SUPPLEMENTAL MATERIAL
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Figure S1. Study patient population development flow chart.

Enrolled 4907 patients admitted primarily for heart failure

Excluded:
32 died during the index hospitalization
9 loss to follow-up
173 lacked baseline blood samples for central assay

4693 patients in evaluating clinical outcomes

Developing cohort: 2344 patients (development of multi-biomarker panel)
Validating cohort: 2349 patients (evaluation of clinical outcome risks)

Excluded:
558 missing KCCQ scores at 6-month interview
236 due to deaths
322 due to incomplete questionnaires

Validating cohort: 1791 patients (evaluation of quality of life)
| Local collaborate center                                           | Number of patients |
|------------------------------------------------------------------|--------------------|
| The First Affiliated Hospital of University of South China       | 388                |
| Affiliated Hospital of Jining Medical University                 | 384                |
| Xinxiang Central Hospital                                        | 289                |
| Hulunbeier People's Hospital                                     | 274                |
| The Second Hospital of Shanxi Medical University                 | 188                |
| The First Affiliated Hospital of Xi'an Jiaotong University       | 186                |
| Xinmin Peoples' Hospital                                         | 186                |
| The Affiliated People Hospital of Inner Mongolia Medical University | 181                |
| Benxi Jinshan Hospital                                           | 169                |
| The First Hospital of Jilin University                           | 168                |
| Affiliated Zhongshan Hospital of Dalian University               | 157                |
| Shanxi Fenyang Hospital                                          | 145                |
| Luoyang Dongfang Hospital                                       | 133                |
| First Affiliated Hospital of Kunming Medical University          | 119                |
| The Second Affiliated Hospital of Baotou Medical College         | 111                |
| The First Affiliated Hospital of Zhengzhou University            | 109                |
| Guangdong General Hospital                                       | 94                 |
| The First Affiliated Hospital of Hebei North University          | 91                 |
| Inner Mongolia People's Hospital                                 | 88                 |
| Fuwai Hospital                                                   | 85                 |
| Name                                                                 | Rank |
|----------------------------------------------------------------------|------|
| AVIC 363 Hospital                                                     | 81   |
| Qinghai Cardiovascular and Cerebrovascular Hospital                  | 78   |
| The Center Hospital of Maanshan                                       | 78   |
| Qingdao Fuwai Hospital                                               | 74   |
| The Second Affiliated Hospital of GZMU                                | 73   |
| Taizhou Hospital of Zhejiang Province                                 | 72   |
| Qinyang People’s Hospital                                            | 61   |
| Nanchong Central Hospital                                            | 54   |
| Xiamen Cardiovascular Hospital Xiamen University                      | 43   |
| People's Government of Tibetan Autonomous Region                     | 35   |
| Shenyang the Fourth Hospital of People                                | 35   |
| The Second Affiliated Hospital of Xuzhou Medical University           | 34   |
| Ningbo First Hospital                                                | 33   |
| Brain Hospital of Hunan Province                                     | 32   |
| Beijing Liangxiang Hospital                                          | 31   |
| Beijing Chaoyang Hospital, Capital Medical University                 | 31   |
| Quwo County People's Hospital                                        | 31   |
| Inner Mongolia Autonomous Region Hospital of Traditional Chinese Medicine | 30   |
| China-Japan Union Hospital of Jilin University                       | 27   |
| Central Hospital of Shenyang Sujiatun District                       | 26   |
| Baogang Hospital                                                     | 22   |
| The People's Hospital of Guangxi Zhuang Autonomous Region            | 22   |
| Hospital Name                                      | Number |
|---------------------------------------------------|--------|
| Shenyang First People's Hospital                  | 21     |
| Xi’an No.1 Hospital                               | 21     |
| International Mongolia Hospital of Inner Mongolia  | 18     |
| Puyang Oilfield General Hospital                  | 15     |
| The First Affiliated Hospital of Chongqing Medical University | 15     |
| Zhejiang Hospital                                 | 14     |
| The Affiliated Yueqing Hospital of Wenzhou Medical University | 13     |
| The Affiliated Hospital of Xuzhou Medical University | 12     |
| Taiyuan City Central Hospital                     | 9      |
| Anshan Changda Hospital                           | 7      |
Data S1. Methods of biomarker assays.

N-terminal pro-B type natriuretic peptide (NT-proBNP)

NT-proBNP was measured using the Roche E601. The limit of detection was 5 ng/L. The intra-assay coefficient of variation was $\leq 3.25\%$, and the inter-assay coefficient of variation was $\leq 8\%$.

High sensitivity Troponin T (hs-cTNT)

Hs-cTNT was measured using the Roche E601. The limit of detection was 3 ng/L. The intra-assay coefficient of variation was $\leq 8.15\%$, and the inter-assay coefficient of variation was $\leq 9.78\%$.

Creatinine

Creatinine was measured using the Beckman Coulter AU680. The limit of detection was 3.15 $\mu$mol/L. The intra-assay coefficient of variation was $\leq 3.75\%$, and the inter-assay coefficient of variation was $\leq 5\%$.

Alanine aminotransferase (ALT)

ALT was measured using the Beckman Coulter AU680. The limit of detection was 1 U/L. The intra-assay coefficient of variation was $\leq 5\%$, and the inter-assay coefficient of variation was $\leq 6.67\%$.

High sensitivity CRP (hsCRP)
HsCRP was measured using the Beckman Coulter AU680. The limit of detection was 0.02 mg/L. The intra-assay coefficient of variation was ≤ 6.21%, and the inter-assay coefficient of variation was ≤ 8.28%.

Glycosylated hemoglobin A1c (HbA1c)

HbA1c was measured using the Arkrey HA-8180. The intra-assay coefficient of variation was ≤ 3%, and the inter-assay coefficient of variation was ≤ 3%.

Total cholesterol (TC)

TC was measured using the Beckman Coulter AU680. The limit of detection was 0.07 mmol/L. The intra-assay coefficient of variation was ≤ 2.50%, and the inter-assay coefficient of variation was ≤ 3.33%.

Low-density lipoprotein cholesterol (LDL-C)

LDL-C was measured using the Beckman Coulter AU680. The limit of detection was 0.012 mmol/L. The intra-assay coefficient of variation was ≤ 3.97%, and the inter-assay coefficient of variation was ≤ 3.97%.

Triglycerides

Triglycerides was measured using the Beckman Coulter AU680. The limit of detection was 0.01 mmol/L. The intra-assay coefficient of variation was ≤ 6.25%, and the inter-assay coefficient of variation was ≤ 8.33%.
High-density lipoprotein cholesterol (HDL-C)

HDL-C was measured using the Beckman Coulter AU680. The limit of detection was 0.002 mmol/L. The intra-assay coefficient of variation was ≤ 7.50%, and the inter-assay coefficient of variation was ≤ 10%.
Table S2. Number and missing rate of biomarker assays included in multi-biomarker panel.

| Biomarker     | No. with data | No. Missing | Missing rate |
|---------------|---------------|-------------|--------------|
| NT-proBNP     | 4691          | 2           | <0.1%        |
| Hs-cTNT       | 4690          | 3           | <0.1%        |
| Hemoglobin    | 4526          | 137         | 2.9%         |
| Albumin       | 4452          | 211         | 4.5%         |
| Creatinine    | 4693          | 0           | 0%           |

Abbreviation: NT-proBNP: N-terminal pro-B type natriuretic peptide; Hs-cTNT: high-sensitivity troponin T.
Data S2. Adjudication criteria for cause of death

1. Cardiovascular death

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF) worsen, death due to stroke, and death due to other cardiovascular causes.

1) Acute Myocardial Infarction

The term MI should only be used when there is evidence of myocardial necrosis consistent with myocardial ischemia in an appropriate clinical context.

In general, the diagnosis of MI requires the following to be true:

| i. Cardiac necrosis |
|---------------------|
| - Cardiac biomarkers | Cardiac biomarker results compatible with acute myocardial necrosis |
| or - Autopsy         | Myocardial necrosis/scar or coronary thrombus of an age consistent with the clinical presentation |

AND  
| ii. Other supporting information: |
|----------------------------------|
| - Presentation                   | i. Symptoms of ischemia; or ii. Death |
| or - ECG                         | i. Ischemic changes (not known to be old); or ii. Development of pathological Q waves |
| or - Imaging                     | i. New myocardial defect; or ii. Acute coronary occlusion |
2) **Sudden Cardiac Death**

Sudden death refers to meet the following circumstances:

- Witnessed death (i.e. participant seen at the time of death or within the preceding few days); and

  - No evidence of an alternative cardiovascular or non-vascular cause of death

(including no evidence to suggest Type 3 myocardial infarction)

3) **Worsening Heart Failure**

Heart failure is defined as the patient exhibits worsening symptoms of heart failure on presentation, has objective evidence of worsening of heart failure, and receives initiation or intensification of treatment specifically for heart failure.

4) **Stroke**

Stroke is defined as an acute symptomatic episode of focal or global neurological dysfunction caused by brain, spinal, or retinal vascular injury as a result of hemorrhage or infarction.

5) **Other cardiovascular death**

Death due to other cardiovascular disease includes deaths that are likely to be due to specific cardiovascular disorders (e.g. valvular heart disease, non-ischemic cardiomyopathy, primary arrhythmia, pulmonary embolism, primary pulmonary hypertension, ruptured aortic
aneurysm, acute limb ischemia), and deaths due to surgical and non-surgical investigations and procedures for other cardiovascular disease.

2. **Non-cardiovascular death**

   Non-cardiovascular death was considered if an unequivocal and documented non-cardiovascular cause could be established as the primary cause of death (e.g., malignancy, infection, respiratory disease, liver disease,).

3. **Presumed cardiovascular death / unknown death**

   Presumed cardiovascular death / unknown death was considered if there is no evidence of an alternative cardiovascular or non-vascular cause of death (including sudden cardiac death).
Table S3. Association between biomarkers and cardiovascular death risk in developing cohort.

| Included biomarkers                          | Adjusted HR | 95% CI     | p       |
|---------------------------------------------|-------------|------------|---------|
| NT-proBNP ≥ 1400 ng/L                       | 2.39        | 1.78, 3.22 | <0.0001 |
| Hs-cTNT > 14 ng/L                           | 1.65        | 1.15, 2.38 | 0.0072  |
| Anemia                                      | 1.42        | 1.09, 1.86 | 0.0100  |
| Albumin ≤ 35 g/L                            | 1.92        | 1.52, 2.43 | <0.0001 |
| Creatinine > 133 μmol/L                     | 1.48        | 1.11, 1.98 | 0.0078  |

| Other biomarkers                            |             |            |         |
|---------------------------------------------|-------------|------------|---------|
| ALT > 40 U/L                                | 1.04        | 0.73, 1.49 | 0.8160  |
| DM                                          | 1.19        | 0.91, 1.56 | 0.2099  |
| HsCRP > 2 mg/L                              | 1.08        | 0.81, 1.44 | 0.6085  |
| Dyslipidemia                                | 1.05        | 0.76, 1.46 | 0.7628  |

| Other candidate covariates                  |             |            |         |
|---------------------------------------------|-------------|------------|---------|
| Demographics                                |             |            |         |
| Age (per year)                              | 1.004       | 0.99, 1.02 | 0.3991  |
| Female                                      | 1.13        | 0.88, 1.45 | 0.3295  |
| Vital sign                                  |             |            |         |
| SBP < 110 mmHg                              | Ref         | Ref        | Ref     |
| SBP 110-129 mmHg                            | 0.76        | 0.57, 1.02 | 0.0662  |
| SBP ≥ 130 mmHg                              | 0.55        | 0.40, 0.75 | 0.0001  |
| Heart Rate Category          | HR   | CI     | p-value |
|------------------------------|------|--------|---------|
| HR < 80 b.p.m.               | Ref  | Ref    | Ref     |
| HR 80-99 b.p.m.              | 0.92 | 0.70, 1.20 | 0.5165  |
| HR ≥ 100 b.p.m.              | 0.97 | 0.73, 1.31 | 0.8606  |

| NYHA Class                  | HR   | CI     | p-value |
|------------------------------|------|--------|---------|
| NYHA class II                | Ref  | Ref    | Ref     |
| NYHA class III               | 1.30 | 0.82, 2.06 | 0.2712  |
| NYHA class IV                | 1.54 | 0.97, 2.45 | 0.0695  |

| Medical History & Risk Factor       | HR   | CI     | p-value |
|-------------------------------------|------|--------|---------|
| Hypertension                        | 0.61 | 0.47, 0.79 | 0.0001  |
| Atrial fibrillation                 | 1.20 | 0.94, 1.54 | 0.1428  |
| Coronary heart diseases             | 1.14 | 0.88, 1.47 | 0.3150  |
| Valvular heart diseases             | 0.77 | 1.04, 1.42 | 0.7874  |
| Previous heart failure              | 1.26 | 0.96, 1.66 | 0.1023  |
| Current smoking                     | 0.87 | 0.65, 1.17 | 0.3698  |

| Heart Failure Subgroup            | HR   | CI     | p-value |
|-----------------------------------|------|--------|---------|
| HFrEF                             | Ref  | Ref    | Ref     |
| HFmrEF                            | 0.99 | 0.73, 1.33 | 0.9350  |
| HFpEF                             | 0.82 | 0.61, 1.12 | 0.2138  |

| Discharge Medication              | HR   | CI     | p-value |
|-----------------------------------|------|--------|---------|
| ACEI/ARBs                         | 0.98 | 0.76, 1.26 | 0.8433  |
| β-blockers                        | 0.80 | 0.61, 1.03 | 0.0864  |
| Aldosterone antagonists           | 1.11 | 0.66, 1.85 | 0.6995  |
CCBs 0.87 0.50, 1.51 0.6276

Abbreviation: HR: hazard ratio; CI: confidential interval; NT-proBNP: N-terminal pro-B type natriuretic peptide; Hs-cTNT: high-sensitivity troponin T; Anemia: Hemoglobin < 120 g/L in men or hemoglobin < 110 g/L in women; DM: diabetes mellitus, glycosylated hemoglobin A1c ≥ 6.5%; HsCRP: high-sensitivity C-reactive protein; SBP: systolic blood pressure; HR: heart rate; NYHA: New York Heart Association; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; CCB: calcium channel blocker.
Table S4. Pearson’s correlation coefficients between included biomarkers.

|                | Hs-cTNT | Hemoglobin | Albumin | Creatinine |
|----------------|---------|------------|---------|------------|
| NT-proBNP      | 0.08    | -0.18      | -0.18   | 0.50       |
| Hs-cTNT        | -0.02   | -0.01      |         | 0.06       |
| Hemoglobin     |         |            | 0.26    | -0.25      |
| Albumin        |         |            |         | -0.15      |

Abbreviation: NT-proBNP: N-terminal pro-B type natriuretic peptide; Hs-cTNT: high-sensitivity troponin T.

Note: Collinearity: Pearson’s correlation coefficient >0.70.
Table S5. Multi-biomarker weight point panel calculated using hazard ratios.

| Abnormal biomarker value(s)                          | Weight | Yes (✓) or No (X) |
|------------------------------------------------------|--------|-------------------|
| NT-proBNP ≥ 1400 ng/L                                | 3      |                   |
| Hs-cTNT > 14 ng/L                                   | 2      |                   |
| Anemia (hemoglobin < 120 g/L for male < 110 g/L for female) | 2      |                   |
| Albumin ≤ 35 g/L                                    | 3      |                   |
| Creatinine > 133 μmol/L                              | 2      |                   |

**Total points (✓)**

Abbreviation: NT-proBNP: N-terminal pro-B type natriuretic peptide; Hs-cTNT: high-sensitivity troponin T.

Note: Biomarker with lowest (anemia) hazard ratio (HR) value was defined as “2” weight, and the weights of other biomarkers were calculated by their HRs (keep round number). Each patient had a multi-biomarker point score ranges from 0 to 12 points.
Table S6. Multi-biomarker points (calculated using hazard ratios) and subgroups.

| Multi-biomarker point(s) | Subgroups      |
|--------------------------|----------------|
| <2 points                | Low point      |
| 2-4 points               | Mid-low point  |
| 5-6 points               | Mid-high point |
| > 6 points               | High point     |
Figure S2. Multi-biomarker point distribution in developing cohort.
Figure S3. Multi-biomarker point distribution in validating cohort.
Table S7. Baseline characteristics by multi-biomarker point groups in developing cohort.

|                          | Total (n=2344) | < 2 points (n=419) | 2-4 points (n=700) | 5-6 points (n=639) | > 6 points (n=586) | p value |
|--------------------------|----------------|-------------------|--------------------|--------------------|--------------------|---------|
| **Demographic**          |                |                   |                    |                    |                    |         |
| Age, year, median (IQR)  | 67 (57, 76)    | 64 (55, 74)       | 66 (55, 75)        | 66 (57, 75)        | 71 (62, 79)        | <0.0001 |
| Female, n (%)            | 867 (37.0)     | 197 (47.0)        | 227 (32.4)         | 233 (36.5)         | 210 (35.8)         | <0.0001 |
| **Clinical characteristics** |              |                   |                    |                    |                    |         |
| SBP, mmHg, median (IQR)  | 130 (117, 149) | 130 (120, 147)    | 130 (119, 150)     | 130 (113, 145)     | 130 (114, 151)     | 0.1404  |
| DBP, mmHg, median (IQR)  | 80 (70, 90)    | 80 (70, 90)       | 80 (70, 90)        | 80 (70, 90)        | 80 (68, 90)        | 0.0258  |
| HR, b.p.m, median (IQR)  | 86 (74, 100)   | 80 (70, 96)       | 85 (74, 100)       | 90 (76, 105)       | 88 (76, 100)       | <0.0001 |
| NYHA class, n (%)        |                |                   |                    |                    |                    |         |
| III                      | 1032 (44.0)    | 196 (46.8)        | 318 (45.4)         | 272 (42.6)         | 246 (42.0)         |         |
| IV                       | 961 (41.0)     | 99 (23.6)         | 254 (36.3)         | 306 (47.9)         | 302 (51.5)         |         |
| **Medical history & Risk factor** |              |                   |                    |                    |                    |         |
| Condition                  | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | p-value |
|---------------------------|---------|---------|---------|---------|---------|---------|
| Hypertension, n (%)       | 1357 (57.9) | 232 (55.4) | 416 (59.4) | 337 (52.7) | 372 (63.5) | 0.0010  |
| Atrial fibrillation, n (%)| 860 (36.7)  | 159 (38.0) | 258 (36.9) | 255 (39.9) | 188 (32.1) | 0.0368  |
| CHD, n (%)                | 1370 (58.5) | 231 (55.1) | 415 (59.3) | 347 (54.3) | 377 (64.3) | 0.0018  |
| MI, n (%)                 | 546 (23.3)  | 69 (16.5)  | 167 (23.9) | 148 (23.2) | 162 (27.7) | 0.0006  |
| VHD, n (%)                | 375 (16.0)  | 63 (15.0)  | 113 (16.2) | 108 (16.9) | 91 (15.5)  | 0.8534  |
| Previous HF, n (%)        | 1646 (70.2) | 263 (62.8) | 484 (69.1) | 469 (73.4) | 430 (73.4) | 0.0006  |
| Stroke, n (%)             | 480 (20.5)  | 84 (20.1)  | 138 (19.7) | 122 (19.1) | 136 (23.2) | 0.2916  |
| COPD, n (%)               | 461 (19.7)  | 85 (20.3)  | 150 (21.4) | 121 (18.9) | 105 (17.9) | 0.4190  |
| Reduced renal function, n (%) | 655 (27.9)  | 40 (9.6)   | 154 (22.0) | 143 (22.4) | 318 (54.3) | <0.0001 |
| DM, n (%)                 | 742 (31.7)  | 94 (22.4)  | 230 (32.9) | 189 (29.6) | 229 (39.1) | <0.0001 |
| Current smoking, n (%)    | 581 (24.8)  | 106 (25.3) | 192 (27.4) | 166 (26.0) | 117 (20.0) | 0.0150  |

**Echocardiograph**

| LVEF, %, median (IQR)      | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | p-value |
|----------------------------|---------|---------|---------|---------|---------|---------|
|                            | 43 (33, 56) | 52 (39, 62) | 44 (35, 56) | 40 (30, 50) | 43 (33, 54) | <0.0001 |

| HF phenotype               | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | p-value |
|----------------------------|---------|---------|---------|---------|---------|---------|
|                            |         |         |         |         |         | <0.0001 |

| HFrEF, n (%)               | 936 (39.9) | 108 (25.8) | 275 (39.3) | 317 (49.6) | 236 (40.3) |         |
| HFrEF, n (%)               | 541 (23.1) | 80 (19.1)  | 162 (23.1) | 152 (23.8) | 147 (25.1) |         |
| Condition                  | In-hospital | Treatment at Discharge |
|---------------------------|-------------|-----------------------|
| HFpEF, n (%)              | 867 (37.0)  | 1204 (51.4)           |
|                           | 231 (55.1)  | 220 (52.5)            |
|                           | 263 (37.6)  | 370 (52.9)            |
|                           | 170 (26.6)  | 351 (54.9)            |
|                           | 203 (34.6)  | 263 (44.9)            |
| Coronary angiography      | 337 (14.4)  | 1483 (63.3)           |
|                           | 78 (18.6)   | 243 (58.0)            |
|                           | 125 (17.9)  | 419 (59.9)            |
|                           | 84 (13.2)   | 454 (71.1)            |
| PCI                       | 104 (4.4)   | 348 (14.9)            |
|                           | 17 (4.1)    | 73 (17.4)             |
|                           | 43 (6.1)    | 107 (15.3)            |
|                           | 19 (3.0)    | 60 (9.4)              |
|                           | 25 (4.3)    | 108 (18.4)            |
| ACEI/ARBs, n (%)          | 0.0030      |                      |
| β-blockers, n (%)         | 0.0144      |                      |
| Aldosterone antagonists, n (%) | <0.0001  |                      |
| CCBs, n (%)               | 0.0001      |                      |
| Diuretics, n (%)          | 0.0001      |                      |

Abbreviation: HF: heart failure; IQR: interquartile range; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; NYHA class: New York Heart Association class; CHD: coronary heart disease; MI: myocardial infarction; VHD: valvular heart disease; HF: heart failure; COPD: chronic obstructive pulmonary disease; Reduced renal function: eGFR <60 ml/L/1.73m²; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; PCI: percutaneous coronary intervention.
coronary intervention; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; CCB: calcium channel blocker.
Table S8. Baseline characteristics by multi-biomarker point groups in validating cohort.

|                          | Total (n=2349) | < 2 points (n=427) | 2-4 points (n=682) | 5-6 points (n=666) | > 6 points (n=574) | p value |
|--------------------------|----------------|-------------------|-------------------|-------------------|-------------------|---------|
| **Demographic**          |                |                   |                   |                   |                   |         |
| Age, year, median (IQR)  | 67 (57, 75)    | 64 (54, 72)       | 66 (56, 75)       | 67 (57, 75)       | 69 (60, 77)       | <0.0001 |
| Female, n (%)            | 896 (38.1)     | 216 (50.6)        | 244 (35.8)        | 247 (37.1)        | 189 (32.9)        | <0.0001 |
| **Clinical characteristics** |                |                   |                   |                   |                   |         |
| SBP, mmHg, median (IQR)  | 130 (116, 148) | 119 (119, 150)    | 119 (119, 150)    | 111 (111, 145)    | 115 (115, 152)    | 0.0067  |
| DBP, mmHg, median (IQR)  | 80 (70, 90)    | 80 (70, 90)       | 80 (70, 90)       | 80 (70, 90)       | 80 (70, 90)       | 0.0708  |
| HR, b.p.m, median (IQR)  | 86 (74, 101)   | 81 (71, 99)       | 85 (72, 100)      | 88 (75, 104)      | 88 (76, 100)      | 0.0001  |
| NYHA class, n (%)        |                |                   |                   |                   |                   | <0.0001 |
| III                      | 1044 (44.4)    | 218 (51.1)        | 307 (45.0)        | 294 (44.1)        | 225 (39.2)        |         |
| IV                       | 971 (41.3)     | 88 (20.6)         | 253 (37.1)        | 314 (47.2)        | 316 (55.1)        |         |
| **Medical history & Risk factor** |            |                   |                   |                   |                   |         |
| Condition                  | n (%)   | n (%)   | n (%)   | n (%)   | n (%)   | p-value  |
|---------------------------|---------|---------|---------|---------|---------|----------|
| Hypertension              | 1393 (59.3) | 229 (53.6) | 414 (60.7) | 369 (55.4) | 381 (66.4) | <0.0001  |
| Atrial fibrillation       | 852 (36.3)  | 174 (40.8)  | 243 (35.6)  | 246 (36.9)  | 189 (32.9)  | 0.0810   |
| CHD                       | 1345 (57.3) | 223 (52.2)  | 400 (58.7)  | 353 (53.0)  | 369 (64.3)  | <0.0001  |
| MI                        | 529 (22.5)   | 70 (16.4)    | 151 (22.1)   | 140 (21.0)   | 168 (29.3)   | <0.0001  |
| VHD                       | 384 (16.4)   | 75 (17.6)    | 100 (14.7)   | 123 (18.5)   | 86 (15.0)    | 0.1831   |
| Previous HF               | 1651 (70.3)  | 285 (66.7)   | 483 (70.8)   | 474 (71.2)   | 409 (71.3)   | 0.3669   |
| Stroke                    | 483 (20.6)   | 82 (19.2)    | 136 (19.9)   | 129 (19.4)   | 136 (23.7)   | 0.1977   |
| COPD                      | 467 (19.9)   | 87 (20.4)    | 142 (20.8)   | 135 (20.3)   | 103 (17.9)   | 0.6022   |
| Reduced renal function    | 690 (29.4)   | 36 (8.4)     | 135 (19.8)   | 172 (25.8)   | 347 (60.5)   | <0.0001  |
| DM                        | 742 (31.6)   | 114 (26.7)   | 199 (29.2)   | 197 (29.6)   | 232 (40.4)   | <0.0001  |
| Current smoking           | 597 (25.4)   | 105 (24.6)   | 182 (26.7)   | 185 (27.8)   | 125 (21.8)   | 0.0820   |

**Echocardiograph**

| LVEF, %, median (IQR) | 44 (34, 56) | 50 (40, 61) | 45 (35, 58) | 40 (30, 50) | 42 (33, 52) | <0.0001  |
|-----------------------|-------------|-------------|-------------|-------------|-------------|----------|
| HF phenotype          | `<0.0001   |
| HFrEF, n (%)          | 890 (37.9)  | 98 (23.0)   | 234 (34.3)  | 318 (47.8)  | 240 (41.8)  |
| HFmrEF, n (%)         | 603 (25.7)  | 108 (25.3)  | 177 (26.0)  | 169 (25.4)  | 149 (26.0)  |
| HFpEF, n (%) | 856 (36.4) | 221 (51.8) | 271 (39.7) | 179 (26.9) | 185 (32.2) |
|-------------|------------|------------|------------|------------|------------|

### In-hospital treatment

| Coronary angiography | 294 (12.5) | 58 (13.6) | 94 (13.8) | 88 (13.2) | 54 (9.4)  | 0.0784 |
| PCI | 107 (4.6) | 13 (3.0) | 34 (5.0) | 32 (4.8) | 28 (4.9) | 0.4293 |

### Treatment at Discharge

| ACEI/ARBs, n (%) | 1251 (53.3) | 240 (56.2) | 387 (56.7) | 357 (53.6) | 267 (46.5) | 0.0016 |
| β-blockers, n (%) | 1369 (58.3) | 258 (60.4) | 417 (61.1) | 379 (56.9) | 315 (54.9) | 0.0956 |
| Aldosterone antagonists, n (%) | 1490 (63.4) | 245 (57.4) | 435 (63.8) | 455 (68.3) | 355 (61.9) | 0.0026 |
| CCBs, n (%) | 338 (14.4) | 72 (16.9) | 93 (13.6) | 62 (9.3) | 111 (19.3) | <0.0001 |
| Diuretics, n (%) | 1627 (69.3) | 267 (62.5) | 466 (68.3) | 481 (72.2) | 413 (72.0) | 0.0028 |

Abbreviation: HF: heart failure; IQR: interquartile range; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; NYHA class: New York Heart Association class; CHD: coronary heart disease; MI: myocardial infarction; VHD: valvular heart disease; HF: heart failure; COPD: chronic obstructive pulmonary disease; Reduced renal function: eGFR <60 ml/L/1.73m²; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; PCI: percutaneous
coronary intervention; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; CCB: calcium channel blocker.
Table S9. Biomarker distribution and multi-biomarker points by HF subgroups.

| Biomarkers                      | Total (n=4693) | HFrEF (n=1826) | HFmrEF (n=1144) | HFpEF (n=1723) | p value |
|--------------------------------|----------------|----------------|-----------------|----------------|---------|
| NT-proBNP, ng/L, median (IQR)  | 1474 (600, 3273) | 2065 (963, 4288) | 1594 (635, 3427) | 929 (350, 2181) | <0.0001 |
| NT-proBNP ≥ 1400ng/L, n (%)     | 2421 (51.6) | 1159 (63.4) | 619 (54.2) | 643 (37.3) | <0.0001 |
| Hs-cTNT, ng/L, median (IQR)     | 21.4 (12.7, 40.5) | 24.4 (15.3, 43.2) | 22.5 (13.0, 47.0) | 17.8 (10.6, 33.3) | <0.0001 |
| Hs-cTNT > 14ng/L, n (%)         | 3320 (70.7) | 1435 (78.5) | 821 (71.8) | 1064 (61.8) | <0.0001 |
| Hemoglobin, g/L, median (IQR)   | 134 (119, 148) | 139 (125, 152) | 132 (118, 146) | 130 (114, 145) | <0.0001 |
| Anemia, n (%)                   | 877 (18.7) | 236 (12.9) | 239 (20.9) | 402 (22.3) | <0.0001 |
| Albumin, g/L, median (IQR)      | 38.8 (35.8, 41.7) | 38.9 (35.8, 41.7) | 38.8 (35.9, 41.6) | 38.8 (35.6, 41.8) | 0.9377 |
| Albumin ≤ 35 g/L, n (%)         | 981 (20.9) | 384 (21.0) | 227 (19.9) | 370 (21.5) | 0.5750 |
| Creatinine, μmol/L, median (IQR)| 93 (78, 112) | 95 (81, 113) | 93 (78, 113) | 90 (76, 109) | <0.0001 |
| Creatinine > 133 μmol/L, n (%) | 628 (13.4) | 227 (12.4) | 157 (13.7) | 244 (14.2) | 0.2907 |
|--------------------------------|------------|------------|------------|------------|---------|
| Multi-biomarker point, median (IQR) | 5 (2, 6) | 5 (2, 7) | 5 (2, 7) | 3 (0, 5) | <0.0001 |
| **Multi-biomarker point group, n (%)** |            |            |            |            | <0.0001 |
| < 2 points | 846 (18.0) | 206 (11.3) | 188 (16.4) | 452 (26.2) |         |
| 2-4 points | 1382 (29.5) | 509 (27.9) | 339 (29.6) | 534 (31.0) |         |
| 5-6 points | 1305 (27.8) | 635 (34.8) | 321 (28.1) | 349 (20.3) |         |
| ≥ 7 points | 1160 (24.7) | 476 (26.1) | 296 (25.9) | 388 (22.5) |         |

Abbreviation: HF: heart failure; IQR: interquartile range; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; NT-proBNP: N-terminal pro-B type natriuretic peptide; Hs-cTNT: high-sensitivity troponin T; Anemia: hemoglobin < 120 g/L in men or hemoglobin < 110 g/L in women.
Figure S4. Clinical outcomes and multi-biomarker points (continuous variable; validating cohort).

| Clinical Outcomes          | Adjusted Hazard Ratio (95%CI) | P value  |
|----------------------------|-------------------------------|----------|
| Cardiovascular death       | 1.14 (1.10, 1.18)             | <0.0001  |
| Rehospitalization for HF   | 1.09 (1.06, 1.11)             | <0.0001  |
| All-cause death            | 1.15 (1.11, 1.19)             | <0.0001  |
| All-cause rehospitalization| 1.06 (1.04, 1.08)             | <0.0001  |

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], heart failure phenotypes [HFrEF, HFmrEF, HFpEF or missing LVEF], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
|                         | C-index |
|-------------------------|---------|
| **Cardiovascular Death**|         |
| Multi-biomarker point   | 0.67    |
| NT-proBNP ≥ 1400 ng/L   | 0.63    |
| Hs-cTNT > 14 ng/L       | 0.60    |
| Anemia                  | 0.52    |
| Albumin ≤ 35 g/L        | 0.54    |
| Creatinine > 133 μmol/L | 0.54    |
| **Rehospitalization for HF** |     |
| Multi-biomarker point   | 0.60    |
| NT-proBNP ≥ 1400 ng/L   | 0.57    |
| Hs-cTNT > 14 ng/L       | 0.56    |
| Anemia                  | 0.54    |
| Albumin ≤ 35 g/L        | 0.52    |
| Creatinine > 133 μmol/L | 0.54    |
| **All-cause Death**     |         |
| Multi-biomarker point   | 0.67    |
| NT-proBNP ≥ 1400 ng/L   | 0.62    |
| Hs-cTNT > 14 ng/L       | 0.61    |
| Anemia                  | 0.54    |
Albumin ≤ 35 g/L 0.55
Creatinine > 133 μmol/L 0.55

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**All-cause Rehospitalization**

- Multi-biomarker point 0.57
- NT-proBNP ≥ 1400 ng/L 0.55
- Hs-cTNT > 14 ng/L 0.54
- Anemia 0.53
- Albumin ≤ 35 g/L 0.51
- Creatinine > 133 μmol/L 0.53

Abbreviation: NT-proBNP: N-terminal pro-B type natriuretic peptide; Hs-cTNT: high-sensitivity troponin T; Anemia: Hemoglobin < 120 g/L in men or hemoglobin < 110 g/L in women.
Figure S5. KCCQ scores and multi-biomarker points (continuous variables; validating cohort).

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], heart failure phenotypes [HFrEF, HFmrEF, HFpEF or missing LVEF], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
Figure S6. Subgroup analysis of clinical outcomes and multi-biomarker point(s) in heart failure with reduced ejection fraction (validating cohort).

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
Figure S7. Subgroup analysis of clinical outcomes and multi-biomarker point(s) in heart failure with mildly reduced ejection fraction (validating cohort).

| Clinical Outcomes (HFmrEF) | Unadjusted Rate (%) | Unadjusted P value | Adjusted Hazard Ratio (95%CI) | P value |
|----------------------------|---------------------|--------------------|------------------------------|---------|
| **Cardiovascular death**   |                     |                    |                              |         |
| Low                        | 3 (2.6)             | <0.0001            | Ref                          |         |
| Mid-low                    | 18 (10.2)           |                    |                              |         |
| Mid-high                   | 34 (20.1)           |                    | 1.62 (0.90, 2.90)            | 0.1068  |
| High                       | 39 (26.2)           |                    | 2.10 (1.17, 3.77)            | 0.0132  |
| **Rehospitalization for HF**|                     |                    |                              |         |
| Low                        | 25 (23.2)           | <0.0001            | Ref                          |         |
| Mid-low                    | 50 (28.3)           |                    | 1.16 (0.71, 1.88)            | 0.5617  |
| Mid-high                   | 63 (37.3)           |                    | 1.50 (0.93, 2.42)            | 0.0959  |
| High                       | 71 (47.7)           |                    | 1.92 (1.18, 3.13)            | 0.0091  |
| **All-cause death**        |                     |                    |                              |         |
| Low                        | 3 (2.6)             | <0.0001            | Ref                          |         |
| Mid-low                    | 19 (10.7)           |                    |                              |         |
| Mid-high                   | 36 (21.3)           |                    | 1.67 (0.95, 2.95)            | 0.0705  |
| High                       | 50 (33.6)           |                    | 2.81 (1.61, 4.91)            | 0.0003  |
| **All-cause rehospitalization** |                 |                    |                              |         |
| Low                        | 39 (36.1)           | 0.0004             | Ref                          |         |
| Mid-low                    | 84 (47.5)           |                    | 1.40 (0.96, 2.06)            | 0.0848  |
| Mid-high                   | 87 (51.5)           |                    | 1.43 (0.97, 2.11)            | 0.0742  |
| High                       | 93 (62.4)           |                    | 1.81 (1.21, 2.70)            | 0.0037  |

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
Figure S8. Subgroup analysis of clinical outcomes and multi-biomarker point(s) in heart failure with preserved ejection fraction (validating cohort).

| Clinical Outcomes (HFpEF) | Unadjusted Rate (%) | Unadjusted P value | Adjusted Hazard Ratio (95%CI) | Adjusted P value |
|---------------------------|---------------------|--------------------|------------------------------|-----------------|
| Cardiovascular death      |                     |                    |                              |                 |
| Low                       | 8 (3.6)             | <0.0001            | Ref                          |                 |
| Mid-low                   | 20 (9.2)            |                    |                              |                 |
| Mid-high                  | 30 (16.6)           |                    |                              |                 |
| High                      | 38 (20.5)           |                    |                              |                 |
| Rehospitalization for HF  |                     |                    |                              |                 |
| Low                       | 34 (15.4)           | <0.0001            | Ref                          |                 |
| Mid-low                   | 73 (26.9)           |                    |                              |                 |
| Mid-high                  | 66 (36.9)           |                    |                              |                 |
| High                      | 84 (45.4)           |                    |                              |                 |
| All-cause death           |                     | <0.0001            |                              |                 |
| Low                       | 10 (4.5)            |                    | Ref                          |                 |
| Mid-low                   | 36 (13.3)           |                    |                              |                 |
| Mid-high                  | 33 (18.4)           |                    |                              |                 |
| High                      | 49 (26.5)           |                    |                              |                 |
| All-cause rehospitalization|                    | <0.0001            |                              |                 |
| Low                       | 75 (33.9)           |                    | Ref                          |                 |
| Mid-low                   | 123 (45.4)          |                    |                              |                 |
| Mid-high                  | 93 (52.0)           |                    |                              |                 |
| High                      | 107 (57.8)          |                    |                              |                 |

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
Figure S9. Subgroup analysis of KCCQ scores and multi-biomarker points (validating cohort).

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
Figure S10. Sensitivity analysis of multi-variable adjusted association between multi-biomarker point group and 1-year clinical outcomes (competing risk model; validating cohort).

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], heart failure phenotypes [HFrEF, HFmrEF, HFpEF or missing LVEF], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
Figure S11. Sensitivity analysis of effect of the burden of multi-biomarker point on quality of life (inverse probably weighting, IPW; validating cohort).

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], heart failure phenotypes [HFrEF, HFmrEF, HFpEF or missing LVEF], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
Table S11. Multi-biomarker weight point panel calculated using beta values.

| Abnormal biomarker value(s)                                           | Weight | Yes (√) or No (X) |
|-----------------------------------------------------------------------|--------|--------------------|
| NT-proBNP ≥ 1400 ng/L                                                 | 2      |                    |
| Hs-cTNT > 14 ng/L                                                    | 1      |                    |
| Anemia (hemoglobin < 120 g/L for male < 110 g/L for female)          | 1      |                    |
| Albumin ≤ 35 g/L                                                     | 2      |                    |
| Creatinine > 133 μmol/L                                              | 1      |                    |

**Total points (√)**

Abbreviation: NT-proBNP: N-terminal pro-B type natriuretic peptide; Hs-cTNT: high-sensitivity troponin T.

Note: Biomarker with lowest (anemia) beta value was defined as “1” weight, and the weights of other biomarkers were calculated by their beta values (keep round number). Each patient had a multi-biomarker point score ranges from 0 to 7 points.
Table S12. Multi-biomarker points (calculated using beta values) and subgroups.

| Multi-biomarker point(s) | Subgroups     | Number of patients (%) |
|--------------------------|---------------|------------------------|
| < points                 | Low point     | 846 (18.0)             |
| 2-4 points               | Mid-low point | 1382 (29.4)            |
| 5-6 points               | Mid-high point| 1258 (26.8)            |
| > 6 points               | High point    | 1207 (25.7)            |
Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], heart failure phenotypes [HFrEF, HFmrEF, HFpEF or missing LVEF], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.
Figure S13. KCCQ scores and multi-biomarker points (calculated using beta values)

subgroups. (validating cohort)

Abbreviation: CI: confidential interval.

Note: Adjusted for age, sex, systolic blood pressure, heart rate, New York Heart Association classification, history of hypertension, atrial fibrillation, coronary heart disease, valvular heart disease, previous heart failure, current smoking [yes or no], heart failure phenotypes [HFrEF, HFmrEF, HFpEF or missing LVEF], discharge use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β-blockers, diuretics, and aldosterone antagonists.