

Patients With Acute Decompensated Heart Failure in an Area With a Super-Aging Society: A Single-Center, Retrospective Cohort Study

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In a super-aging society, the characteristics of acute heart failure (HF) are increasingly shaped by patients of advanced age who are rarely represented in clinical trials. We retrospectively evaluated patients aged ≥ 18 years hospitalized with acute HF between April 2016 and March 2021 at a single center and classified them as HF with reduced left ventricular ejection fraction (LVEF) (HF_rEF, $\leq 40\%$) or non-reduced LVEF (HF_{non-r}EF, $>40\%$). Of 524 admissions, 437 patients were discharged (136 HF_rEF, 301 HF_{non-r}EF). The cohort had a median age of 85 years—markedly older than typical trial cohorts—and, overall, patients with HF_{non-r}EF were older. One-year composite outcomes (HF readmission and cardiovascular death) occurred in 37.7%, with higher rates in HF_rEF than in HF_{non-r}EF (43.8% vs. 34.9%, $P = 0.03$). One-year all-cause mortality was 19.7%. These event rates exceeded those reported in younger populations, and the use of guideline-directed therapies remained limited. Among patients with HF_rEF, the use of ACEI/ARB, beta-blockers, and MRAs was 61.0%, 72.8%, and 30.9%, respectively. The findings underscore a

substantial evidence gap and indicate an increasing need for HF management strategies tailored not only to LVEF but also to patient age, particularly in older adults.

Keywords: heart failure, ejection fraction, older adults, mortality, readmission

INTRODUCTION

Japan has one of the longest life expectancies worldwide, with 81.6 years for males and 87.7 years for females, and its aging rate (the proportion of the population aged ≥ 65 years) has reached 28.9%, which is high by global standards (as of 2020) [1]. Accordingly, Japan is classified as a “super-aging society,” defined as a country in which the aging rate exceeds 21%. With this demographic shift, the number of patients with heart failure (HF) continues to rise. However, most available data on HF treatment and prognosis are derived from cohorts with a mean age of 65–70 years, leaving limited evidence for patients aged ≥ 75 years [2]. The management of older patients with HF is not fully addressed in current HF practice guidelines and requires individualized care [3–7]. In this study we examined the clinical background, medication use, and outcomes of older patients with HF in super-aging society.

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MATERIALS AND METHODS

Study design

This single-center, retrospective observational study included patients aged ≥ 18 years admitted to Saiseikai Gotsu General Hospital with acute HF between April 1, 2016, and March 31, 2021. The requirement for informed consent was waived, and an opt-out model was used. The study adhered with the Declaration of Helsinki and institutional ethical standards. Approval was obtained from the Institutional Review Boards of Saiseikai Gotsu General Hospital. Gotsu City, Shimane Prefecture, Japan, has approximately 23,000 residents and an aging rate of 39.2%. As the only general hospital in the area, nearly all patients with acute HF in this region present to this facility.

Study endpoints

The primary endpoint was the comparison of cumulative incidence of a composite of HF readmission and cardiovascular death within 1 year after discharge between the two left ventricular ejection fraction (LVEF) groups. The secondary endpoint was the comparison of cumulative incidence of all-cause death within 1 year after discharge between the two LVEF groups. Cardiovascular death included death due to HF, myocardial infarction, cardiogenic shock, sudden cardiac death (non-traumatic and unexpected, occurring within 24 hours after last being seen alive if unwitnessed), or other cardiovascular causes. Post-discharge outcomes were obtained from electronic medical records.

Diagnostic criteria

ADHF was defined using the Universal Definition of HF or the Framingham Acute HF criteria [1, 4]. Patients with acute coronary syndrome (ACS) who met acute HF criteria were included. Medical information, including age, sex, body mass index (BMI), comorbidities, laboratory data at admission, length of hospital stay, and discharge prescriptions, was collected from electronic medical records. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula, and chronic kidney disease (CKD) was defined as $eGFR < 60$ mL/min/1.73 m².

Chronic respiratory disease included chronic obstructive pulmonary disease, asthma, interstitial pneumonia, or pulmonary tuberculosis.

Patients were classified into two categories based on LVEF obtained on echocardiography after admission: HF with reduced LVEF (HFrEF) for LVEF $\leq 40\%$ and HF with non-reduced LVEF (HFnon-rEF) for LVEF $> 40\%$. Prognosis after discharge was monitored until March 31, 2022, allowing follow-up of the outcomes at 12 months. Analyses excluded patients who died during hospitalization, and follow-up time was calculated from discharge.

Statistical analysis

Categorical variables are presented as percentages, and continuous variables as medians with interquartile ranges (IQR). The Mann–Whitney U test was used to compare clinical characteristics between HFrEF and HFnon-rEF. Categorical variables were evaluated using the chi-square test or Fisher's exact test. Differences in clinical outcomes between LVEF groups were assessed using the log-rank test. Kaplan–Meier curves were generated for the composite outcomes of HF readmission and cardiovascular death, all-cause death, HF readmission, cardiovascular death. Univariate and multivariate Cox proportional hazards analyses were performed to examine associations between clinical characteristics and composite endpoints within each LVEF group. All P values were two-sided, and $P \leq 0.05$ was considered statistically significant. Analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and a modified version of R Commander that incorporates statistical functions frequently used in biostatistics [8].

RESULTS

Patient population and demographics

A total of 524 patients with ADHF were admitted to Saiseikai Gotsu General Hospital between April 1, 2016, and March 31, 2021. Fifteen patients lacked echocardiographic LVEF data, and seventy-two patients died in the hospital. Among the 437 patients discharged, 136 (31.1%) had HFrEF and

301 (68.9%) had HFnon-rEF (Fig. 1). Table 1 presents the clinical characteristics. The overall median age was 85 years (IQR 76–91). Patients with HFnon-rEF were older than those with HFrEF and included a higher proportion of females. BMI was not recorded in four patients, but no significant differences existed between LVEF groups. Comorbidity rates, including coronary artery disease, atrial fibrillation, hypertension, diabetes mellitus, lipid abnormalities, CKD, and chronic respiratory disease, did not differ significantly according to LVEF groups. Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) were recorded separately by patients: 125 patients had BNP data, 286 had NT-proBNP, and 26 patients had no records. Levels were higher in HFrEF than in HFnon-rEF. The median length of hospital stay was 24 days (IQR 15–42), with no significant differences by LVEF group.

At discharge, patients received a median of eight medications (IQR 6–10), with no significant between-group difference in medication count. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), sodium-glucose cotransporter 2 inhibitors (SGLT2I), tolvaptan, and loop diuretics were prescribed more frequently in the HFrEF group than in the HFnon-rEF group; however, for Ca channel blocker,

the prescription rates were higher in the HFnon-rEF group than in the HFrEF group. No significant differences were observed in LVEF among antithrombotic (anti-coagulant and anti-platelet), anti-diabetic, and statin therapies.

Post-discharge cause-specific outcomes

The cumulative incidence of the composite outcomes of HF readmission and cardiovascular death was significantly higher in HFrEF than in HFnon-rEF (Figure 2). One-year composite event rates were 43.8% (95% CI: 35.3–53.3) for HFrEF and 34.9% (95% CI: 29.4–41.2) for HFnon-rEF ($P = 0.03$). One-year all-cause mortality and cardiovascular mortality did not differ significantly between groups (Table 2).

Predictors of post-discharge outcomes

In HFrEF, univariate analysis identified age as the only significant predictor of 1-year composite outcomes, and multivariate analysis confirmed this association. In HFnon-rEF, univariate analysis showed significant associations with age, female sex, BMI, coronary artery disease, atrial fibrillation, CKD, chronic respiratory disease, and ACEI/ARB and MRA use; however, multivariate analysis identified age as the only independent predictor (Tables 3 and 4).

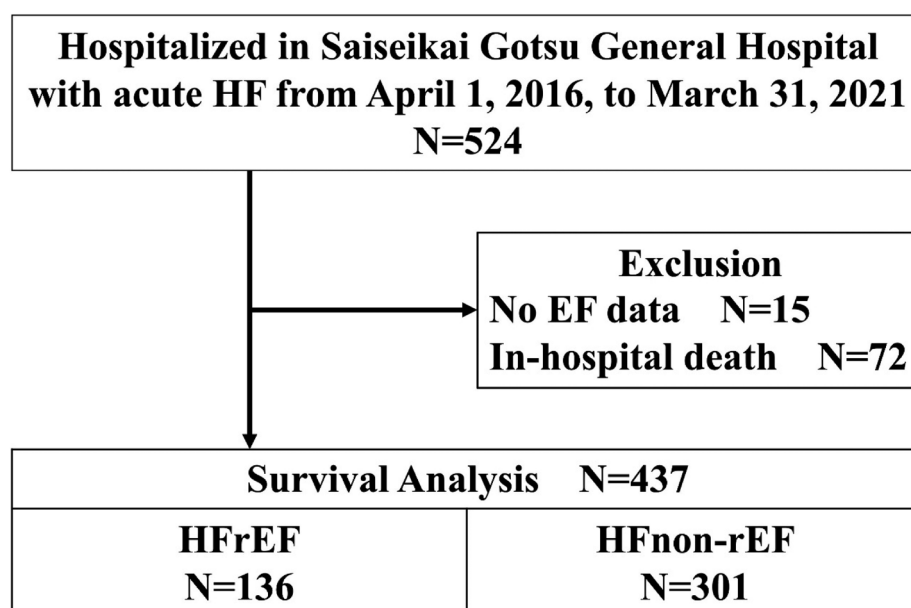


Fig. 1. Study outline. Flow diagram showing patient selection and classification.

Table 1. Baseline characteristics of patients according to LVEF groups

| | All (N = 437) | Missing value | HFrEF (N = 136) | HFnon-rEF (N = 301) | P-value |
|--------------------------------------|------------------|---------------|--------------------|------------------------|---------|
| Patient characteristics | | | | | |
| Age, years | 85 [76-91] | 0 | 82 [74-89] | 87 [79-92] | 0.002 |
| Female sex | 242 (55.4%) | 0 | 59 (43.4%) | 183 (60.8%) | <0.001 |
| BMI, kg/m ² | 22.2 [20.0-24.8] | 4 (0.9%) | 22.6 [19.4-25.4] | 22.2 [20.4-24.6] | 0.70 |
| Medical history | 0 | | | | |
| Coronary artery disease | 156 (35.7%) | | 52 (38.2%) | 104 (34.6%) | 0.52 |
| Acute coronary syndrome on admission | 52 (11.9%) | | 9 (6.6%) | 43 (14.3%) | 0.02 |
| Atrial fibrillation | 168 (38.4%) | | 57 (41.9%) | 111 (36.9%) | 0.34 |
| Hypertension | 322 (73.7%) | | 93 (68.4%) | 229 (76.1%) | 0.10 |
| Diabetes mellitus | 133 (30.4%) | | 50 (36.8%) | 83 (27.8%) | 0.057 |
| Dyslipidemia | 205 (46.9%) | | 64 (47.1%) | 141 (46.8%) | 1.00 |
| Chronic Kidney Disease | 335 (76.7%) | | 105 (77.2%) | 230 (76.4%) | 0.90 |
| Hemodialysis | 7 (1.6%) | | 2 (1.5%) | 5 (1.7%) | 1.00 |
| Chronic respiratory disease | 85 (19.5%) | | 24 (17.6%) | 61 (20.3%) | 0.60 |
| Laboratory data on admission | | | | | |
| BNP, pg/mL (N = 125) | 536 [282-838] | 0 | 661 [470-851] | 425 [181-831] | 0.004 |
| NT-proBNP, pg/mL (N = 286) | 3993 [1526-8787] | 26 (6.0%) | 7916 [4052-13539] | 2596 [1096-6850] | <0.001 |
| Cr, mg/dL | 1.08 [0.81-1.53] | 0 | 1.14 [0.84-1.55] | 1.06 [0.80-1.50] | 0.28 |
| eGFR, mL/min/1.73m ² | 43.6 [30.5-57.8] | 0 | 42.7 [30.3-58.7] | 43.8 [30.5-57.7] | 0.73 |
| LVEF, % | 53 [36-64] | 0 | 30 [25-35] | 60 [52-69] | <0.001 |
| Length of hospital stay, days | 24 [15-42] | 0 | 26 [17-43] | 23 [15-41] | 0.13 |
| Medication at discharge | 0 | | | | |
| Number of agents | 8 [6-10] | | 8 [6-10] | 8 [6-10] | 0.77 |
| ACEI/ARB | 231 (52.9%) | | 83 (61.0%) | 148 (49.2%) | 0.02 |
| BB | 234 (53.5%) | | 99 (72.8%) | 135 (44.9%) | <0.001 |
| MRA | 105 (24.0%) | | 42 (30.9%) | 63 (20.9%) | 0.03 |
| SGLT2I | 15 (3.4%) | | 9 (6.6%) | 6 (2.0%) | 0.02 |
| Tolvaptan | 79 (18.1%) | | 34 (25.0%) | 45 (15.0%) | 0.02 |
| Loop diuretics | 314 (71.9%) | | 117 (86.0%) | 197 (65.4%) | <0.001 |
| Ca channel blocker | 148 (33.9%) | | 32 (23.5%) | 116 (38.5%) | 0.002 |
| Anti-coagulants | 152 (34.8%) | | 55 (40.4%) | 97 (32.2%) | 0.10 |
| Warfarin | 62 (14.2%) | | 21 (15.4%) | 41 (13.6%) | 0.66 |
| DOAC | 90 (20.6%) | | 34 (25.0%) | 56 (18.6%) | 0.13 |
| Anti-platelet | 172 (39.3%) | | 52 (38.2%) | 120 (39.9%) | 0.83 |
| Anti-diabetic | 85 (19.5%) | | 33 (24.3%) | 52 (17.3%) | 0.09 |
| Statin | 184 (42.1%) | | 57 (41.9%) | 127 (42.2%) | 1.00 |

Table 2. Clinical outcomes according to LVEF groups

| | 1-year event rate, % (95%CI) | All | HFrEF | HFnon-rEF | P-value |
|---|---------------------------------|----------------------|----------------------|----------------------|---------|
| Composite outcomes (HF readmission + Cardiovascular death) | | 37.7% (33.0-43.0) | 43.8% (35.3-53.3) | 34.9% (29.4-41.2) | 0.026 |
| HF readmission | | 33.6% (28.9-38.7) | 41.1% (32.7-50.8) | 30.0% (24.7-36.2) | 0.035 |
| Cardiovascular death | | 12.0% (9.0-15.9) | 13.2% (8.1-20.9) | 11.4% (7.9-16.2) | 0.276 |
| All-cause death | | 19.7% (16.0-24.2) | 20.4% (14.1-28.9) | 19.4% (15.0-24.9) | 0.381 |

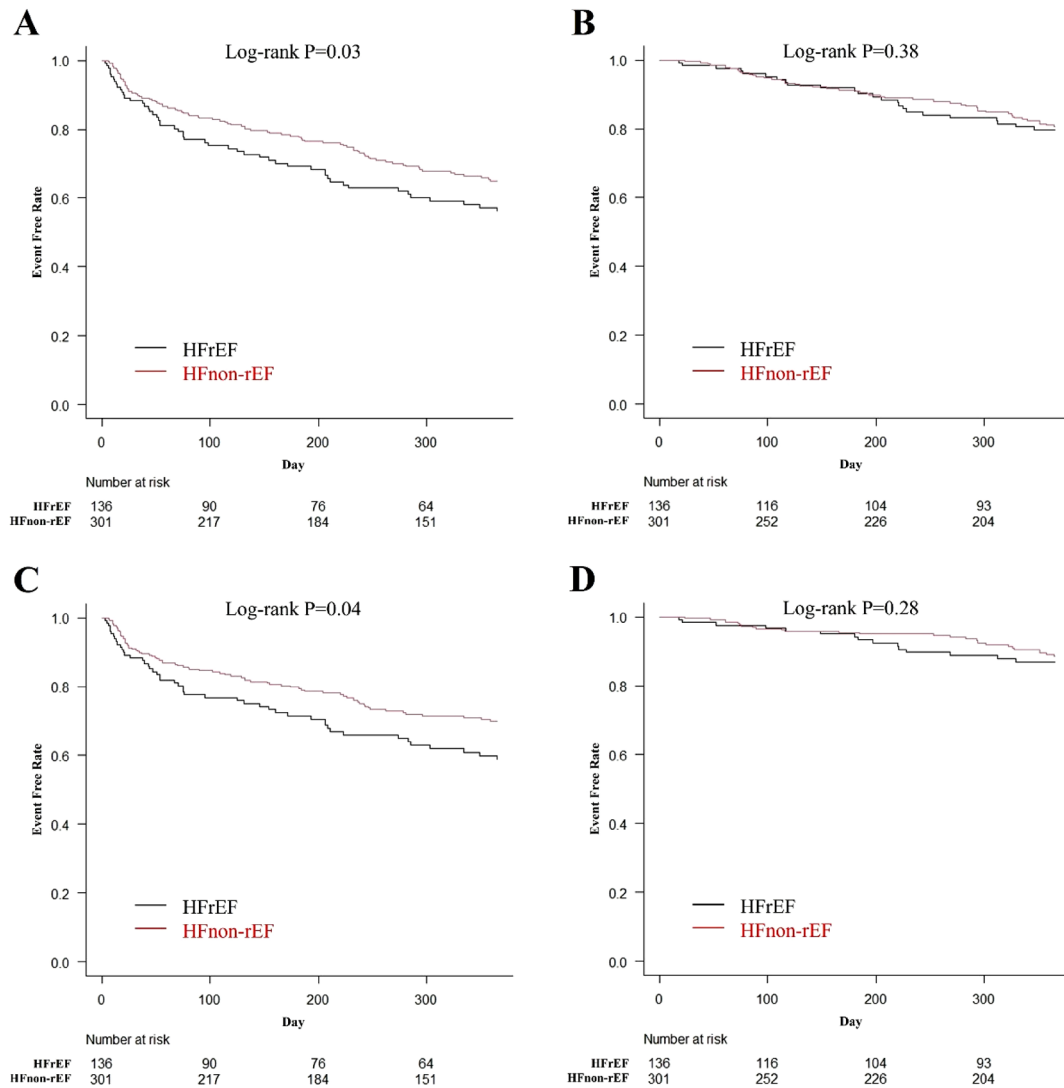


Fig. 2. Kaplan-Meier curves for survival analysis.

(A) Composite outcomes, including both heart failure readmission and cardiovascular death. (B) All-cause death. (C) Heart failure readmission. (D) Cardiovascular death. Black line, HFrEF; red line, HFnon-rEF.

Table 3. Univariate Cox proportional hazards analysis for composite outcomes (HF readmission and cardiovascular death) in HFrEF and HFnon-rEF

| | HFrEF | | HFnon-rEF | |
|-----------------------------|------------------|---------|------------------|---------|
| | HR (95%CI) | P-value | HR (95%CI) | P-value |
| Age | 1.03 (1.00-1.05) | 0.03 | 1.07 (1.04-1.09) | <0.001 |
| Female | 0.97 (0.60-1.57) | 0.91 | 1.75 (1.18-2.59) | 0.01 |
| BMI | 1.02 (0.96-1.07) | 0.55 | 0.95 (0.90-1.00) | 0.03 |
| Coronary artery disease | 1.07 (0.66-1.73) | 0.79 | 0.50 (0.33-0.76) | 0.001 |
| Atrial fibrillation | 1.10 (0.68-1.78) | 0.71 | 1.66 (1.15-2.40) | 0.01 |
| Hypertension | 0.84 (0.50-1.39) | 0.50 | 0.84 (0.56-1.27) | 0.41 |
| Diabetes mellitus | 0.83 (0.50-1.36) | 0.46 | 1.26 (0.85-1.86) | 0.25 |
| Chronic kidney disease | 0.94 (0.53-1.66) | 0.82 | 1.62 (1.02-2.58) | 0.04 |
| Chronic respiratory disease | 1.07 (0.58-1.95) | 0.83 | 1.75 (1.15-2.66) | 0.01 |
| ACEI/ARB | 1.11 (0.67-1.83) | 0.68 | 0.59 (0.41-0.85) | 0.005 |
| BB | 1.05 (0.62-1.78) | 0.86 | 1.31 (0.91-1.89) | 0.14 |
| MRA | 0.75 (0.44-1.29) | 0.31 | 1.64 (1.07-2.51) | 0.02 |

Table 4. Multivariate Cox proportional hazards analysis for composite outcomes (HF readmission and cardiovascular death) in HF_rEF and HF_{non-r}EF

| | HF _r EF | | HF _{non-r} EF | |
|-------------------------|--------------------|---------|------------------------|---------|
| | HR (95%CI) | P-value | HR (95%CI) | P-value |
| Age | 1.04 (1.01-1.06) | 0.008 | 1.06 (1.03-1.08) | <0.001 |
| Coronary artery disease | 1.32 (0.78-2.22) | 0.30 | 0.87 (0.55-1.38) | 0.55 |
| Atrial fibrillation | 1.19 (0.71-1.98) | 0.52 | 1.28 (0.86-1.91) | 0.22 |
| ACEI/ARB | 1.36 (0.80-2.32) | 0.25 | 0.79 (0.54-1.17) | 0.24 |
| BB | 1.17 (0.67-2.04) | 0.59 | 1.16 (0.78-1.71) | 0.46 |
| MRA | 0.68 (0.39-1.19) | 0.18 | 1.25 (0.81-1.93) | 0.32 |

DISCUSSION

In this study we examined the clinical features, medication patterns, and outcomes of older patients with HF a super-aging society. While prior acute HF studies reported a mean age of 65–70 years [2], the median age in this cohort was 85 years, representing a substantially older population with longer-than-average life expectancy. These patients have been underrepresented in previous studies, underscoring the need for more systematic investigation.

Characteristics of patients with HF in a super-aging society

The proportion of patients with HF_{non-r}EF was high (68.9%). Patients in this group were older and had a higher proportion of females, consistent with earlier reports showing that preserved LVEF is more common among older individuals and females [9–11]. Previous studies have also found that patients with HF_rEF more frequently have coronary artery disease, whereas those with preserved LVEF experience more atrial fibrillation; however, these differences were not observed in this cohort [9–11]. BNP and NT-proBNP levels mirrored findings from earlier studies and were higher in HF_rEF.

Pharmacotherapy of patients with HF in a super-aging society

Although guidelines recommend ACEI/ARB, BB, and MRA for improving outcomes in HF_rEF, the induction rates of ACEI/ARB, BB, and MRA tended to be low for HF_rEF in this study (61.0%, 72.8%, and 30.9%, respectively). These rates are lower than those reported in previous studies and may reflect advanced age and impaired renal function [12–14]. Among patients with HF_rEF, the incidence of com-

posite outcomes did not differ significantly between those treated with and without ACEI/ARB, BB, or MRA. Previous reports demonstrated reduced composite outcomes rates when guideline-based medical treatment (GBMT), defined as combined ACEI/ARB and BB use, was applied for patients with HF_rEF aged <80 years; results in the present cohort were similar because there was no significant difference in composite outcomes between patients with HF_rEF aged >80 years with and without GBMT [4]. In HF_{non-r}EF, univariate analysis showed lower composite event rates with ACEI/ARB use and higher rates with MRA use. Previous studies in patients with preserved LVEF similarly reported no significant differences in HF readmission or cardiovascular death with ACEI/ARB, although outcomes tended to be more favorable [15]. Studies evaluating BB and MRA found no significant differences in HF readmission or cardiovascular death [16, 17]. In the present multivariate analysis, these associations were attenuated, suggesting that age and disease severity may have influenced the results.

Outcomes of patients with HF in a super-aging society

The 1-year composite outcomes rate was 37.7%, exceeding the previously reported 23.7% [18], and remained significantly higher for HF_rEF than for HF_{non-r}EF. Prior studies showed variable relationships between LVEF and prognosis, with some reporting outcomes for preserved LVEF that were comparable to reduced LVEF, whereas others demonstrated worse outcomes for HF_rEF, consistent with the present findings. The 1-year incidence of all-cause death in earlier Japanese reports ranged from 7.3% to 21.8% [19, 20], and the overall rate in this study was higher at 19.7%. The trend toward worse

outcomes (composite events and all-cause death) in the present study was likely driven largely by age. Despite their younger age, patients with HF_rEF experienced a higher composite event rate than those with HF_{non-r}EF. This difference may reflect lower prescription rates of cardioprotective agents such as ACEI/ARB, BB, and MRA. In older patients, lower prescription rates of guideline-directed medical therapy may not simply reflect underuse, but rather clinical complexity. Hemodynamic fragility such as hypotension, renal dysfunction, polypharmacy, and frailty frequently complicates the initiation and up-titration of these agents in older patients with HF [21]. Nevertheless, emerging real-world data suggests that newer therapeutic options may still confer prognostic benefit even in older populations. Recent observational studies have reported associations between sodium–glucose cotransporter 2 (SGLT2) inhibitor use and improved outcomes in older patients, including those aged ≥ 80 years, although treatment discontinuation due to frailty or adverse events remains a concern [22, 23]. Similarly, post hoc analyses of trials evaluating sacubitril/valsartan have continued to explore its effects across heterogeneous patient profiles, underscoring the importance of age-tailored implementation strategies rather than a one-size-fits-all approach [24]. Because patients of advanced age with HF have not been well represented in large clinical studies, the effectiveness of these medications in patients aged ≥ 80 years requires prospective investigation.

Study Limitations

This study has several limitations. First, LVEF data were collected during the index hospitalization; however, the exact timing of echocardiography was unknown and may have been influenced by coexisting conditions. Because only one LVEF measurement was obtained and follow-up data were unavailable, changes in LVEF could not be assessed. Second, in-hospital treatment was determined by the attending physician, and discharge prescriptions may not reflect long-term therapy because medications may have been continued, discontinued, adjusted, or newly initiated. Third, during the study period, angiotensin receptor neprilysin inhibitors and SGLT2I were not yet approved for HF treatment; therefore, these agents were not introduced, and their introduc-

tion rates were very low. Fourth, because the hospital's adopted biomarker changed between BNP and NT-proBNP during the study period, consistent measurements could not be obtained. Therefore, these biomarkers could not be included in the analysis of their association with clinical outcomes. Fifth, although frailty influences HF outcomes, previous studies have reported conflicting results regarding whether patients with frailty derive greater or lesser benefit from HF medications [25]. This study involved older adults' cohort likely to include many patients with frailty; however, frailty data were insufficient to evaluate these associations. Sixth, because analyses using more granular classifications such as HF with mildly reduced EF, preserved EF, and supernormal EF were not performed, differences within the HF_{non-r}EF population could not be assessed. Accordingly, the interpretation of the clinical outcomes should be made with caution due to the remaining uncertainty [26]. Seventh, nursing home residence and caregiving support may influence HF readmission risk; however, such social factors could not be analyzed [27]. Potential confounding factors therefore cannot be ruled out, and conclusions suggesting that HF_{non-r}EF has a more favorable prognosis should be made cautiously. Eighth, although patients with ACS were included because they met the criteria for ADHF, the inclusion of this heterogeneous ACS subgroup may have influenced the overall clinical outcome results. Finally, the study sample was small, and this was a single-center observational study, limiting generalizability and precluding definitive conclusions.

CONCLUSION

With a median age of 85 years, this cohort represents a population rarely captured in previous literature. The high incidence of composite outcomes and all-cause mortality in these older adults group highlights the need for prospective evaluation of appropriate treatment strategies and individualized goal setting for these patients.

Ethical Approval

This manuscript followed the Declaration of Helsinki and the ethical standards of the responsible com-

mittee on human experimentation. The Institutional Review Boards of Saiseikai Gotsu General Hospital (R3-2) approved this study.

Author Contribution

JT, HS, and KT conceived and designed the study. JT, HS, KO, AM, AE, and YN collected the data. JT analyzed the data and drafted the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

All authors declare no conflicts of interest associated with this manuscript.

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