIOSTAT-CHF and ASIAN-HF.







A: Receiver operating characteristic (ROC) curve of the model in combining ten clinical predictors (including sex, IHD, HR, LVEF, LVED diameter, LVES diameter, LA diameter, LBBB, platelet count, Gamma GT) for prediction of HFimpEF in patients who had HFrEF at baseline in BIOSTAT-CHF.

B: Receiver operating characteristic (ROC) curve of the model in combining five clinical predictors (including absence of IHD, smaller LVES diameter, smaller LA diameter, absence of LBBB and higher platelet count) for prediction of HFimpEF in patients who had HFrEF at baseline in BIOSTAT-CHF.

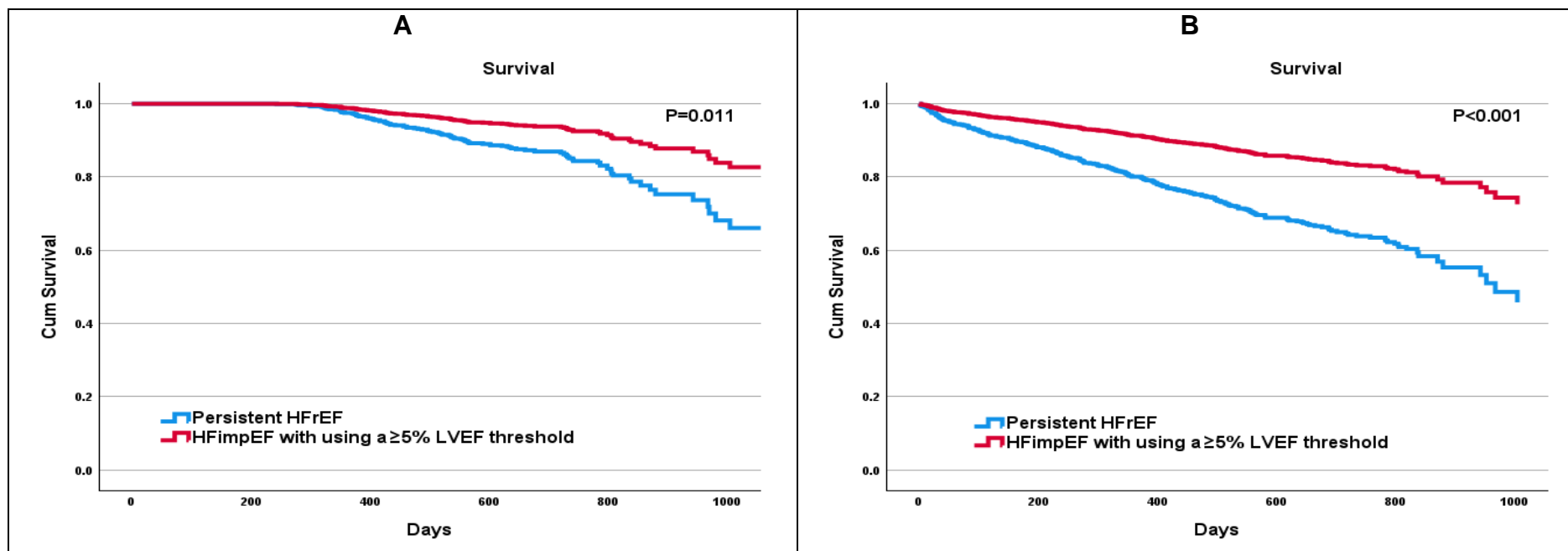
C: Receiver operating characteristic (ROC) curve of the model in combining only three clinical predictors (including absence of IHD, smaller LVES diameter and absence of LBBB with missing smaller LA diameter and higher platelet count) for prediction of HFimpEF in patients who had HFrEF at baseline in ASIAN-HF Registry).

D: Receiver operating characteristic (ROC) curve of the model in combining five common predictors (including female sex, absence of IHD, higher LVEF, smaller LVED and LVES diameter) for prediction of HFimpEF in patients who had HFrEF at baseline in BIOSTAT-CHF.

E: Receiver operating characteristic (ROC) curve of the model in combining five common predictors (including female sex, absence of IHD, higher LVEF, smaller LVED and LVES diameter) for prediction of HFimpEF in patients who had HFrEF at baseline in ASIAN-HF Registry.

AUC, area under the receiver operating characteristic curve; **HFimpEF**, heart failure with improved ejection fraction; **HFrEF**, heart failure with reduced ejection fraction.

Supplementary Figure S4: Clinical outcomes according to HFimpEF (using the 5% LVEF threshold for the HFimpEF classification) and persistent HFrEF in BIOSTAT-CHF.



- A.** Cox regression survival curves for all-cause mortality according to HFimpEF (using the 5% LVEF threshold for the HFimpEF classification) and persistent HFrEF.
- B.** Cox regression survival curves for the composite of HF rehospitalisation or all-cause mortality according to HFimpEF (using the 5% LVEF threshold for the HFimpEF classification) and persistent HFrEF.

HFimpEF, heart failure with improved ejection fraction; **HFrEF**, heart failure with reduced ejection fraction.