Risk factors of short-term, intermediate-term, and long-term cardiac events in patients hospitalized for HFmrEF

Yunlong Zhu1†, Xin Peng1,2†, Mingxin Wu1†, Haobo Huang1, Na Li1,2†, Yongliang Chen1,2, Sha Xiao1,2, Hui Zhang1,2, Yuying Zhou1,2, Sihao Chen1,2, Zhican Liu1,2, Liqing Yi1, Yiqun Peng1, Jie Fan1 and Jianping Zeng1,2*

1Department of Cardiology, Xiangtan Central Hospital, Xiangtan, China; and 2Graduate Collaborative Training Base of Xiangtan Central Hospital, Hengyang Medical School, University of South China, Hengyang, China

Abstract

Aims Clinical data on the prognostic determinants over varying periods within the same cohort of heart failure with mid-range or mildly reduced ejection fraction (HFmrEF) remain scarce. This study aimed to identify the short-term, intermediate-term, and long-term risk factors of adverse cardiovascular (CV) outcomes in patients hospitalized for HFmrEF.

Methods and results This retrospective study included 1691 consecutive HFmrEF patients admitted to our hospital between January 2015 and August 2020. Baseline data including clinical characteristics, laboratory and cardiac imaging examinations were obtained. Patients completed at least 1 year clinical follow-up after discharge by telephone interview, clinical visit, or community visit. The primary endpoint was defined as a composite of CV death or rehospitalization for heart failure (CV events) at 3, 12, and 33 months after the diagnosis of HFmrEF. Mean age of the whole cohort was 69 (61–77) years and 64.8% were male. The median clinical follow-up was 33 (20–50) months. CV events were 17.5%, 28.2%, and 57.8% at 3, 12, and 33 months after discharge, respectively. Independent risk factors for CV events were uric acid >382 μmol/L, creatinine >100 μmol/L, N-terminal pro-B type natriuretic peptide (NT-proBNP) >3368 pg/mL and haemoglobin <120 g/L for men and <110 g/L for women at 3 and 12 months. Pulmonary artery systolic pressure >35 mmHg and the ratio of early transmitral flow velocity to early mitral annular velocity >18 served as independent risk factors for CV events at 12 months. At 33 months, uric acid >382 μmol/L, NT-proBNP >3368 pg/mL, and pulmonary artery systolic pressure >35 mmHg were the independent risk factors of CV events.

Conclusions Higher uric acid, creatinine, NT-proBNP, and lower haemoglobin levels at baseline are valuable serum biomarkers for risk stratification of short-term and long-term CV outcomes of HFmrEF patients. Future studies are needed to verify if intensive heart failure therapy for identified high-risk HFmrEF patients based on these four serum biomarkers could improve their short-term and long-term CV outcomes or not.

Keywords HFmrEF; outcome; CV events; risk factors; biomarkers

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*Correspondence to: Jianping Zeng, Department of Cardiology, Xiangtan Central Hospital Affiliated to University of South China, Heping Road No. 120, Yuhu District, Xiangtan 411100, China. Tel: 0086-731-58214988. Email: xhjiang2@hnust.edu.cn

†Yunlong Zhu, Xin Peng, and Mingxin Wu authors contributed equally to this work.

Introduction

Clinical data on heart failure (HF) with mid-range ejection fraction (HFmrEF) is emerging since the introduction of the term of HFmrEF by the 2016 European Society of Cardiology heart failure guidelines. The term of HFmrEF has changed to heart failure with mildly reduced left ventricle ejection fraction (LVEF) in the 2021 ESC/HFA heart failure guidelines.
and the new HFmrEF refers to HF patients with LVEF between 41–49%, instead of 40–49%. Up to 25% of HF patients could be categorized as HFmrEF.\textsuperscript{3,4} According to the previous data ≥ 0.003 for all). Biomarkers that predicted HFmrEF included natriuretic peptides, cystatin-C, and high-sensitivity troponin (P ≤ 0.0004 for all).\textsuperscript{6} Most clinical studies compared the clinical outcome among patients with various LVEF categories. Data on determinants of outcome in HFmrEF cohort are relatively scarce now. A prospective international multi-ethnic cohort study showed that plasma levels of NT-proBNP were independently predictive of 2 year death in HFmrEF patients.\textsuperscript{7} HFmrEF biomarker profile and outcomes were characterized in 134 patients and results showed that biomarkers commonly used for HFREF risk prediction are also valuable for HFmrEF risk stratification.\textsuperscript{8} The clinical characteristics, prognosis, and treatment responses of patients with HFmrEF hospitalized for acute decompensated HF were analysed in 651 patients and patients underwent a median of 724 days follow-up. Results showed that age, anaemia, hyponatraemia, elevated blood urea nitrogen, chronic kidney disease, and elevated plasma brain natriuretic peptide levels were significant predictors of composite outcomes, defined as all-cause death and heart failure readmission, as well as all-cause death alone, in HFmrEF.\textsuperscript{9} Clinical data exploring risk factors of short-term and long-term outcomes in HFmrEF patients are rare. In one study, Cho et al. observed the 3 year outcome of 844 hospitalized HFmrEF patients due to acute heart failure. They found that age and low systolic blood pressure, hyponatraemia, and renal failure were significantly associated with death at 3 months after discharge in these patients, while male sex, age, BMI, anaemia, hyponatraemia, elevated B type natriuretic peptide or NT-proBNP, and renal failure were risk factors related to 3 year mortality after discharge in these patients.\textsuperscript{10}

The purpose of this study was to identify the prognostic determinants of HFmrEF patients at different time points after discharge (i.e. at 3 months, at 12 months, and at study end-point). We sought to determine the common or distinct risk factors of these patients at the three stages after discharge. Our data might be helpful to provide clinical evidence of risk stratification, monitoring progress, and decision-making for treatment planning of high-risk HFmrEF patients at different phases after discharge in the future.

**Methods**

**Study population**

This retrospective cohort study included consecutive HFmrEF patients aged at least 18 years and admitted to our hospital. The inclusion criteria were as follows: (i) hospitalized patients in the cardiology department of our hospital between 1 January 2015 and 31 August 2020, who were clinically diagnosed chronic HF patients with New York Heart Association (NYHA) functional class II, III, or IV, according to the 2012 guidelines of the ESC Working Group\textsuperscript{11}; (ii) hospitalization echocardiography detected LVEF of 41–49%. Chronic HF was defined if patients had a history of decompensated HF events within the last 12 months prior to admission. Exclusion criteria was malignancy or other non-cardiac condition limiting life expectancy to <1 year. Finally, we included 1691 patients in the study for final analysis (Figure 1). The investigation was in line with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Xiangtan Central Hospital. Written informed consent was obtained from all patients or their guardians before the study began.

**Standard echocardiographic measurements**

All patients underwent standard transthoracic echocardiography (GE, Norway). In the parasternal long axis view of the left ventricle, end-diastolic left ventricular dimension (LVD), left ventricular end-diastolic posterior wall thickness (LVPWd), and end-diastolic septal wall thickness (IVSd) were measured using M-mode. At the end of systolic period, end-systolic left atrial anteroposterior diameter (LAs) was measured using M-mode. LVEF was measured by the two-plane Simpson method in apical four-chamber and two-chamber views. Pulsed-wave Doppler derived mitral peak early diastolic filling velocity (E) was measured. Tissue-Doppler derived early diastolic mitral annular velocity (e') was acquired at the septal and lateral mitral annular sites and then average e' and E/e' were calculated. Pulmonary artery systolic pressure (PASP) was derived from a simplified Bernoulli equation combined
with the estimated right atrial pressure (RAP): \[ \text{PASP} = 4 \times V^2 + \text{RAP} \], where \( V \) represented maximal tricuspid regurgitation velocity with continuous-wave Doppler, and RAP was estimated based on changes in inferior vena cava diameter and respiration. For patients without detectable tricuspid regurgitation on echocardiography, PASP was set as 8 mmHg.

**Clinical data collection and serum biomarker measurement**

Clinical data were recorded based on the information in the patient’s medical record. Blood pressure (BP) was taken as the average of the two measures of sitting position. Hypertension was defined as systolic blood pressure \( \leq 140 \text{ mmHg} \), diastolic blood pressure \( \leq 90 \text{ mmHg} \), or the use of antihypertensive drugs. Diabetes was defined as a fasting blood glucose level of 7.0 mmol/L, a random blood glucose level of 11.1 mmol/L, or the use of hypoglycaemic drugs. Current studies included the following serum biomarkers: N-terminal pro-B type natriuretic peptide (NT-proBNP), troponin T (TnT), haemoglobin (Hb), uric acid (UA), creatinine (Cr), potassium (K), total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), and high density lipoprotein (HDL). These biomarkers were selected for the first serological test results of HFmrEF patients after admission. The medication lists recorded at discharge were collected.

**Clinical follow-up and outcomes**

Follow-up is conducted by our team members (residents and nurses working in the department of cardiology of our hospital) through clinical visits, telephone interviews,
or community visits. The patients were not included in a disease-management program, and they were not followed-up regularly in the outpatient clinic or with telemedicine. The final follow-up was dated on 31 August 2021. All patients completed at least 1 year clinical follow-up. Median follow-up was 33 (20–50) months. Clinical short-term (at 3 months), intermediate-term (at 12 months), and long-term (at 33 months) outcome after echocardiographic diagnosis of HFmRF was analysed. The primary endpoint was defined as a composite of cardiovascular (CV) death or rehospitalization for heart failure (CV events) at 3 months, 12 months, and 33 months. CV deaths were defined as deaths from an acute myocardial infarction (MI), sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV haemorrhage, death due to other CV causes, or heart transplantation. Deaths from unknown causes were assumed to be deaths from CV causes.

Statistical analysis

Continuous variables are expressed as the median (quartile range). Unpaired t-tests were performed for data with a normal distribution, and nonparametric tests (Mann–Whitney U-tests) were used for data with a skewed distribution. The categorical data were compared with the use of similar methods ($\chi^2$ and Fisher precision tests, where appropriate). Multiple imputation method was used to deal with the missing values of the major variables that were identified before the main analyses. The number of imputations was determined by the median value for this variable.

For survival analysis, Kaplan–Meier curves were plotted and log-rank tests were used for comparison. Univariable and multivariable Cox proportional hazard regression models were used to determine independent risk factors associated with CV events at 3, 12, and 33 months. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence interval (CI) were calculated. All clinical parameters and medications with a $P$ value <0.10 in univariable Cox regression models were defined as clinical covariates. Each biomarker and echocardiographic markers plus all identified clinical covariates from the univariable models were then entered into the multivariable Cox model with enter method. Youden’s index was used as the criterion for determining the optimum cut-off point of predictors. Because the distribution of the NT-proBNP and creatinine values were non-normal, natural logarithmic transformation was used to make them conform to normal distribution. The $P$ value <0.05 for a two-tailed test is considered significant. Statistical analysis was performed using IBM SPSS Statistics 28.0.0 (SPSS Inc., Chicago, IL, USA) and EmpowerStats 2.2 (American X&Y Solutions Inc., USA).

Results

Baseline characteristics associated with cardiovascular events

The baseline parameters were summarized in Table 1. Among 1691 HFmRF patients enrolled in our study, CV events were obtained in 977 patients including 390 cardiac deaths at 33 months follow-up. All-cause death occurred in 457 patients (27.0%). Higher age, systolic and diastolic blood pressure, less percutaneous coronary intervention (PCI), previous atrial fibrillation (AF) and stroke history, higher NT-proBNP, TnT, UA, Cr, and lower Hb levels at admission were related to higher risks of CV events. LAs, LVD, and higher E/e′, and PASP values were also larger in CV events group than in non-CV events group (all $P < 0.05$).

Unadjusted risk factors associated with cardiovascular events at 3, 12, and 33 months

Unadjusted risk factors associated with 3, 12, and 33 month CV events in this patient cohort were presented in Table 2. It was shown that aging, higher NYHA classification, renal insufficiency, history of hypertension, AF, diabetes, coronary heart disease (CHD), higher NT-proBNP, lower Hb, higher UA and Cr levels, larger LAs, E/e′, PASP values are risk factors of CV events at 3 months after discharge (all $P < 0.05$). Aging, male sex, higher NYHA classification, renal insufficiency, history of hypertension, AF, diabetes, CHD, PCI, chronic obstructive pulmonary disease (COPD), higher NT-proBNP, lower Hb, higher UA and Cr levels, larger LAs, E/e′, PASP values are risk factors of CV events at 12 months after discharge (all $P < 0.05$). Aging, higher systolic and diastolic blood pressure, NYHA classification, history of AF, higher NT-proBNP, lower Hb, higher UA levels, larger LAs, and PASP values are risk factors of CV events at 33 months after discharge (all $P < 0.05$).

Adjusted risk factors associated with cardiovascular events at 3, 12, and 33 months

Adjusted risk factors associated with CV events at 3, 12, and 33 months were shown in Table 3. After adjustment of clinical covariates including age, sex, heart rate, NYHA class, hypertension, previous AF, diabetes, CHD, renal insufficiency, use of angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists (ACEI/ARB), and use of diuretics, multiple regression analysis showed that higher NT-proBNP level (>3368 pg/mL), anaemia, higher UA (>382 μmol/L), and Cr (>100 μmol/L) values at admission...
remained as independent risk factors of CV events at 3 months after discharge. After adjustment of clinical covariates including age, sex, heart rate, NYHA class, hypertension, previous AF, diabetes, previous MI, COPD, renal insufficiency, use of ACEI/ARB, and use of diuretics, multiple regression analysis showed that higher NT-proBNP level (>3368 pg/mL), higher UA (>382 μmol/L), and PASP >35 mmHg remained as independent risk factors of CV events at 33 months after discharge.

Age adjusted clinical outcomes at 3, 12, and 33 months

As shown in Figure 2, all-cause death, CV death, and CV events at 3 months, 12 months, and 33 months were all
Table 2 Unadjusted risk factors associated with 3, 12, and 33 month CV events in patients with HFmrEF

| CV events [n (%)] | 3 months (296/1691 (17.5)) | 12 months (477/1691 (28.2)) | 33 months (977/1691 (57.8)) |
|------------------|-----------------------------|-----------------------------|-----------------------------|
|                  | Unadjusted hazard ratio (95% CI) | Wald | P-value | Unadjusted hazard ratio (95% CI) | Wald | P-value | Unadjusted hazard ratio (95% CI) | Wald | P-value |
| Age (years)      | 1.025 (1.015–1.035) 22.719 <.0001 | 1.027 (1.019–1.036) 43.894 <.0001 | 1.008 (1.003–1.014) 9.594 0.002 |
|                  | 0.959 (0.956–1.215) 0.121 0.728 | 0.744 (0.620–0.893) 10.104 0.001 | 0.959 (0.842–1.093) 0.387 0.534 |
| Male vs. female  | 1.000 (0.995–1.004) 0.003 0.960 | 1.002 (0.998–1.005) 1.084 0.298 | 1.004 (1.001–1.006) 9.811 0.002 |
| Systolic blood pressure (mmHg) | 0.995 (0.987–1.002) 2.154 0.142 | 0.995 (0.989–1.001) 3.012 0.083 | 1.006 (1.002–1.009) 8.377 0.004 |
| Diastolic blood pressure (mmHg) | 1.005 (1.000–1.011) 3.817 0.051 | 1.004 (1.000–1.008) 3.573 0.059 | 1.003 (1.000–1.006) 3.855 0.050 |
| Heart rate (b.p.m.) | 1.005 (1.000–1.011) 3.817 0.051 | 1.004 (1.000–1.008) 3.573 0.059 | 1.003 (1.000–1.006) 3.855 0.050 |
| NYHA class [n (%)] | 1.856 (1.452–2.372) 24.396 <.0001 | 1.754 (1.441–2.135) 31.328 <.0001 | 1.182 (1.018–1.372) 4.812 0.028 |
| IV vs. II-III    | 1.811 (1.426–2.300) 23.671 <.0001 | 1.733 (1.432–2.079) 31.894 <.0001 | 1.107 (0.924–1.234) 0.794 0.373 |
| Cardiac risk factors and co-morbidities [n (%)] | 1.671 (1.271–2.197) 13.509 <.0001 | 1.489 (1.209–1.833) 14.075 <.0001 | 1.079 (0.996–1.166) 0.954 0.338 |
| Renal insufficiency | 1.450 (1.106–1.900) 7.218 0.007 | 1.559 (1.261–1.927) 16.885 <.0001 | 1.243 (1.061–1.545) 1.275 0.532 |
| Hypertension     | 1.307 (1.034–1.653) 6.010 0.025 | 1.438 (1.197–1.727) 15.023 <.0001 | 1.111 (0.973–1.269) 0.248 0.618 |
| Atrial fibrillation | 0.975 (0.777–1.225) 0.466 0.183 | 0.694 (0.579–0.832) 15.628 <.0001 | 0.936 (0.826–1.062) 1.056 0.304 |
| Diabetes         | 0.894 (0.707–1.132) 0.861 0.354 | 0.703 (0.580–0.851) 12.996 <.0001 | 0.887 (0.778–1.011) 2.224 0.173 |
| CHD              | 1.223 (0.885–1.690) 1.493 0.222 | 1.345 (1.049–1.726) 5.441 0.020 | 1.133 (0.943–1.362) 1.783 0.182 |
| Previous MI      | 1.272 (1.183–1.367) 42.591 <.0001 | 1.377 (1.299–1.460) 116.162 <.0001 | 1.077 (1.037–1.118) 14.532 <.0001 |
| PCI              | 0.985 (0.981–0.990) 38.763 <.0001 | 0.986 (0.983–0.990) 53.847 <.0001 | 0.970 (0.994–1.000) 4.835 0.028 |
| COPD             | 1.003 (1.002–1.004) 36.741 <.0001 | 1.003 (1.002–1.003) 51.693 <.0001 | 1.001 (1.000–1.001) 8.045 0.005 |
| Blood test       | 1.533 (1.336–1.760) 37.003 <.0001 | 1.495 (1.341–1.676) 52.273 <.0001 | 1.032 (0.942–1.132) 0.465 0.695 |
| NT-proBNPa      | 1.027 (1.009–1.045) 9.153 0.0002 | 1.041 (1.027–1.055) 35.318 <.0001 | 1.015 (1.005–1.025) 8.544 0.0003 |
| HB (g/L)         | 1.024 (1.011–1.037) 13.954 <.0001 | 1.028 (1.018–1.038) 32.456 <.0001 | 1.006 (0.998–1.014) 2.453 0.117 |
| UA (μmol/L)      | 1.013 (1.005–1.020) 11.842 <.0001 | 1.022 (1.017–1.028) 60.408 <.0001 | 1.004 (1.001–1.007) 8.924 0.003 |
| Cr (mg/dL)       | 1.037 (1.299–1.460) 116.162 <.0001 | 1.077 (1.037–1.118) 14.532 <.0001 |
| E/e'             | 1.027 (1.009–1.045) 9.153 0.0002 | 1.041 (1.027–1.055) 35.318 <.0001 |
| PASP (mmHg)      | 1.024 (1.011–1.037) 13.954 <.0001 | 1.028 (1.018–1.038) 32.456 <.0001 |
| CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Cr, creatinine; E/e', ratio of early transmirtal flow velocity to early mitral annular velocity; HB, haemoglobin; LAs, end-systolic left atrial diameter; MI, myocardial infarction; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; UA, uric acid.

aNatural log transformation for NT-proBNP.
Table 3  Adjusted blood and echocardiography biomarkers associated with CV events in patients with HfmrEF

|                  | Model 1                        | Model 2                        | Model 3                        | Model 4                        |
|------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                  | Age and sex adjusted HR (95% CI) | Wald                          | P-value                        | Clinical covariates adjusted HR (95% CI) | Wald                          | P-value                        |
| 3 month CV events|                                |                                |                                |                                |                                |                                |
| Blood test       |                                |                                |                                |                                |                                |                                |
| NT-proBNP       | 1.254 (1.162–1.352)            | 34.262                         | <0.001                         | 1.543 (1.183–2.013)             | 10.218                        | 0.001                          |
| > vs. ≤3368 pg/mL| 1.930 (1.500–2.483)            | 26.164                         | <0.001                         | 1.348 (1.055–1.724)             | 5.694                         | 0.017                          |
| Hb (per 10 g/L increase) | 0.867 (0.826–0.910)       | 33.266                         | <0.001                         | 1.543 (1.183–2.013)             | 10.218                        | 0.001                          |
| Anaemia vs. no anaemia | 1.650 (1.310–2.078)     | 18.129                         | <0.001                         | 1.348 (1.055–1.724)             | 5.694                         | 0.017                          |
| UA (per 100 μmol/L increase) | 1.332 (1.218–1.457) | 39.527                         | <0.001                         | 1.543 (1.183–2.013)             | 10.218                        | 0.001                          |
| > vs. ≤382 μmol/L| 1.970 (1.565–2.480)            | 33.331                         | <0.001                         | 1.543 (1.183–2.013)             | 10.218                        | 0.001                          |
| Cr<sup>3</sup>   | 1.664 (1.437–1.926)            | 46.385                         | <0.001                         | 1.543 (1.183–2.013)             | 10.218                        | 0.001                          |
| > vs. ≤100 μmol/L| 1.878 (1.492–2.365)            | 28.795                         | <0.001                         | 1.543 (1.183–2.013)             | 10.218                        | 0.001                          |
| Echocardiography |                                |                                |                                |                                |                                |                                |
| LAs (per 10 mm increase) | 1.312 (1.100–1.565) | 9.133                          | 0.003                          | 1.117 (0.859–1.451)             | 0.680                         | 0.410                          |
| > vs. ≤42 mm     | 1.368 (1.074–1.742)            | 6.451                          | 0.011                          | 1.117 (0.859–1.451)             | 0.680                         | 0.410                          |
| E/e<sup>′</sup> (per 1 increase) | 1.037 (1.010–1.063) | 12.257                         | <0.001                         | 1.117 (0.859–1.451)             | 0.680                         | 0.410                          |
| > vs. ≤18        | 1.476 (1.163–1.873)            | 10.270                         | 0.001                          | 1.117 (0.859–1.451)             | 0.680                         | 0.410                          |
| PASP (per 10 mmHg increase) | 1.114 (1.036–1.197) | 8.512                          | 0.004                          | 1.117 (0.859–1.451)             | 0.680                         | 0.410                          |
| > vs. ≤35 mmHg   | 1.425 (1.132–1.794)            | 9.078                          | 0.003                          | 1.117 (0.859–1.451)             | 0.680                         | 0.410                          |
| 12 month CV events|                                |                                |                                |                                |                                |                                |
| Blood test       |                                |                                |                                |                                |                                |                                |
| NT-proBNP       | 1.346 (1.267–1.429)            | 93.266                         | <0.001                         | 1.649 (1.330–2.045)             | 20.727                        | <0.001                         |
| > vs. ≤3368 pg/mL| 2.135 (1.749–2.608)            | 55.398                         | <0.001                         | 1.649 (1.330–2.045)             | 20.727                        | <0.001                         |
| Hb (per 10 g/L increase) | 0.888 (0.854–0.924) | 35.262                         | <0.001                         | 1.649 (1.330–2.045)             | 20.727                        | <0.001                         |
| Anaemia vs. no anaemia | 1.606 (1.339–1.926) | 26.092                         | <0.001                         | 1.649 (1.330–2.045)             | 20.727                        | <0.001                         |
| UA (per 100 μmol/L increase) | 1.328 (1.237–1.425) | 61.459                         | <0.001                         | 1.649 (1.330–2.045)             | 20.727                        | <0.001                         |
| > vs. ≤382 μmol/L| 1.870 (1.561–2.241)            | 46.013                         | <0.001                         | 1.649 (1.330–2.045)             | 20.727                        | <0.001                         |
| Cr<sup>3</sup>   | 1.647 (1.467–1.848)            | 71.902                         | <0.001                         | 1.649 (1.330–2.045)             | 20.727                        | <0.001                         |
| > vs. ≤100 μmol/L| 2.063 (1.720–2.473)            | 61.078                         | <0.001                         | 1.649 (1.330–2.045)             | 20.727                        | <0.001                         |
| Echocardiography |                                |                                |                                |                                |                                |                                |
| LAs (per 10 mm increase) | 1.515 (1.324–1.733) | 36.497                         | <0.001                         | 1.219 (0.991–1.500)             | 3.500                         | 0.061                          |
| > vs. ≤42 mm     | 1.552 (1.286–1.874)            | 20.927                         | <0.001                         | 1.219 (0.991–1.500)             | 3.500                         | 0.061                          |
| E/e<sup>′</sup> (per 1 increase) | 1.026 (1.016–1.036) | 26.019                         | <0.001                         | 1.219 (0.991–1.500)             | 3.500                         | 0.061                          |
| > vs. ≤18        | 1.625 (1.350–1.958)            | 26.201                         | <0.001                         | 1.219 (0.991–1.500)             | 3.500                         | 0.061                          |
| PASP (per 10 mmHg increase) | 1.218 (1.152–1.288) | 47.504                         | <0.001                         | 1.219 (0.991–1.500)             | 3.500                         | 0.061                          |
| > vs. ≤35 mmHg   | 1.739 (1.450–2.084)            | 35.727                         | <0.001                         | 1.219 (0.991–1.500)             | 3.500                         | 0.061                          |
|                | Model 5                                                                 | Model 6                                                                 |
|----------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Age and sex adjusted HR (95% CI) | Wald | P-value | Clinical covariates adjusted HR (95% CI) | Wald | P-value |
| **Blood test** |                                                                                   |                                                                                           |
| NT-proBNP<sup>a</sup> | 1.066 (1.024–1.109) | 9.827 | 0.002 | 1.166 (1.011–1.343) | 4.483 | 0.034 |
| > vs. ≤3368 pg/mL | 1.275 (1.112–1.463) | 12.062 | <0.001 | 1.036 (0.906–1.184) | 0.262 | 0.609 |
| Hb (per 10 g/L increase) | 0.976 (0.949–1.004) | 2.765 | 0.092 | 1.153 (1.013–1.311) | 4.676 | 0.031 |
| Anaemia vs. no anaemia | 1.093 (0.959–1.245) | 1.779 | 0.182 |                                                                                   |                                               |
| UA (per 100 μmol/L increase) | 1.082 (1.027–1.140) | 8.684 | 0.003 |                                                                                   |                                               |
| > vs. ≤382 μmol/L | 1.217 (1.072–1.382) | 9.205 | 0.002 | 1.149 (1.007–1.311) | 4.267 | 0.039 |
| **Echocardiography** |                                                                                   |                                                                                           |
| LAs (per 10 mm increase) | 1.155 (1.045–1.276) | 7.979 | 0.005 | 1.153 (1.013–1.311) | 4.676 | 0.031 |
| > vs. ≤42 mm | 1.164 (1.016–1.334) | 4.766 | 0.028 | 1.050 (0.907–1.216) | 0.429 | 0.512 |
| PASP (per 10 mmHg increase) | 1.060 (1.019–1.104) | 8.319 | 0.004 | 1.153 (1.013–1.311) | 4.676 | 0.031 |
| > vs. ≤35 mmHg | 1.224 (1.077–1.391) | 9.553 | 0.002 | 1.149 (1.007–1.311) | 4.267 | 0.039 |

AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; Cr, creatinine; E/e', ratio of early transmitral flow velocity to early mitral annular velocity; Hb, haemoglobin; HDL, high density lipoprotein; IVSd, end-diastolic interventricular septal wall thickness; K, potassium; LAs, end-systolic left atrial anteroposterior diameter; LDL, low density lipoprotein; LVD, end-diastolic left ventricle dimension; LVEF, left ventricular ejection fraction; LVPWd, end-diastolic left ventricular posterior wall thickness; MI, myocardial infarction; NT-proBNP, N-terminal pro-B type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; TC, total cholesterol; TG, triglyceride; TnT, troponin T; UA, uric acid.

Each biomarker and echocardiographic marker plus clinical covariates were entered into the multivariable Cox regression model with enter method.

<sup>a</sup>Natural log transformation for NT-proBNP.
<sup>b</sup>Natural log transformation for Cr.
<sup>c</sup>Clinical covariates associated with 3-month CV events included age, heart rate, NYHA class, hypertension, AF, diabetes, CHD, renal insufficiency, use of ACEI/ARB, and use of diuretics.
<sup>d</sup>Clinical covariates associated with 12-month CV events included age, heart rate, NYHA class, hypertension, AF, diabetes, previous MI, COPD, renal insufficiency, use of ACEI/ARB, and use of diuretics.
<sup>e</sup>Clinical covariates associated with 33-month CV events included age, sex, systolic blood pressure, heart rate, NYHA class, AF, use of ACEI/ARB, and use of diuretics.
significantly higher in HFmrEF patients ≥75 years old as compared with HFmrEF patients <75 years old.

**Survival analysis of cardiovascular events in heart failure with mid-range or mildly reduced ejection fraction patients**

*Figure 3* displayed the Kaplan–Meier curves of blood biomarkers for predicting CV events in HFmrEF patients. Patients with NT-proBNP >3368 pg/mL, anaemia, UA > 382 μmol/L, and Cr > 100 μmol/L were associated with an increased risk of CV events. *Figure 4* displayed the Kaplan–Meier curves of echocardiographic parameters for predicting CV events in HFmrEF patients. LAs > 42 mm, E/e’ > 18, and PASP >35 mmHg were related higher risk of CV events.

**Impact of medication on cardiovascular events of heart failure with mid-range or mildly reduced ejection fraction patients**

*Table 4* shows the impact of medication on outcome of HFmrEF patients. It was shown that underused ACEI or ARB and more frequent use of diuretics during hospitalization were related to higher CV events after adjustment of age and sex.
Age and sexes differences of independent risk factors for cardiovascular events in heart failure with mid-range or mildly reduced ejection fraction at 3, 12, and 33 months

Age and sexes differences of independent risk factors for CV events in HFmrEF patients aged <75 years and HFmrEF patients ≥75 years at 3 and 12 months and significantly related to higher CV events in HFmrEF patients aged <75 years at 33 months. NT-proBNP >3368 pg/mL was significantly related to higher CV events in both age groups and both sex at 3 months and 12 months after discharge. E/e’ > 18 was significantly related to higher CV events in both age groups and both sex at 12 months after discharge. PASP >35 mmHg was significantly related to higher CV events in both age groups and both sex at 12 months and 33 months after discharge.

Incremental impact of serum biomarkers on cardiovascular events at 3, 12, and 33 months

CV events in HFmrEF patients with 0, 1, 2, 3, or 4 increased blood biomarkers were 10.4%, 12.3%, 22.0%, 27.0%, and 31.1% at 3 months; 14.4%, 25.3%, 32.4%, 45.2%, and 45.1% at 12 months; 47.0%, 55.4%, 61.3%, 68.3%, and 64.6% at 33 months after discharge.

Discussion

Data from this large cohort of HFmrEF patients in the real world show that higher uric acid, creatinine, NT-proBNP, and lower haemoglobin levels at baseline are valuable serum biomarkers for risk stratification of short-term and long-term
cardiac prognosis. In addition to these serum biomarkers, echocardiography derived PASP > 35 mmHg could be used to predict increased risk of CV events at 12 and 33 months after discharge, and E/e' > 18 is an independent risk factor for the increased risk of CV events at 12 months after discharge (Figure 5).

**Value and clinical implication of serum biomarker on risk stratification of heart failure with mid-range or mildly reduced ejection fraction patients**

Results from multi-nation data show that NT-proBNP is related to all-cause mortality in patients with HFmrEF independent of the covariates, and is similarly predictive of death in the three HF phenotypes. According to the acute decompen-sation HF data from the Japanese multicentre registry, blood urea nitrogen and NT-proBNP levels, as well as other clinical predictors, including age, anaemia, chronic kidney disease, and hyponatraemia, are important predictors of all-cause death or HF readmission in HFmrEF. Data from a contemporary-treated cohort of HF outpatients show that high serum uric acid is an independent prognosticator of CV death/HF hospitalization in HEREF and HFpEF patients, but not in HFmrEF patients. Anaemia is also associated with similar risk of all-cause death regardless of LVEF. However, large-scale studies focusing on the prognostic values of serum biomarkers for outcomes in patients with HFmrEF are scarce. In the present study, 1691 HFmrEF patients were followed up for a median of 33 months, results showed that UA > 382 μmol/L, Cr > 100 μmol/L, NT-proBNP > 3368 pg/mL, and Hb < 120 g/L for men and <110 g/L for women are related to increased risk of CV events at 3 months and 12 months after discharge. UA > 382 μmol/L, and NT-proBNP > 3368 pg/mL are related increased risk of CV events at 33 months after discharge. To our best knowledge, this is the first clinical observation based on data from large cohort data of real-world patients to determine the key role of these 4 serum biomarkers in short-term and long-term cardiac outcomes of patients with HFmrEF. Determination of circulating biomarkers is valuable for risk stratification of HF patients, and numerous novel circulating biomarkers are available for predicting the outcome of HF patients. However, the true value of novel biomarker candidates in HF prognostication remains unclear. The present study focuses on the predictive value of commonly used serum biomarkers among HFmrEF patients, thus providing a simple and feasible method to determine the outcome of HFmrEF patients in daily clinical practice. NT-proBNP is the best studied natriuretic peptide in patients with heart failure. Increased circulating NT-proBNP level usually reflects increased myocardial stretch, mainly due to volume overload. It is known that anaemia is common in HF patients with all LVEF categories and related to worse outcomes in HF patients. Worsening renal function, indicated by an increase in creatinine, is an important determinant of adverse in-hospital and 1 year outcomes in both
HFrEF and HFpEF patients. At the same time, presence of renal dysfunction could also aggravate anaemia. Coexistence of anaemia and renal dysfunction might form a vicious circle, leading to worse outcomes of HF patients. Serum uric acid could be regarded as a marker of renal dysfunction, which is also related to poor outcome in HF patients. Higher serum uric acid level is also related to excessive inflammatory response and congestion in HF patients. Moreover, higher serum uric acid was associated with lower systolic blood pressure and LVEF, higher natriuretic peptides, and more serious real impairment. Taken together, presence of anaemia, increased levels of NT-proBNP, creatinine, and uric acid collectively reflect almost the whole spectrum of HF pathophysiology. Our results showed that among HFmrEF patients with

| Medications [n (%)]          | Total   | Non-CV events | CV events | P-value | Age and sex adjusted hazard ratio (95% CI) | Wald     | P-value | N available (%) |
|-----------------------------|---------|---------------|-----------|---------|------------------------------------------|----------|---------|-----------------|
| Beta-blockers               | 1350 (79.8) | 579 (81.1)    | 780 (78.9) | 0.270   | 0.063 | 0.821 (0.716–0.941) | 7.987   | 0.005   | 1691 (100)       |
| ACEI or ARB                 | 1198 (70.8) | 523 (73.2)    | 675 (69.1) | 0.006   | 0.151 (1.013–1.307) | 4.690   | 0.030   | 1691 (100)       |
| Diuretics                   | 895 (52.9)  | 347 (48.6)    | 548 (61.2) | 0.002   | 1.137 (1.014–1.270) | 4.421   | 0.038   | 1691 (100)       |
| Statins                     | 1422 (84.1) | 607 (85.0)    | 815 (83.4) | 0.376   | 1.151 (1.013–1.270) | 4.690   | 0.030   | 1691 (100)       |
| Antiplatelet Drugs          | 1394 (82.4) | 599 (83.9)    | 795 (81.4) | 0.178   | 1.151 (1.013–1.270) | 4.690   | 0.030   | 1691 (100)       |
| NOAC                        | 877 (51.9)  | 358 (50.1)    | 519 (53.1) | 0.225   | 0.225 | 1.067 (0.788–1.446) | 0.177   | 0.674   | 1691 (100)       |
| Digoxin                     | 64 (3.8)    | 20 (2.8)      | 44 (4.5)  | 0.070   | 0.070 | 1.067 (0.788–1.446) | 0.177   | 0.674   | 1691 (100)       |
| Positive inotropic drugs    | 102 (6.0)   | 38 (5.3)      | 64 (6.6)  | 0.295   | 0.295 | 1.067 (0.788–1.446) | 0.177   | 0.674   | 1691 (100)       |
| ARNI (from 12.2017)         | 79 (8.3)    | 41 (9.0)      | 38 (7.7)  | 0.469   | 0.469 | 1.067 (0.788–1.446) | 0.177   | 0.674   | 1691 (100)       |
| Spironolactone              | 775 (45.8)  | 334 (46.8)    | 441 (45.1) | 0.504   | 0.504 | 1.067 (0.788–1.446) | 0.177   | 0.674   | 1691 (100)       |
| Mechanical ventilation      | 33 (2.0)    | 8 (1.1)       | 25 (2.6)  | 0.035   | 0.035 | 1.358 (0.912–2.020) | 2.271   | 0.132   | 1691 (100)       |

Values are expressed as n (%).
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor antagonists; NOAC, new oral anticoagulants; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval.
or without increased blood biomarkers (from 0 to 4), CV events rate increased from 10.4% to 31.1% at 3 months after discharge, from 14.4% to 45.1% at 12 months after discharge, and from 47.0% to 64.6% at 33 months after discharge. Determination of these 4 circulating biomarkers, together with increased E/e′ (>18) and PASP (>35 mmHg), two echocardiographic indices indicating the presence of diastolic dysfunction,\textsuperscript{22} might thus be a reliable strategy of risk stratification of HFmrEF patients to filter out the high-risk HFmrEF patients. It is reasonable to administer a more intensive HF medication plan and closer follow-up for patients with high-risk HFmrEF, which defined by above 4 serum biomarkers in combination with or without the two echocardiographic indices (E/e′ > 18 and PASP >35 mmHg). Future clinical studies are warranted to observe whether the intensive HF management options can improve the cardiac outcomes of patients with high-risk HFmrEF defined by the above 4 circulating biomarkers. It is to note that age and sex should also be taken into account in risk stratification of HFmrEF patients (Supporting Information, Table S1).

Serum biomarkers among heart failure with preserved ejection fraction, heart failure with mid-range or mildly reduced ejection fraction, and heart failure with reduced ejection fraction patients

It is important to know whether there are differences in prognostic role of circulating biomarkers in HF patients with different LVEF categories. NT-proBNP is the gold standard for diagnostic role of circulating biomarkers in HF patients with different LVEF categories. NT-proBNP is the gold standard for diagnostic role of circulating biomarkers in HF patients with different LVEF categories. NT-proBNP is the gold standard for diagnostic role of circulating biomarkers in HF patients.\textsuperscript{23} Previous data showed important differences in the prognostic value of NT-proBNP in HFrEF versus HFpEF, in which NT-proBNP showed less prognostic value in HFrEF as compared with HFpEF.\textsuperscript{24} A prospective clinical study demonstrated that anaemic patients had poor prognosis compared with non-anaemic patients in HFpEF patients with chronic kidney disease, but not those without chronic kidney disease.\textsuperscript{25} Carnicelli and his colleagues observed the impact of elevated baseline serum uric acid in HFpEF patients who participated in the RELAX trial, and found that serum uric acid was an important indicator of co-morbidities and functional status of HFpEF patients. However, there was no significant association between baseline serum uric acid levels and the composite of death or cardiovascular/renal hospitalization at 24 weeks.\textsuperscript{26} Another clinical study including 424 HFpEF patients found that hyperuricaemia was related to arterial stiffness, impaired exercise capacity and high mortality in HFpEF patients.\textsuperscript{27} In patients with acute heart failure, worsening renal function as expressed by increased creatinine level was found to be an independent predictor of adverse in-hospital and follow-up outcomes in HFpEF and HFrEF.\textsuperscript{28} There is a large amount of data on association between various circulating biomarkers and outcomes in patients with HFrEF, which indicates prognostic values of higher NT-proBNP, uric acid and presence of anaemia in HFrEF patients.\textsuperscript{29}

It is to note that the data in the literature rarely describe the sum of these circulating parameters in a unique patient cohort. Previous studies usually explore the prognostic impact of individual parameters among HF patients. Our data comprehensively evaluated the prognostic importance of circulating parameters commonly used in daily practice, and this work might have more translational impact on risk stratification of patients with HFmrEF.

Study limitations

The findings of this study have to be seen in light of some limitations. Given the retrospective nature of our study, limitations like selection bias, recall bias, or misclassification bias are inevitable for this study. Caution is needed in the interpretation of results from this study. Moreover, future research needs to validate the predictors for worse outcomes defined in this study with other HFmrEF cohorts. In this study, we used LVEF during hospitalization as grouping criteria of patients. However, LVEF is a constantly changing variable during follow-up. Previous studies show that patients with HFmrEF present with the greatest variability in LVEF during 1 year follow-up compared with patients with HFrEF.\textsuperscript{29} The transition from HFmrEF to HFrEF is associated with increased all-cause mortality, and outcome is better when LVEF improved to HfEF, but when LVEF remains unchanged or worsened, outcome is worse.\textsuperscript{29,30} In the present study, information prior to admission on HFpEF, HFmrEF, and HFrEF was not available and longitudinal changes in LVEF and outcomes were also not explored. Future studies are warranted to clarify the outcome determinants of HFmrEF with improved or decreased LVEF, as well as HFmrEF from HfEF or HFrEF in this cohort.

In conclusion, data from this real-world large HFmrEF cohort suggest that anaemia, higher circulating NT-proBNP, creatinine, and uric acid levels are valuable predictors for poor short-term, intermediate-term, and long-term cardiac outcomes of HFmrEF patients. Future studies are required to verify if intensive HF management program for high-risk HFmrEF patients identified by the outcome determinants derived from this study could improve their cardiac outcome or not.

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**Conflict of interest**

None declared.

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**Supporting information**

Additional supporting information may be found in the Supporting Information section at the end of the article.

**Table S1.** Age and sexes of independent risk factors for CV events in HfmrEF.
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